Bioorganic & Medicinal Chemistry 18 (2010) 7132–7143

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis and biological activities of new di- and trimeric quinoline derivatives

Sidonie Broch [a,b], Hélène Hénon [a,b], Anne-Laure Debaud [c,d,e], Marie-Laure Fogeron [c,d,e], Nathalie Bonnefoy-Bérard [c,d,e], Fabrice Anizon [a,b], Pascale Moreau [a,b,*]

[a] Clermont Université, Université Blaise Pascal, SEESIB, BP 10448, F-63000 Clermont-Ferrand, France
[b] CNRS, UMR 6504, SEESIB, F-63177 Aubière, France
[c] Université de Lyon, France
[d] Inserm, U851, 21 Avenue Tony Garnier, Lyon F-69007, France
[e] Université Lyon 1, IFR128, France

ARTICLE INFO

Article history:
Received 1 April 2010
Revised 12 July 2010
Accepted 13 July 2010
Available online 16 July 2010

Keywords:
Helix mimetic
Quinoline
Bcl-2 protein
Apoptosis

ABSTRACT

The synthesis of non-peptidic helix mimetics based on a trimeric quinoline scaffold is described. The ability of these new compounds, as well as their synthetic dimeric intermediates, to bind to various members of the Bcl-2 protein anti-apoptotic group is also evaluated. The most interesting derivative of this new series (compound **A**) inhibited Bcl-x_L/Bak, Bcl-x_L/Bax and Bcl-x_L/Bid interactions with IC_{50} values around 25 μM.

1. Introduction

Altered apoptosis is a central step in cancer development that leads to resistance of tumour cells to conventional cytotoxic therapy. Consequently, an attractive approach for anticancer therapeutics is to overcome this resistance to apoptosis by directly activating the normal cell death machinery.

B-cell lymphoma-2 (Bcl-2) family members are important regulators of apoptosis.[1,2] Anti-apoptotic proteins such as Bcl-x_L, Bcl-w, Mcl-1, Bcl-2 and Bfl-1 can form heterodimers with pro-apoptotic members such as Bax, Bak, Bad, Bid, Bim and PUMA sequestering them and preventing them from inducing apoptosis by disrupting outer mitochondrial membrane integrity and enabling cytochrome *c* release. Heterodimer formation relies on the capacity of the α-helix of Bcl-2 Homology-3 (BH3) pro-apoptotic proteins to interact with the hydrophobic groove formed by BH1, 2 and 3 domains of anti-apoptotic proteins.[3] Increased expression of pro-survival members is a hallmark of many cancers, and drugs that can prevent their action are very valuable.

In cancer cells, balance between pro- and anti-apoptotic proteins is often abolished, and increased expression of anti-apoptotic members is a characteristic of many cancers. One strategy for the development of new therapeutics for cancer therapy is to identify small molecule drugs that fit into the groove of the pro-survival members (BH3 mimetics), prevent these protein–protein interactions, and reinstate the ability of the cells to self-destruct in response to stress stimuli. Based on such strategy, several non-peptidic small molecule inhibitors of anti-apoptotic Bcl-2 proteins have already been reported in the literature[4–17] (Fig. 1). One of them, the ABT-737, a synthetic inhibitor that target Bcl-x_L, Bcl-w and Bcl-2 anti-apoptotic members, has recently entered clinical development.[18,19]

The design of the compounds described in this paper is based on the structure of known inhibitors and the analysis of the Protein Data Bank (PDB) 1BXL structure that shows the binding interactions between Bcl-x_L and Bak BH3 peptide.[20] Thus, we decided to target poly-aromatic systems that can mimic the helical BH3 domain of pro-apoptotic protein, and more particularly, new trimeric quinoline derivatives (Fig. 2). As illustrated in a previous paper, molecular modelling studies have shown that, due to atropoisomerism, these compounds could adopt a helical structure.[21] The first aim of the present paper was to report the synthesis of new trimeric quinoline derivative **A**, bearing alkyl groups that are identical to the side chains of the aminoacid residues directly implicated in the interaction between Bcl-x_L and the Bak BH3 α-helix (Fig. 2). Moreover, to start a structure–activity relationship study in this series, another analogue (compound **37**, Scheme 4) was also prepared. Finally, the ability of these compounds to bind to various members of the Bcl-2 protein anti-apoptotic group was also evaluated.

---

* Corresponding author. Tel.: +33 4 73 40 79 63; fax: +33 4 73 40 77 17.
E-mail address: Pascale.MOREAU@univbpclermont.fr (P. Moreau).

0968-0896/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2010.07.029

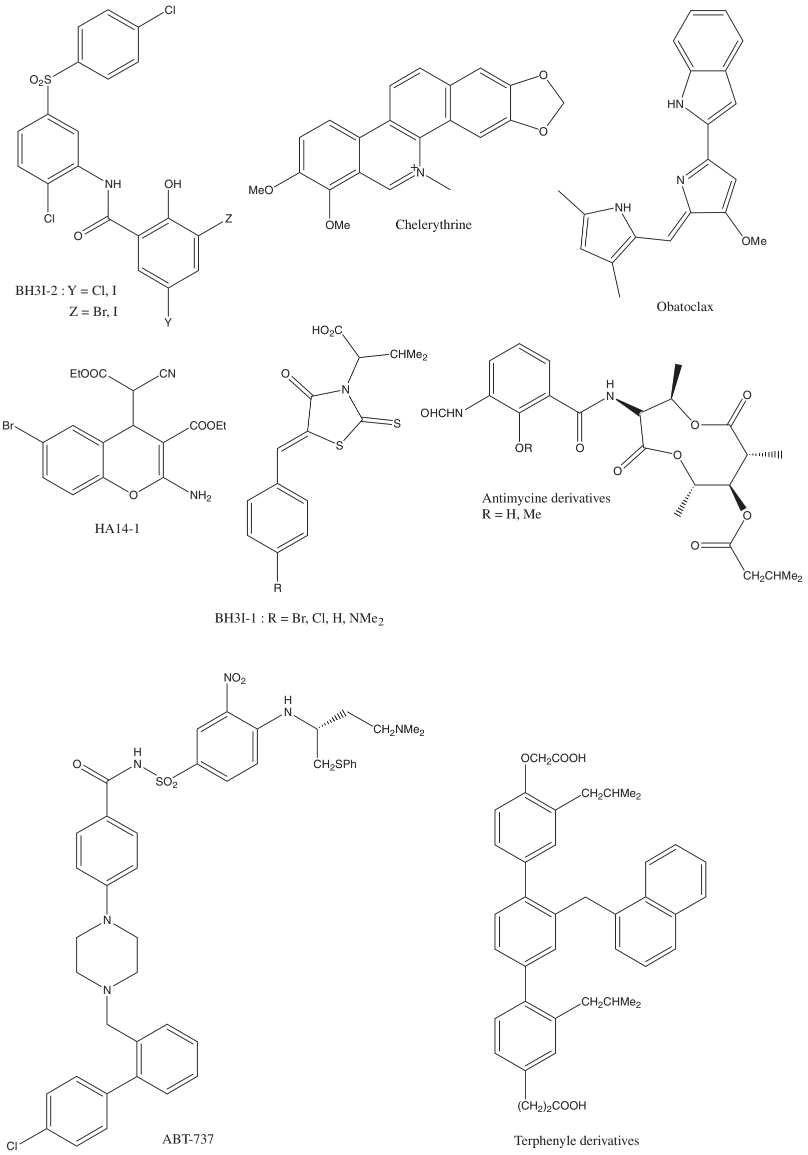


Figure 1. Few examples of Bcl-2 family non-peptidic inhibitors.

2. Chemistry

The key steps in the synthetic approach reported here are Suzuki cross-coupling reactions between quinoline-3-boronic acids and 7-bromo-quinoline derivatives. The synthesis of compound **A** was performed from the 2-methoxyquinolines **15**, **18** and **23** bearing the suitable substituents (Scheme 1).

These compounds were prepared by a convergent approach from 3-aminobenzoic acid **1** or 3-amino-5-bromobenzoic acid **2** (Scheme 2). The methylic esters **3** and **4** prepared in good yields by reacting the corresponding carboxylic acid **1** and **2** with thionyl chloride in methanol were reacted with (*E*)-3-ethoxyprop-2-enoyl chloride to give anilides **5** and **6** in good yields. The cyclisation of anilides **5** or **6** in an acidic medium afforded the expected quinolones as a mixture of regioisomers **7**/**8** and **9**/**10** in 89% and 86% yields, respectively.[22,23] In both cases the major isomer was the one bearing the methoxycarbonyl group in the 5-position. The regioisomeric ratio (10:1 for **7**/**8** and 9.5:1 for **9**/**10**) was determined from the ^{1}H NMR spectrum on the signals of the H_3 and H_4 protons. Major isomers were isolated by recrystallisation from ethanol, leading to **7** and **9** in 47% and 50% yields, respectively. The structure of the major isomers **7** and **9** were determined by HMBC ^{1}H–^{15}N, HMBC ^{1}H–^{13}C and HSQC ^{1}H–^{13}C analysis.

Compound **15** was prepared in 37% overall yield in five steps from **9**. The 2-chloroquinoline **11** was obtained by treatment of **9** with thionyl chloride. The displacement of the chlorine atom in the presence of sodium methylate afforded compound **12**. The corresponding Weinreb amide **13** was obtained from **12** by reaction with *i*PrMgCl and Me(OMe)NH·HCl.[24] The acetylated analogue **14** was obtained by treatment of **13** with methyl magnesium bromide. Finally, compound **15** was prepared by a Wittig reaction between **14** and ethyltriphenylphosphonium bromide.

Compound **18** was obtained in three steps from **12**. The reduction of the methylic ester was performed in the presence of DIBAL-H to give **16** in 73% yield. The corresponding aldehyde **17** was prepared in 75% yield by oxidation of **16** using Dess–Martin Periodinane (DMP). Compound **18** was finally obtained in 93% yield by a Wittig reaction between **17** and isopropyltriphenylphosphonium iodide.

Compound **23** was prepared in 54% overall yield in five steps from **7**. The tertiary alcohol **19** obtained from **7** by a Grignard reaction using methyl magnesium bromide was dehydrated in the

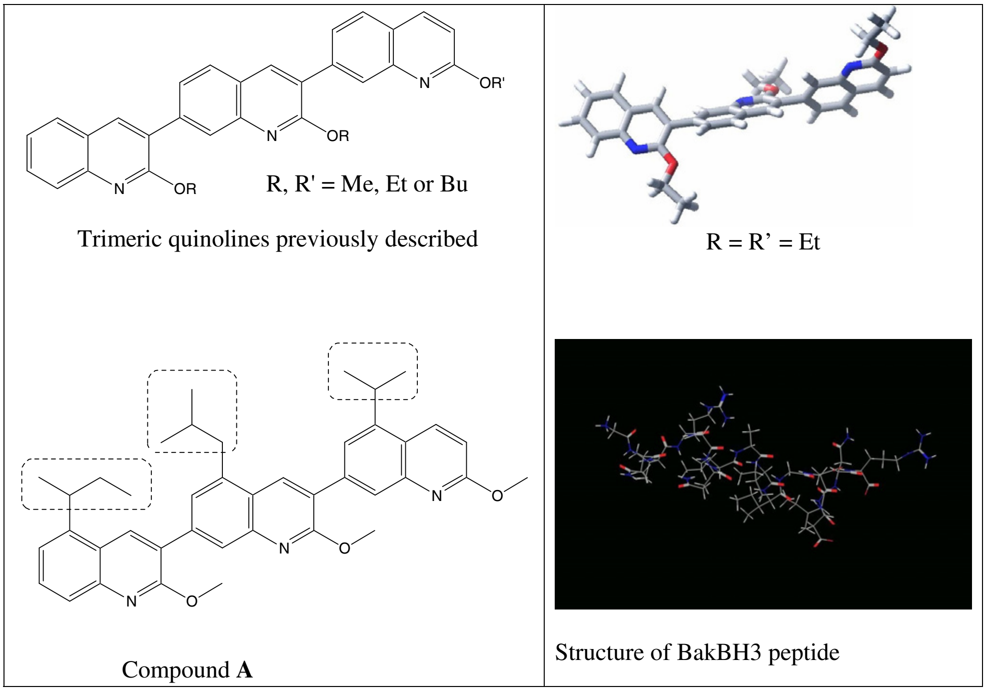
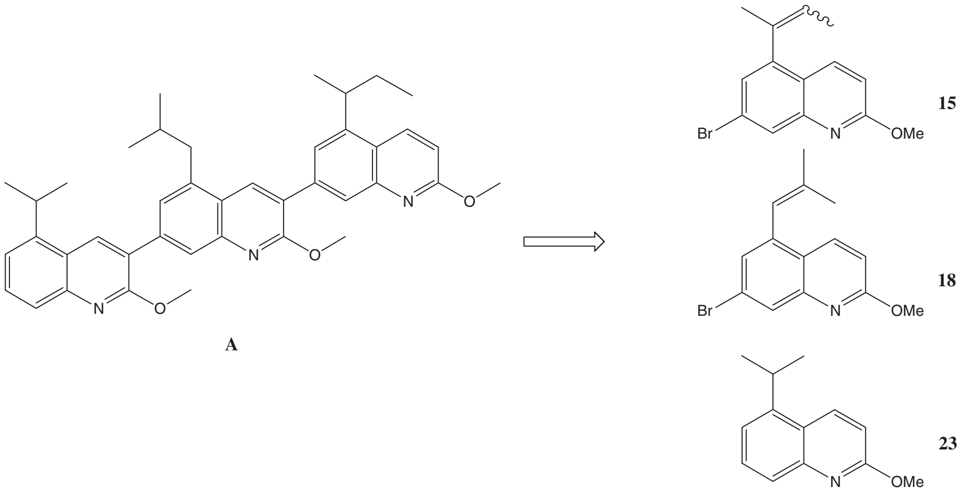


Figure 2. Structure of trimeric quinoline derivatives.



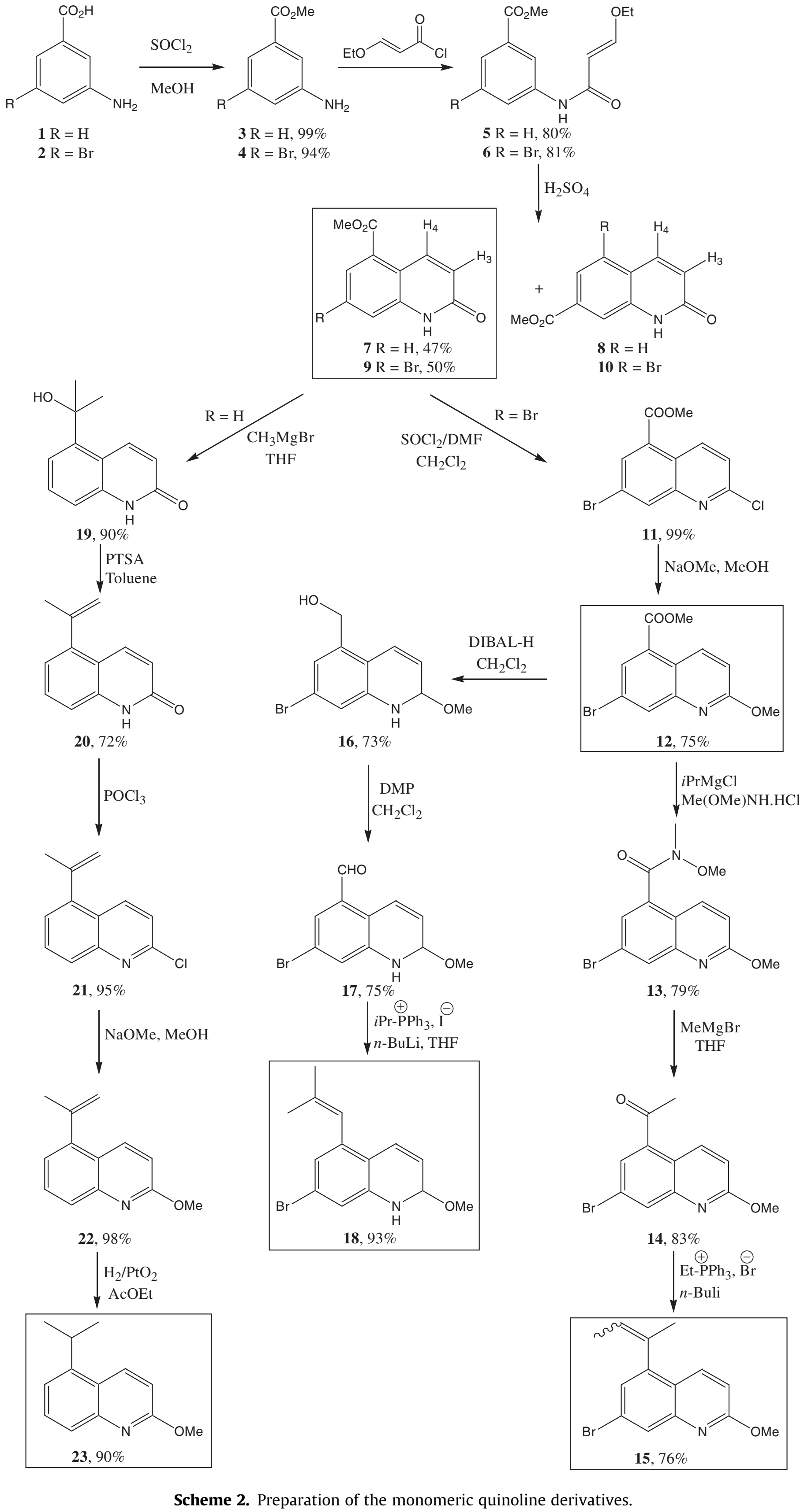
Scheme 1. Retrosynthetic approach.

presence of *p*-toluene sulphonic acid (PTSA) to give the corresponding alkene **20**. Compound **22** was obtained using the classical two-step procedure to convert the quinolin-2-one moiety into the corresponding 2-methoxyquinoline analogue. The catalytic hydrogenation of compound **22** unsaturated side chain provided compound **23**.

The dimeric moiety **25** required for the preparation of compound **A** was obtained by Suzuki coupling between **18** and boronic acid **24** that was produced by reaction of **23** with triisopropyl borate in the presence of lithium diisopropylamide (LDA)[21] (Scheme 3). Due to the degradation of boronic acid **24** when we tried to purify the corresponding reaction mixture, we decided to use the crude reaction mixture of **24** to undertake the following Suzuki coupling. After reduction of the double bond, compound **25** was obtained in 78% yield from **18**.

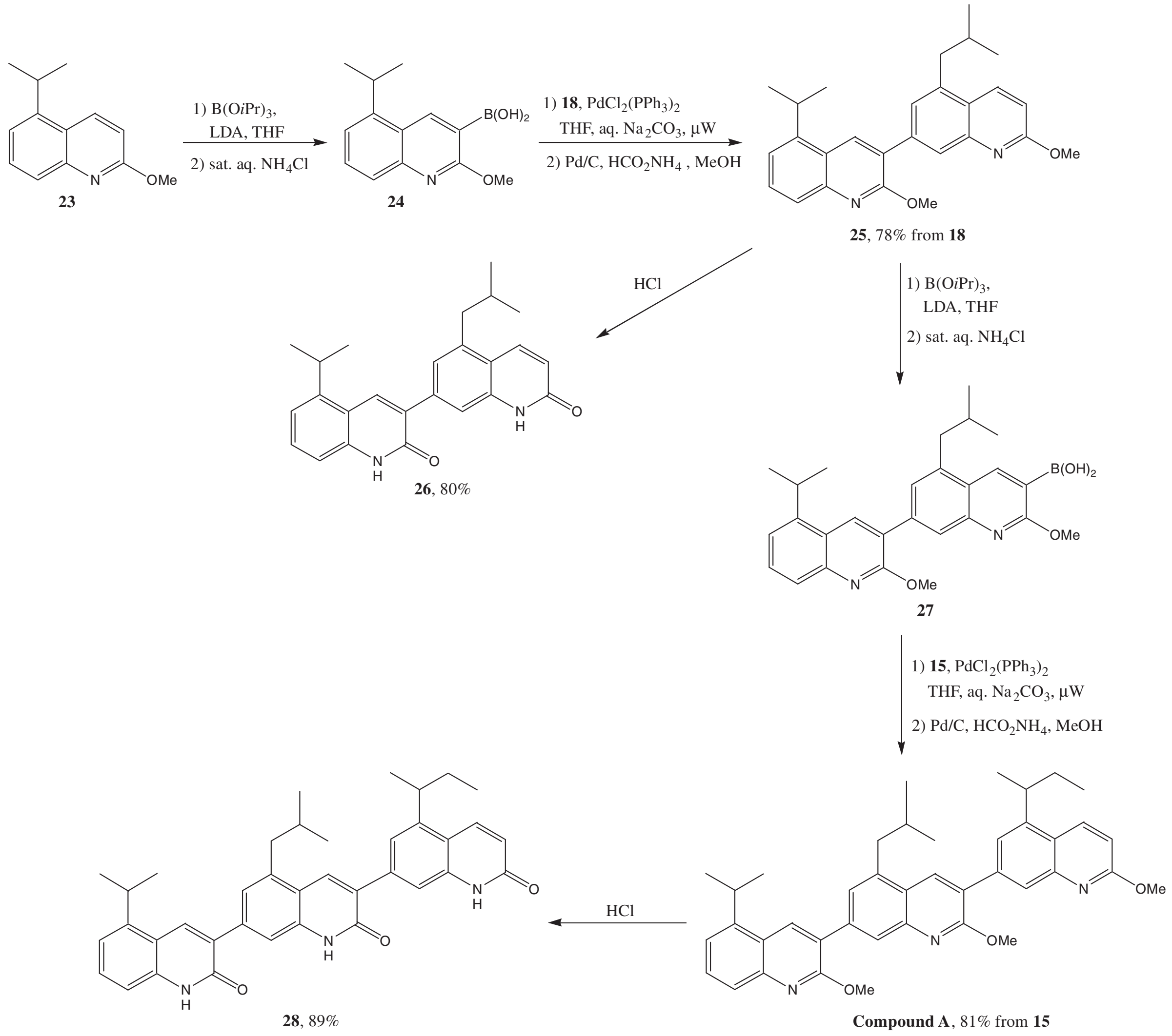
Finally, compound **A** was obtained, as described for **25**, by Suzuki coupling between **15** and boronic acid **27** that was produced by reaction of **25** with triisopropyl borate in the presence of LDA (Scheme 3). As mentioned above for **25**, the coupling reaction was performed directly on the crude boronic acid **27**, and the double bond of the trimeric intermediate was subsequently reduced. To get an insight into the influence of the alkoxy group in the 2-position of the quinoline moieties, compound **A** was deprotected in the presence of HCl to give compound **28** in 89% yield. Moreover, in order to compare the biological activities of compound **28** with the one of its dimeric analogue, compound **25** was treated in the presence of HCl to give **26** in 80% yield.

Finally, to evaluate the substitution profile of the heteroaromatic moiety on the biological activities of this series, compound **37** was also prepared (Scheme 4).



Scheme 2. Preparation of the monomeric quinoline derivatives.

Compound **33** was obtained in five steps with 56% overall yield from **9** using the same synthetic approach as the one described for the preparation of the non-brominated analogue **23**. Dimeric derivative **35** was obtained in 88% yield by Suzuki coupling between **33** and boronic acid **34** which was prepared as previously described. Compound **37** was prepared, as described for compound **A**, by



Scheme 3. Synthesis of compounds **25**, **26**, **A** and **28**.

Suzuki coupling between **33** and boronic acid **36** that was produced by reaction of **35** with triisopropyl borate in the presence of LDA (Scheme 4). Unfortunately, the deprotection reaction carried out on derivative **37** led to an insoluble compound **38** for which we never manage to get NMR spectra. The only data we obtained was the high-resolution mass spectrometry (HRMS) (ESI+) analysis (calcd for $C_{33}H_{30}N_3O_3$ $(M+H)^+$ 516.2287, found 516.2286 and calcd for $C_{33}H_{29}N_3NaO_3$ $(M+Na)^+$ 538.2107, found 538.2088).

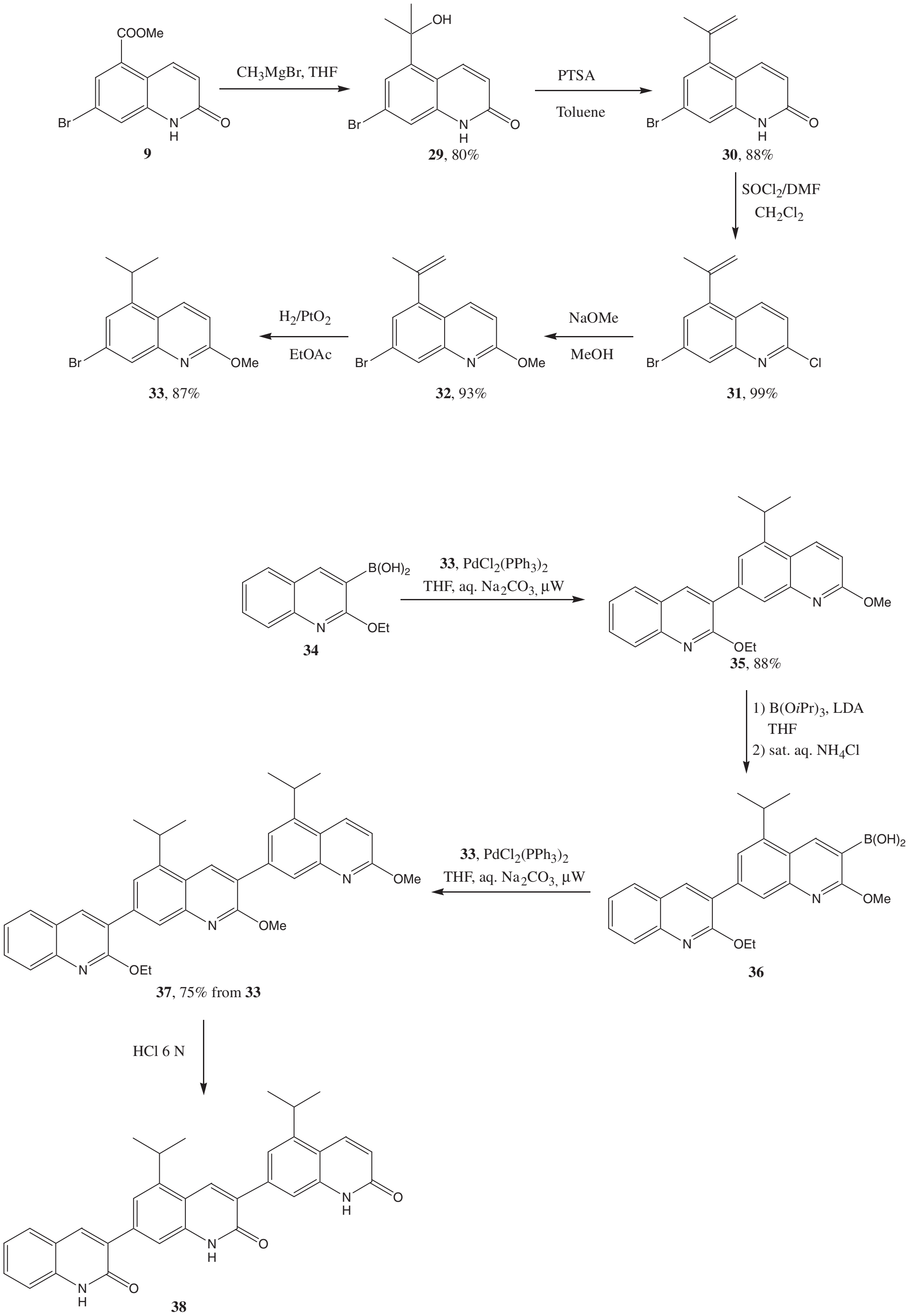
3. Results and discussion

The binding properties of di- and trimeric quinoline new derivatives towards Bcl-x_L were evaluated by competitive fluorescence polarisation assays. As a first step we first determined binding capacity of Bcl-2 anti-apoptotic members towards different pro-apoptotic BH3 peptides (Table 1A). Results obtained under our experimental conditions are in agreement with data already published.[25,26]

Then, the binding properties of compounds **25**, **26**, **28**, **A** and **37** against Bcl-x_L were evaluated. Compounds **26** and **28** having quinolin-2-one moieties were found to be inefficient to disrupt these interactions (data not shown). Oppositely, compounds **25**, **37** and **A**, showing 2-alkoxyquinoline units, exhibited inhibition potencies towards Bcl-x_L interactions with pro-apoptotic peptides in the micromolar range (Table 1B). The most potent compound was compound **A** which inhibited the interaction between Bcl-x_L/Bak, Bcl-x_L/Bax and Bcl-x_L/Bid with IC_{50} values of 25 μM, 26 μM and 27 μM, respectively. Compound **37** most efficiently inhibited the interaction between Bcl-x_L/Bid with IC_{50} value of 21 μM. Compound **25** was the less active derivative, inhibiting only the Bcl-x_L/Bim interaction with an IC_{50} value of 29 μM. Values observed with these compounds are however one log higher than values observed with the ABT-737 Bcl-x_L inhibitor identified by Abbott laboratories.

In addition to Bcl-x_L, other members of the Bcl-2 family are known to play critical roles in tumour cell survival. Therefore, the capacity of compound **A**, that is, the most potent compound, was also evaluated for its capacity to disrupt interaction between Bax BH3 peptide and Bcl-2, Bfl-1 or Mcl-1. As shown in Table 1C, compound **A** also disrupted Bax BH3 binding to other anti-apoptotic Bcl-2 family members although IC_{50} values are slightly higher than the one obtained against Bcl-x_L.

These preliminary results have shown that the diversely substituted trimeric derivatives **A** and **37**, bearing either methoxy or ethoxy group on the quinoline moiety inhibit the interaction between Bcl-x_L and Bak, Bax, Bid, Bim and PUMA pro-apoptotic BH3 peptides with IC_{50} values in the micromolar range. Moreover, the dimeric derivative **25** also decreased the binding between Bcl-x_L/Bim with an IC_{50} value of 29 μM.



Scheme 4. Synthesis of compound **37**.

4. Conclusion

The versatile synthetic approach reported here allows the preparation of diversely substituted di- and trimeric quinoline derivatives bearing different alkoxy groups in the 2-position as well as various alkyl chains in the 5-position of the quinoline moieties. The preliminary structure–activity relationship study has shown that, compared to their quinolin-2-one analogues, the 2-alkoxyquinoline derivatives are more potent modulators of the Bcl-2 family protein interactions. This could be due to the better solubility of 2-alkoxyderivatives compared to their quinolin-2-one counterparts. Especially, compound **A**, that was designed to

Table 1
Fluorescence polarisation assay evaluating compounds inhibiting capacities

A		Bak	Bax	Bid	Bim	PUMA
	Bcl-xl	15 ± 6	47 ± 16	71 ± 16	6 ± 2	65 ± 4
	Bcl-2	2700 ± 100	148 ± 3	3000 ± 100	12 ± 6	287 ± 100
	Bfl-1	216 ± 42	68 ± 17	17 ± 3	22 ± 5	336 ± 22
	Mcl-1	25 ± 20	124 ± 5	118 ± 85	14 ± 9	1083 ± 217
B		Peptide				
	Molecule	Bak	Bax	Bid	Bim	PUMA
	25	>1 mM	>1 mM	>1 mM	29 ± 10 μM	>1 mM
	A	25 ± 9 μM	26 ± 4 μM	27 ± 23 μM	92.5 ± 4.5 μM	42 ± 1 μM
	37	74 ± 11.5 μM	243 ± 187 μM	21 ± 4.5 μM	47 ± 19 μM	54 ± 1 μM
	ABT737	10 ± 2 nM	23 ± 3 nM	48.5 ± 0.5 nM	2 ± 2 nM	0.3 ± 0.2 nM
C		Bax				
	Bcl-xl	26 ± 4				
	Bcl-2	43 ± 12				
	Bfl-1	68 ± 10				
	Mcl-1	45.5 ± 7.5				

(A) Interactions between anti-apoptotic Bcl-2 family members and pro apoptotic BH3 peptides. IC_{50} values are in nM (+/- standard deviation).
(B) Bcl-x_L xl/BH3 peptides interaction inhibition by synthesized compounds and ABT737 as positive control. IC_{50} values are in μM or nM as indicated (+/- standard deviation).
(C) Anti apoptotic protein/Bax peptide interaction inhibition by compound **A**. IC_{50} values are in μM as indicated (+/- standard deviation).

interact with Bcl-x_L, inhibited Bcl-x_L/Bak, Bcl-x_L/Bax and Bcl-x_L/Bid interactions with IC_{50} values around 25 μM.

Therefore, these new scaffolds could be of potential interest for the development of new Bcl-2 anti-apoptotic group inhibitors. In order to increase the affinity of these poly-quinoline derivatives toward Bcl-2 anti-apoptotic members, the preparation of additional diversely substituted trimeric 2-alkoxyquinolines with an improved solubility is currently under investigation in our group.

5. Experimental

5.1. Fluorescence polarisation assays

Fluorescence polarisation assays were done using recombinant GST-Bcl-xl, -Bcl-2, -Bfl-1 or -Mcl-1 without their C-terminal tail and N-terminal FITC-conjugated BH3 peptides (Bim: DMRPEIWIAQELRRIGDEFNAYYAR; Bid: EDIIRNIARHLAQVGDSMDR; Bak: KGGGQVGRQLAIIGDDINRRYDS; Bax: VPQDASTKKLSECLKRIGDELDSNMELQR; PUMA: EQWAREIGAQLRRMADDLNA). 100 nM of recombinant proteins were incubated with 15 nM FITC-conjugated peptide (or 120 nM in the case of PUMA) in the dark in the presence of various concentrations of the molecule (from 100 μM to 1 μM). Fluorescence polarisation was measured using a Mithras LB940 equipment. IC_{50} determinations were performed using GraphPad Prism software (GraphPad, Inc., San Diego, CA).

5.2. Chemistry

IR spectra were recorded on Shimadzu FTIR-8400S or Perkin–Elmer Paragon 500 spectrometers ($\bar{\nu}$ in cm^{-1}). NMR spectra were performed on a Bruker AVANCE 400 (^1H: 400 MHz, ^{13}C: 100 MHz) or Bruker AVANCE 500 (^1H: 500 MHz, ^{13}C: 125 MHz), chemical shifts δ in ppm, the following abbreviations are used: singlet (s), doublet (d), triplet (t), quadruplet (q), sext (sextuplet), hept (heptuplet), doublet of doublet (dd), doublet of triplet (dt), doublet of doublet of doublet (ddd), multiplet (m), broad signal (br s). Mass spectra (ESI+) were determined on a high-resolution Micro Q-Tof apparatus (CRMP, Université Blaise Pascal, Clermont-Ferrand, France) or on a Waters Q-Tof 2 apparatus (CRMPO, Université de Rennes, France). Chromatographic purifications were performed by flash silica gel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography. Reactions were monitored by TLC using fluorescent silica gel plates (60 F254 from Merck). Experiments under microwave irradiation were performed using a CEM Discover Benchmate apparatus. Melting points were measured on a Reichert microscope and are uncorrected.

5.2.1. Methyl 3-aminobenzoate (3)

A solution of 3-aminobenzoic acid **1** (5.00 g, 36.5 mmol) in methanol (100 mL) was cooled to 0 °C before dropwise addition of $SOCl_2$ (6.6 mL, 10.8 g, 91 mmol). The mixture was stirred at room temperature for 24 h, evaporated and neutralised by addition of a saturated aqueous $NaHCO_3$ solution. After extraction with EtOAc, the assembled organic fractions were dried over $MgSO_4$ and evaporated to give **3** (5.48 g, 36.3 mmol, 99%) as a brown solid. This compound was partially described by Gaudreault.[27] In this reference the signal of the methyl group was incorrectly given at 2.52 ppm.

Mp = 44 °C; IR (KBr): 3459, 3372, 3229, 1710, 1626, 1604, 1319, 1295, 1243 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 3.79 (3H, s), 5.33–5.39 (2H, br s, NH_2), 6.79 (1H, ddd, $J_1 = 7.5$ Hz, $J_2 = 2.5$ Hz, $J_3 = 1.5$ Hz), 7.08 (1H, dt, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 7.13 (1H, t, $J = 7.5$ Hz), 7.19 (1H, t, $J = 2.0$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 51.8 (CH_3), 114.1, 116.3, 118.3, 129.1 (CH_{arom}), 130.2, 149.0 (C_{arom}), 166.7 (C=O); HRMS (ESI+) calcd for $C_8H_{10}NO_2$ $(M+H)^+$ 152.0712, found 152.0696.

5.2.2. Methyl 3-amino-5-bromobenzoate (4)

The same procedure as described above for the preparation of compound **3** (3-amino-5-bromobenzoic acid **2** (2.25 g, 10.4 mmol), methanol (25 mL) and $SOCl_2$ (1.5 mL, 2.46 g, 20.7 mmol)) yielded compound **4** (2.25 g, 9.8 mmol, 94%) as a beige solid.

Mp = 96 °C (Lit. 83–88 °C)[28]; IR (KBr): 3413, 3325, 3218, 1714, 1644, 1605, 1574, 1311, 1245 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 3.81 (3H, s), 5.68–5.78 (2H, br s, NH_2), 6.96 (1H, t, $J = 2.0$ Hz), 7.12 (1H, t, $J = 1.5$ Hz), 7.16 (1H, dd, $J_1 = 2.0$ Hz, $J_2 = 1.5$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 52.2 (CH_3), 113.3, 118.0, 119.8 (CH_{arom}), 122.0, 132.0, 150.6 (C_{arom}), 165.5 (C=O); HRMS (ESI+) calcd for $C_8H_9{}^{79}BrNO_2$ $(M+H)^+$ 229.9817, found 229.9821.

5.2.3. Methyl 3-[(*E*)-3-ethoxyprop-2-enoylamino]benzoate (5)

To a solution of **3** (7.47 g, 49.4 mmol) in CH_2Cl_2 (700 mL) were added pyridine (6.6 mL, 6.5 g, 82 mmol) and a solution of (*E*)-3-ethoxyprop-2-enoyl chloride (10.9 g, 81 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at room temperature for 2.5 h and carefully poured into water, acidified with concentrated hydrochloric acid and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (CH_2Cl_2 then CH_2Cl_2/EtOAc 95:5) to give **5** (9.90 g, 39.7 mmol, 80%) as a white solid.

Mp = 105 °C; IR (KBr): 3245, 1728, 1656, 1617, 1602, 1296 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 1.27 (3H, t, $J = 7.0$ Hz), 3.84 (3H, s), 3.96 (2H, q, $J = 7.0$ Hz), 5.51 (1H, d, $J = 12.5$ Hz), 7.43 (1H, t, $J = 8.0$ Hz), 7.51 (1H, d, $J = 12.5$ Hz), 7.60 (1H, ddd, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, $J_3 = 1.0$ Hz), 7.86 (1H, ddd, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz, $J_3 = 1.0$ Hz), 8.28 (1H, t, $J = 2.0$ Hz), 9.95 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 14.5, 52.1 (CH_3), 66.6 (CH_2), 99.6, 119.4, 123.3 (2C), 129.2, 159.9 (CH), 130.1, 140.0 (C_{arom}), 164.9, 166.2 ($C{=}O$); HRMS (ESI+) calcd for $C_{13}H_{15}NNaO_4$ $(M+Na)^+$ 272.0899, found 272.0888.

5.2.4. Methyl 3-bromo-5-[(*E*)-3-ethoxyprop-2-enoylamino] benzoate (6)

The same procedure as described above for the preparation of compound **5** (compound **4** (5.14 g, 22.3 mmol) in CH_2Cl_2 (40 mL), pyridine (3.8 mL, 3.7 g, 47 mmol) and (*E*)-3-ethoxyprop-2-enoyl chloride (6.40 g, 47.6 mmol) in CH_2Cl_2 (20 mL), for 2 h) yielded, after flash chromatography (cyclohexane/EtOAc 9:1 then 8:2), compound **6** (5.93 g, 18.1 mmol, 81%) as an orange solid.

Mp = 121 °C; IR (KBr): 3361, 1715, 1682, 1602, 1290, 1140 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 1.27 (3H, t, $J = 7.0$ Hz), 3.86 (3H, s), 3.97 (2H, q, $J = 7.0$ Hz), 5.47 (1H, d, $J = 12.5$ Hz), 7.54 (1H, d, $J = 12.5$ Hz), 7.68 (1H, t, $J = 1.5$ Hz), 8.14 (1H, t, $J = 1.5$ Hz), 8.22 (1H, t, $J = 2.0$ Hz), 10.13 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 14.5, 52.6 (CH_3), 66.8 (CH_2), 99.2, 118.3, 125.1, 125.3, 160.5 (CH), 121.7, 131.9, 141.5 (C_{arom}), 164.8, 165.1 ($C{=}O$); HRMS (ESI+) calcd for $C_{13}H_{15}{}^{79}BrNO_4$ $(M+H)^+$ 328.0184, found 328.0187.

5.2.5. Methyl 2-oxo-1,2-dihydroquinoline-5-carboxylate (7)

A solution of **5** (3.00 g, 12.0 mmol) in concentrated sulphuric acid (95–97%, 30 mL) was stirred at room temperature for 6 h and then poured into ice-water. The precipitate was filtered off and washed with Et_2O. The solid was recrystallized from 96% ethanol to give **7** (1.15 g, 5.7 mmol, 47%) as a beige solid.

Mp = 259 °C; IR (KBr): 3415, 1716, 1668, 1606, 1142 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 3.90 (3H, s), 6.64 (1H, dd, $J_1 = 10.0$ Hz, $J_2 = 2.0$ Hz), 7.55 (1H, d, $J = 7.5$ Hz), 7.60 (1H, t, $J = 7.5$ Hz), 7.71 (1H, dd, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 8.62 (1H, d, $J = 10.0$ Hz), 11.95–12.01 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 52.5 (CH_3), 119.8, 123.7, 124.4, 129.8, 137.0 (CH), 117.3, 127.4, 139.8 (C_{arom}), 161.1, 166.6 ($C{=}O$); HRMS (ESI+) calcd for $C_{11}H_{10}NO_3$ $(M+H)^+$ 204.0661, found 204.0654.

5.2.6. Methyl 7-bromo-2-oxo-1,2-dihydroquinoline-5-carboxylate (9)

The same procedure as described above for the preparation of compound **7** (compound **6** (6.35 g, 19.4 mmol) in concentrated sulphuric acid (95–97%, 40 mL)) yielded **9** (2.74 g, 9.7 mmol, 50%) as a beige solid.

Mp = 263 °C; IR (KBr): 3434, 1729, 1668, 1591, 1239, 1140 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 3.91 (3H, s), 6.68 (1H, d, $J = 10.0$ Hz), 7.71 (1H, d, $J = 1.5$ Hz), 7.78 (1H, d, $J = 2.0$ Hz), 8.55 (1H, d, $J = 10.0$ Hz), 11.99–12.06 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 52.8 (CH_3), 121.5, 124.1, 126.5, 136.6 (CH), 116.5, 122.3, 129.1, 140.8 (C_{arom}), 160.9, 165.2 ($C{=}O$); HRMS (ESI+) calcd for $C_{11}H_9{}^{79}BrNO_3$ $(M+H)^+$ 281.9766, found 281.9771.

5.2.7. Methyl 7-bromo-2-chloroquinoline-5-carboxylate (11)

To a solution of **9** (1.33 g, 4.71 mmol) in CH_2Cl_2 (40 mL) were added $SOCl_2$ (0.45 mL, 0.74 g, 6.2 mmol) and DMF (0.39 mL, 0.37 g, 5.1 mmol). The mixture was refluxed for 3 h, cooled and poured into water. After extraction with EtOAc, the assembled organic fractions were dried over $MgSO_4$ and evaporated to give **11** (1.40 g, 4.66 mmol, 99%) as a white solid.

Mp = 126 °C; IR (KBr): 1717, 1592, 1255, 1122 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 3.95 (3H, s), 7.75 (1H, d, $J = 9.0$ Hz), 8.26 (1H, d, $J = 2.0$ Hz), 8.41 (1H, dd, $J_1 = 2.0$ Hz, $J_2 = 0.5$ Hz), 9.10 (1H, dd, $J_1 = 9.0$ Hz, $J_2 = 0.5$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 53.0 (CH_3), 124.3, 133.3, 134.8, 137.7 (CH_{arom}), 122.9, 123.8, 128.6, 148.0, 151.5 (C_{arom}), 164.8 ($C{=}O$); HRMS (ESI+) calcd for $C_{11}H_8{}^{79}Br^{35}ClNO_2$ $(M+H)^+$ 299.9427, found 299.9432.

5.2.8. Methyl 7-bromo-2-methoxyquinoline-5-carboxylate (12)

A solution of **11** (700 mg, 2.33 mmol) and NaOMe (10.5 mmol, prepared from 241 mg of Na) in MeOH (8.7 mL) was heated in an oil bath at 65 °C for 2 h. The mixture was poured into a saturated aqueous NH_4Cl solution cooled to 0 °C. After extraction with CH_2Cl_2, the assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **12** (518 mg, 1.75 mmol, 75%) as a white solid.

Mp = 95–97 °C; IR (ATR): 1721, 1613, 1240, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.98 (3H, s), 4.05 (3H, s), 7.00 (1H, d, $J = 9.5$ Hz), 8.15 (1H, d, $J = 2.0$ Hz), 8.20 (1H, dd, $J_1 = 2.0$ Hz, $J_2 = 0.5$ Hz), 9.07 (1H, dd, $J_1 = 9.5$ Hz, $J_2 = 0.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 52.6, 53.6 (CH_3), 114.9, 131.0, 134.7, 136.8 (CH_{arom}), 122.1, 122.7, 127.9, 148.0, 162.8, 166.1 (C_{arom}, $C{=}O$); HRMS (ESI+) calcd for $C_{12}H_{11}{}^{79}BrNO_3$ $(M+H)^+$ 295.9922, found 295.9932.

5.2.9. 7-Bromo-*N*,2-dimethoxy-*N*-methylquinoline-5-carboxamide (13)

A solution of **12** (495 mg, 1.67 mmol) and *N*,*O*-dimethylhydroxylamine (1.5 equiv) in THF (8.5 mL) was cooled to −15 °C before dropwise addition of a solution of *i*PrMgCl in THF (1 M, 3 equiv). The mixture was stirred at −15 °C for 30 min and a saturated aqueous NH_4Cl solution was added. After extraction with EtOAc, the assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 4:1) to give **13** (427 mg, 1.31 mmol, 79%) as a white solid.

Mp = 106–108 °C; IR (ATR): 1645, 1613, 1505, 1379, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.30–3.48 (3H, br s), 3.36–3.58 (3H, br s), 4.05 (3H, s), 6.94 (1H, d, $J = 9.0$ Hz), 7.52 (1H, d, $J = 2.0$ Hz), 8.00 (1H, d, $J_1 = 9.0$ Hz, $J_2 = 0.5$ Hz), 8.09 (1H, dd, $J_1 = 2.0$ Hz, $J_2 = 1.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 33.4*, 53.7, 61.6 (CH_3), 114.3, 125.8, 131.2, 136.0 (CH_{arom}), 120.8, 122.4, 134.3, 147.4, 163.1 (C_{arom}). The chemical shift of the indicated carbon (*) was determined for the HSQC ^{1}H–13C spectrum. The carbonyl carbon was not detected; HRMS (ESI+) calcd for $C_{13}H_{14}{}^{79}BrN_2O_3$ $(M+H)^+$ 325.0188, found 325.0204.

5.2.10. 1-(7-Bromo-2-methoxyquinolin-5-yl)ethan-1-one (14)

A solution of **13** (357 mg, 1.10 mmol) in THF (8.5 mL) was cooled to 0 °C before dropwise addition of a solution of MeMgBr in Et_2O (3 M, 3 equiv). The mixture was stirred at room temperature for 3 h and then poured into a saturated aqueous NH_4Cl solution cooled to 0 °C. After extraction with EtOAc, the assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **14** (256 mg, 0.91 mmol, 83%) as a white solid.

Mp = 102–105 °C; IR (ATR): 1684, 1614, 1501, 1316, 1242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.72 (3H, s), 4.06 (3H, s), 7.00 (1H, d, $J = 9.5$ Hz), 7.92 (1H, d, $J = 2.0$ Hz), 8.21 (1H, dd, $J_1 = 2.0$ Hz, $J_2 = 0.5$ Hz), 8.90 (1H, dd, $J_1 = 9.5$ Hz, $J_2 = 0.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 29.6, 53.6 (CH_3), 115.2, 129.8, 134.4, 137.1 (CH_{arom}), 121.4, 121.9, 136.1, 148.3, 163.0 (C_{arom}), 199.8 ($C{=}O$); HRMS (ESI+) calcd for $C_{12}H_{11}{}^{79}BrNO_2$ $(M+H)^+$ 279.9973, found 279.9979.

5.2.11. (*Z*,*E*)-7-Bromo-5-(but-2-en-2-yl)-2-methoxyquinoline (15)

A solution of ethylphosphonium bromide (5 equiv) in THF (2.14 mL/mmol) was cooled to 0 °C before dropwise addition of a solution of *n*-BuLi in hexane (2.4 M, 0.9 equiv/ethylphosphonium bromide). The mixture was stirred at 0 °C for 30 min and a solution of **14** (256 mg, 0.91 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at room temperature for 20 h and a 1 M aqueous NH_4Cl solution was added. After extraction with EtOAc, the assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 99:1) to give **15** (203 mg, 0.69 mg, 76%) as a mixture of diastereoisomers which was directly used for the preparation of compound **28**.

5.2.12. 7-Bromo-2-methoxyquinolin-5-ylmethanol (16)

A solution of DIBAL in CH_2Cl_2 (1 M, 5.7 mL, 5.70 mmol) was added dropwise to a solution of **12** (562 mg, 1.90 mmol) in CH_2Cl_2 (20 mL). After stirring for 30 min at room temperature, a saturated aqueous NH_4Cl solution was added. The mixture was poured into a 1 M aqueous Rochelle salt solution. After stirring for 30 min, the mixture was extracted with EtOAc and the assembled organic fractions were washed with a 0.1 M aqueous HCl solution, water, brine and then dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **16** (372 mg, 1.39 mmol, 73%) as a white solid.

Mp = 148 °C; IR (ATR): 3327, 1616, 1593, 1574, 1504, 1314, 1261 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 3.98 (3H, s), 4.91 (2H, d, J = 5.5 Hz), 5.50 (1H, t, J = 5.5 Hz), 7.07 (1H, d, J = 9.0 Hz), 7.58 (1H, m), 7.87 (1H, d, J = 1.5 Hz), 8.36 (1H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 53.3 (CH_3), 60.1 (CH_2), 113.0, 125.1, 127.8, 135.7 (CH_{arom}), 121.3, 122.7, 141.3, 147.2, 162.3 (C_{arom}); HRMS (ESI+) calcd for $C_{11}H_{11}{}^{79}BrNO_2$ $(M+H)^+$ 267.9973, found 267.9988.

5.2.13. 7-Bromo-2-methoxyquinoline-5-carbaldehyde (17)

A solution of Dess–Martin periodinane in CH_2Cl_2 (15 wt %, 4.0 mL, 1.93 mmol) was added to a solution of **16** (340 mg, 1.27 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred at room temperature for 10 min, poured into a 1 M aqueous NaOH solution and extracted with Et_2O. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **17** (254 mg, 0.95 mmol, 75%) as a white solid.

Mp = 143 °C; IR (ATR): 1692, 1611, 1586, 1503, 1265 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 4.00 (3H, s), 7.22 (1H, d, J = 9.5 Hz), 8.19 (1H, d, J = 2.0 Hz), 8.21 (1H, d, J = 2.0 Hz), 9.19 (1H, d, J = 9.5 Hz), 10.29 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): 53.4 (CH_3), 115.7, 134.7, 135.0, 135.5 (CH_{arom}), 121.0, 122.2, 132.5, 147.4, 162.6 (C_{arom}), 193.0 (CHO); HRMS (ESI+) calcd for $C_{11}H_9{}^{79}BrNO_2$ $(M+H)^+$ 265.9817, found 265.9833.

5.2.14. 7-Bromo-2-methoxy-5-(2-methylpropen-1-yl)quinoline (18)

n-BuLi (2.5 M in hexane, 0.60 mL, 1.50 mmol) was added to a suspension, cooled to 0 °C, of isopropyltriphenylphosphonium iodide (715 mg, 1.65 mmol) in THF (8 mL). The mixture was stirred at 0 °C for 30 min and a solution of **17** (220 mg, 0.83 mmol) in THF (5 mL) was added. After stirring for 2 h at 0 °C, the mixture was poured into water and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 98:2) to give **18** (225 mg, 0.77 mmol, 93%) as a white solid.

Mp = 63 °C; IR (ATR): 1611, 1582, 1497, 1312 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.66 (3H, d, J = 1.0 Hz), 1.98 (3H, d, J = 1.5 Hz), 3.98 (3H, s), 6.60 (1H, m), 7.03 (1H, d, J = 9.0 Hz), 7.32 (1H, dd, J_1 = 2.0 Hz, J_2 = 1.0 Hz), 7.85 (1H, m), 8.20 (1H, dd, J_1 = 9.0 Hz, J_2 = 0.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 19.4, 25.8, 53.3 (CH_3), 113.1, 120.4, 127.1, 127.3, 136.7 (CH), 122.2, 122.4, 137.9, 139.1, 147.1, 162.4 (C); HRMS (ESI+) calcd for $C_{14}H_{15}{}^{79}BrNO$ $(M+H)^+$ 292.0337, found 292.0350.

5.2.15. 5-(2-Hydroxypropan-2-yl)quinolin-2(1*H*)-one (19)

A solution of **7** (1.16 g, 5.71 mmol) in THF (50 mL) was cooled to 0 °C before dropwise addition of MeMgBr (3.0 M in Et_2O, 11.5 mL, 34.5 mmol). The mixture was stirred at room temperature for 15 h and poured into a saturated aqueous NH_4Cl solution. After extraction with EtOAc, the assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **19** (1.04 g, 5.12 mmol, 90%) as a beige solid.

Mp = 238 °C; IR (ATR): 3397, 1638, 1611, 1549, 1425, 1134 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 1.59 (6H, s), 5.39 (1H, s, OH), 6.46 (1H, d, J = 10.0 Hz), 7.17 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 7.24 (1H, d, J = 8.0 Hz), 7.38 (1H, t, J = 8.0 Hz), 11.69 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 31.8 ($2CH_3$), 71.9 (C), 114.8, 118.6, 120.0, 129.4, 139.9 (CH), 116.8, 140.4, 146.4 (C_{arom}), 161.2 ($C{=}O$); HRMS (ESI+) calcd for $C_{12}H_{14}NO_2$ $(M+H)^+$ 204.1025, found 204.1037.

5.2.16. 5-(Propen-2-yl)quinolin-2(1*H*)-one (20)

PTSA monohydrate (852 mg, 4.48 mmol) was added to a solution of **19** (1.14 g, 5.61 mmol) in toluene (80 mL). The mixture was refluxed for 15 h using a Dean-Stark apparatus. After cooling, the mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 1:1) to give **20** (747 mg, 4.03 mmol, 72%) as a white solid.

Mp = 184 °C; IR (ATR): 1682, 1655, 1641, 1611, 1557, 1445 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 2.09 (3H, s), 4.92 (1H, m), 5.40 (1H, m), 6.49 (1H, d, J = 10.0 Hz), 7.02 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 7.23 (1H, d, J = 8.5 Hz), 7.45 (1H, dd, J_1 = 8.5 Hz, J_2 = 7.5 Hz), 7.92 (1H, d, J = 10.0 Hz), 11.77 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 24.8 (CH_3), 114.2, 120.5, 121.7, 130.0, 137.5 (CH), 115.9, 117.0, 139.4, 142.2, 142.5 ($=CH_2$, C), 161.6 ($C{=}O$); HRMS (ESI+) calcd for $C_{12}H_{12}NO$ $(M+H)^+$ 186.0919, found 186.0925.

5.2.17. 2-Chloro-5-(propen-2-yl)quinoline (21)

A solution of **20** (790 mg, 4.27 mmol) in $POCl_3$ (20 mL) was refluxed for 2 h. After cooling, the mixture was poured into water and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography to give **21** (827 mg, 4.06 mmol, 95%) as a colourless oil.

IR (ATR): 1601, 1584, 1568, 1489, 1111 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 2.18 (3H, dd, J_1 = 1.5 Hz, J_2 = 1.0 Hz), 5.03 (1H, m), 5.51 (1H, m), 7.52 (1H, dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz), 7.58 (1H, d, J = 9.0 Hz), 7.79 (1H, dd, J_1 = 8.5 Hz, J_2 = 7.0 Hz), 7.89 (1H, dt, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 8.45 (1H, dd, J_1 = 9.0 Hz, J_2 = 1.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 24.8 (CH_3), 122.3, 125.4, 127.0, 130.5, 137.7 (CH_{arom}), 117.7, 124.1, 142.1, 142.2, 147.6, 149.7 ($=CH_2$, C); HRMS (ESI+) calcd for $C_{12}H_{11}{}^{35}ClN$ $(M+H)^+$ 204.0580, found 204.0585.

5.2.18. 2-Methoxy-5-(propen-2-yl)quinoline (22)

A solution of NaOMe (2.35 mmol, prepared from 54 mg of Na) in methanol (5 mL) was added to compound **21** (95 mg, 0.47 mmol) and the mixture was refluxed for 15 h. After evaporation, water was added and the mixture was extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$ and evaporated to give **22** (91 mg, 0.46 mmol, 98%) as a colourless oil.

IR (ATR): 1611, 1578, 1503, 1485, 1397, 1316, 1263 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 2.15 (3H, dd, J_1 = 1.5 Hz, J_2 = 1.0 Hz), 3.98 (3H, s), 4.97 (1H, m), 5.45 (1H, m), 7.01 (1H, d, J = 9.0 Hz), 7.28 (1H, dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz), 7.62 (1H, dd, J_1 = 8.5 Hz, J_2 = 7.0 Hz), 7.70 (1H, ddd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, J_3 = 1.0 Hz), 8.26 (1H, dd, J_1 = 9.0 Hz, J_2 = 1.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 24.9, 53.1 (CH_3), 112.7, 122.5, 125.9, 129.2, 136.8 (CH_{arom}), 116.9, 121.9, 141.8, 143.0, 146.3, 161.6 (=CH_2, C); HRMS (ESI+) calcd for $C_{13}H_{14}NO$ (M+H)$^+$ 200.1075, found 200.1081.

5.2.19. 5-Isopropyl-2-methoxyquinoline (23)

A mixture of **22** (300 mg, 1.51 mmol) and PtO_2 (68 mg, 0.30 mmol) in EtOAc (10 mL) was hydrogenated for 15 h before filtration on Celite. After evaporation, the residue was purified by flash chromatography (cyclohexane/EtOAc 98:2) to give **23** (272 g, 1.35 mmol, 90%) as a colourless oil.

IR (ATR): 1611, 1578, 1508, 1487, 1400, 1308, 1265 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 1.30 (6H, d, J = 7.0 Hz), 3.67 (1H, hept, J = 7.0 Hz), 3.98 (3H, s), 7.02 (1H, d, J = 9.0 Hz), 7.31–7.38 (1H, m), 7.58–7.65 (2H, m), 8.47 (1H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 23.5 (2C), 27.8, 53.0 (CH_3, CH), 112.3, 120.0, 125.0, 129.5, 135.1 (CH_{arom}), 122.5, 145.1, 146.4, 161.3 (C_{arom}); HRMS (ESI+) calcd for $C_{13}H_{16}NO$ (M+H)$^+$ 202.1232, found 202.1231.

5.2.20. 2,2′-Dimethoxy-5′-isobutyl-5-isopropyl-3,7′-biquinoline (25)

Step A. A solution of diisopropylamine (0.31 mL, 2.19 mmol) in THF (2 mL) was cooled to 0 °C before dropwise addition of *n*-BuLi (2.5 M in hexane, 0.80 mL, 2.00 mmol). The mixture was stirred at 0 °C for 1 h and was added dropwise to a solution, cooled to −78 °C, of **23** (109 mg, 0.54 mmol) and triisopropylborate (0.50 mL, 2.16 mmol) in THF (5 mL). After stirring for 4 h at −78 °C, the mixture was allowed to reach room temperature and was stirred for 15 h. After addition of a saturated aqueous NH_4Cl solution, the mixture was extracted with EtOAc and the assembled organic fractions were dried over $MgSO_4$ and evaporated to give **24** (132 mg) as a pale yellow solid.

Step B. To a solution of **18** (132 mg, 0.45 mmol) in THF (4 mL) were added $PdCl_2(PPh_3)_2$ (15.9 mg, 23 μmol), a 2 M aqueous Na_2CO_3 solution (1.1 mL, 2.2 mmol) and boronic acid **24** from step A (221 mg). The mixture was stirred under microwave irradiation (65 °C, 50 W, P_{atm}) for 20 min, poured into water and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 99:1) to give the intermediate dimer (169 mg, 0.41 mmol) as a white solid.

Step C. To a solution of the intermediate dimer from step B (169 mg, 0.41 mmol) in MeOH (2 mL) were added ammonium formate (258 mg, 4.10 mmol) and 10% Pd/C (41 mg). The mixture was refluxed for 15 h before filtration on Celite. Water was added and the mixture was extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 98:2) to give **25** (146 mg, 0.35 mmol, 78% from **18**) as a white solid.

Mp = 141 °C; IR (ATR): 1611, 1570, 1458, 1263 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.02 (6H, d, J = 6.5 Hz), 1.40 (6H, d, J = 7.0 Hz), 2.01 (1H, m), 2.93 (2H, d, J = 7.0 Hz), 3.71 (1H, hept, J = 7.0 Hz), 4.13 (2 × 3H, 2s), 6.95 (1H, d, J = 9.0 Hz), 7.35 (1H, d, J = 7.0 Hz), 7.50 (1H, d, J = 1.5 Hz), 7.62 (1H, t, J = 8.0 Hz), 7.80 (1H, d, J = 8.5 Hz), 8.00 (1H, s), 8.24 (1H, d, J = 9.0 Hz), 8.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 22.8 (2C), 23.9 (2C), 28.7, 30.2, 53.8, 53.9 (CH_3, CH), 42.1 (CH_2), 112.6, 120.3, 125.0, 125.8, 127.2, 129.6, 134.6, 135.5 (CH_{arom}), 123.3, 123.4, 125.6, 137.8, 138.4, 145.5, 146.5, 147.0, 159.3, 162.3 (C_{arom}); HRMS (ESI+) calcd for $C_{27}H_{31}N_2O_2$ (M+H)$^+$ 415.2386, found 415.2382.

5.2.21. 5′-Isobutyl-5-isopropyl-3,7′-biquinoline-2,2′(1*H*,1′*H*)-dione (26)

A suspension of **25** (16 mg, 39 μmol) in a 6 M aqueous HCl solution (1.5 mL) was refluxed for 4 h. The mixture was poured into water and extracted with CH_2Cl_2. The assembled organic fractions were dried over $MgSO_4$ and evaporated to give **26** (12 mg, 31 μmol, 80%) as a beige solid.

Mp = 246 °C; IR (ATR): 1655, 1616, 1549, 1439, 1225 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.02 (6H, d, J = 6.5 Hz), 1.41 (6H, d, J = 7.0 Hz), 1.98 (1H, m), 2.90 (2H, d, J = 7.0 Hz), 3.63 (1H, hept, J = 7.0 Hz), 6.82 (1H, d, J = 9.5 Hz), 7.20 (1H, d, J = 7.0 Hz), 7.27 (1H, s), 7.47 (1H, d, J = 8.0 Hz), 7.52 (1H, t, J = 7.5 Hz), 8.11 (1H, d, J = 9.5 Hz), 8.44 (1H, s), 8.71 (1H, s), 13.50 (1H, br s, NH), 13.95 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 22.7 (2C), 23.7 (2C), 28.8, 30.5 (CH_3, CH), 42.0 (CH_2), 114.4, 116.2, 119.3, 120.7, 123.8, 131.0, 135.3, 137.6 (CH_{arom}), 117.9, 118.6, 129.1, 137.9, 138.9, 139.3, 139.4, 146.2 (C_{arom}), 163.4, 165.2 (C=O); HRMS (ESI+) calcd for $C_{25}H_{27}N_2O_2$ (M+H)$^+$ 387.2073, found 387.2086.

5.2.22. (*R*,*S*)-5″-(Butan-2-yl)-5′-isobutyl-5-isopropyl-2,2′,2″-trimethoxy-3,7′:3,7″-terquinoline (A)

Step A. A solution of diisopropylamine (0.14 mL, 0.99 mmol) in THF (1 mL) was cooled to 0 °C before dropwise addition of *n*-BuLi (2.5 M in hexane, 0.36 mL, 0.90 mmol). The mixture was stirred for 1 h at 0 °C and was added dropwise to a solution, cooled to −78 °C, of **25** (100 mg, 0.24 mmol) and triisopropylborate (0.22 mL, 0.95 mmol) in THF (2 mL). After stirring for 4 h at −78 °C, the mixture was allowed to reach room temperature and was stirred for 15 h. After addition of a saturated aqueous NH_4Cl solution, the mixture was extracted with EtOAc and the assembled organic fractions were dried over $MgSO_4$ and evaporated to give **27** (112 mg) as a pale yellow solid.

Step B. To a solution of **15** (24 mg, 82 μmol) in THF (2 mL) were added $PdCl_2(PPh_3)_2$ (2.9 mg, 4 μmol), a 2 M aqueous Na_2CO_3 solution (0.21 mL, 0.42 mmol) and boronic acid **27** from step A (112 mg). The mixture was stirred under microwave irradiation (65 °C, 50 W, P_{atm}) for 20 min, poured into water and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 99:1) to give the intermediate trimer (47 mg, 75 μmol) as a white solid.

Step C. To a solution of the intermediate trimer from step B (47 mg, 75 μmol) in MeOH (1 mL) were added ammonium formate (95 mg, 1.5 mmol) and 10% Pd/C (7.5 mg). The mixture was refluxed for 6 days before filtration on Celite. Water was added and the mixture was extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 98:2) to give **A** (42 mg, 67 μmol, 81% from **15**) as a white solid.

Mp = 131 °C; IR (ATR): 1609, 1570, 1261 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (3H, t, J = 7.5 Hz), 1.04 (6H, d, J = 6.5 Hz), 1.42 (9H, d, J = 7.0 Hz), 1.71–1.96 (2H, m), 2.10 (1H, m), 2.99 (2H, d, J = 7.0 Hz), 3.46 (1H, sext, J = 7.0 Hz), 3.74 (1H, hept, J = 7.0 Hz), 4.13 (3H, s), 4.15 (3H, s), 4.16 (3H, s), 6.96 (1H, d, J = 9.0 Hz), 7.36 (1H, d, J = 7.5 Hz), 7.53 (1H, d, J = 1.5 Hz), 7.59 (1H, d, J = 1.5 Hz), 7.62 (1H, t, J = 8.0 Hz), 7.80 (1H, d, J = 8.5 Hz), 8.00 (1H, s), 8.02 (1H, s), 8.34 (1H, d, J = 9.0 Hz), 8.34 (1H, s), 8.45 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 12.2, 21.5, 22.8 (2C), 23.9 (2C), 28.7, 30.1, 35.6, 53.6, 53.8, 53.9 (CH_3, CH), 30.7, 42.2 (CH_2), 112.7, 120.3, 122.9, 125.1, 125.7 (2C), 127.3, 129.5, 134.4, 134.6, 134.9 (CH_{arom}), 123.0, 123.5, 123.9, 125.8, 126.1, 137.9, 138.2, 138.4, 143.7, 145.4, 146.6, 146.7, 147.2, 159.3, 159.8, 162.3 (C_{arom}); HRMS (ESI+) calcd for $C_{41}H_{46}N_3O_3$ (M+H)$^+$ 628.3539, found 628.3552.

5.2.23. (*R,S*)-5″-(Butan-2-yl)-5′-isobutyl-5-isopropyl-3,7′:3,7″-terquinoline-2,2′,2″(1*H*,1′*H*,1″*H*)-trione (28)

A suspension of **A** (29 mg, 46 μmol) in a 6 M aqueous HCl solution (1.5 mL) was refluxed for 7 days. The mixture was poured into water and extracted with CH_2Cl_2. The assembled organic fractions were dried over $MgSO_4$ and evaporated to give **28** (24 mg, 41 μmol, 89%) as a yellow solid.

Mp = 281 °C; IR (ATR): 1653, 1616, 1551 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 0.99 (3H, t, J = 7.0 Hz), 1.07 (6H, d, J = 6.5 Hz), 1.43 (9H, d, J = 7.0 Hz), 1.73–1.94 (2H, m), 2.05 (1H, m), 2.98 (2H, d, J = 7.0 Hz), 3.39 (1H, sext, J = 7.0 Hz), 3.65 (1H, hept, J = 7.0 Hz), 6.82 (1H, dd, J_1 = 10.0 Hz, J_2 = 1.5 Hz), 7.21 (1H, d, J = 7.0 Hz), 7.29 (1H, s), 7.36 (1H, s), 7.47 (1H, d, J = 8.0 Hz), 7.53 (1H, t, J = 7.5 Hz), 8.21 (1H, d, J = 10.0 Hz), 8.35 (1H, s), 8.45 (1H, s), 8.73 (1H, s), 8.75 (1H, s), 13.60 (1H, br s), 13.99 (1H, br s), 14.14 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): 12.2, 21.6, 22.8 (2C), 23.8 (2C), 28.8, 30.8, 35.6 (CH_3, CH), 30.9, 42.2 (CH_2), 114.4, 115.8, 116.0, 119.3, 119.6, 120.6, 123.9, 131.1, 135.2, 135.8, 136.8 (CH), 117.9, 118.1, 118.8, 129.1, 129.6, 138.0, 138.2, 138.9, 139.0, 139.3, 139.6, 145.1, 146.1, 163.4, 163.8, 165.1 (C); HRMS (ESI+) calcd for $C_{38}H_{40}N_3O_3$ (M+H)$^+$ 586.3070, found 586.3070.

5.2.24. 7-Bromo-5-(2-hydroxypropan-2-yl)quinolin-2(1*H*)-one (29)

A solution of **9** (250 mg, 0.89 mmol) in THF (15 mL) was cooled to 0 °C before dropwise addition of MeMgBr (3.0 M in Et_2O, 1.8 mL, 5.4 mmol). The mixture was stirred at room temperature for 15 h, poured into a saturated aqueous NH_4Cl solution and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **29** (201 mg, 0.71 mmol, 80%) as a pale yellow solid.

Mp = 258 °C; IR (ATR): 3372, 3322, 1647, 1595, 1549 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 1.58 (6H, s), 5.51 (1H, s, OH), 6.51 (1H, dd, J_1 = 10.0 Hz, J_2 = 2.0 Hz), 7.30 (1H, d, J = 2.0 Hz), 7.43 (1H, d, J = 1.5 Hz), 8.79 (1H, d, J_1 = 10.0 Hz, J_2 = 0.5 Hz), 11.77 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 31.5 (2CH_3), 71.7 (C), 116.9, 120.7, 121.6, 139.2 (CH), 115.7, 122.7, 141.4 (C_{arom}), 148.9, 161.0 (C=O); HRMS (ESI+) calcd for $C_{12}H_{13}{}^{79}BrNO_2$ (M+H)$^+$ 282.0130, found 282.0139.

5.2.25. 7-Bromo-5-(propen-2-yl)quinolin-2(1*H*)-one (30)

PTSA monohydrate (133 mg, 0.70 mmol) was added to a solution of **29** (246 mg, 0.87 mmol) in toluene (15 mL). The mixture was refluxed for 15 h using a Dean-Stark apparatus. After cooling, the mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 1:1) to give **30** (202 mg, 0.76 mmol, 88%) as a white solid.

Mp = 225 °C; IR (ATR): 1665, 1653, 1597, 1549 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 2.09 (3H, dd, J_1 = 1.5 Hz, J_2 = 1.0 Hz), 4.96 (1H, m), 5.43 (1H, m), 6.53 (1H, d, J = 10.0 Hz), 7.19 (1H, d, J = 2.0 Hz), 7.42 (1H, dd, J_1 = 2.0 Hz, J_2 = 0.5 Hz), 7.88 (1H, dd, J_1 = 10.0 Hz, J_2 = 0.5 Hz), 11.85 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 24.4 (CH_3), 116.4, 122.3, 123.1, 137.2 (CH), 115.1, 117.9, 123.0, 140.5, 141.3, 144.2 (=CH_2, C), 161.4 (C=O); HRMS (ESI+) calcd for $C_{12}H_{11}{}^{79}BrNO$ (M+H)$^+$ 264.0024, found 264.0042.

5.2.26. 7-Bromo-2-chloro-5-(propen-2-yl)quinoline (31)

To a solution of **30** (185 mg, 0.70 mmol) in CH_2Cl_2 (8 mL) were added $SOCl_2$ (66 μL, 108 mg, 0.91 mmol) and DMF (70 μL, 67 mg, 0.91 mmol). The mixture was refluxed for 3 h, cooled and poured into water. After extraction with EtOAc, the assembled organic fractions were dried over $MgSO_4$ and evaporated to give **31** (195 mg, 0.69 mmol, 99%) as a beige solid.

Mp = 108 °C; IR (ATR): 1591, 1582,1560, 1113 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 2.17 (3H, dd, J_1 = 1.5 Hz, J_2 = 1.0 Hz), 5.07 (1H, m), 5.54 (1H, m), 7.63 (1H, d, J = 9.0 Hz), 7.68 (1H, d, J = 2.0 Hz), 8.13 (1H, dd, J_1 = 2.0 Hz, J_2 = 1.0 Hz), 8.43 (1H, dd, J_1 = 9.0 Hz, J_2 = 1.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 24.5 (CH_3), 122.9, 128.3, 128.9, 138.0 (CH_{arom}), 118.7, 123.2, 123.8, 141.0, 144.1, 148.2, 151.0 (=CH_2, C); HRMS (ESI+) calcd for $C_{12}H_{10}{}^{79}Br^{35}ClN$ (M+H)$^+$ 281.9685, found 281.9700.

5.2.27. 7-Bromo-2-methoxy-5-(propen-2-yl)quinoline (32)

Compound **31** (180 mg, 0.64 mmol) was added to a solution of NaOMe (2.87 mmol, prepared from 66 mg of Na) in MeOH (5 mL) and the mixture was refluxed form 15 h. After evaporation, water was added and the mixture was extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$ and evaporated to give **32** (164 mg, 0.59 mmol, 93%) as a colourless oil.

IR (ATR): 1611, 1580, 1570, 1497, 1316 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 2.15 (3H, dd, J_1 = 1.5 Hz, J_2 = 1.0 Hz), 3.98 (3H, s), 5.01 (1H, m), 5.48 (1H, m), 7.05 (1H, d, J = 9.0 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.89 (1H, dd, J_1 = 2.0 Hz, J_2 = 1.0 Hz), 8.24 (1H, dd, J_1 = 9.0 Hz, J_2 = 1.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 24.6, 53.4 (CH_3), 113.4, 125.3, 127.8, 137.0 (CH_{arom}), 117.9, 121.0, 122.5, 141.7, 143.9, 147.3, 162.5 (=CH_2, C); HRMS (ESI+) calcd for $C_{13}H_{13}{}^{79}BrNO$ (M+H)$^+$ 278.0181, found 278.0185.

5.2.28. 7-Bromo-5-isopropyl-2-methoxyquinoline (33)

A mixture of **32** (83 mg, 0.30 mmol) and PtO_2 (13.4 mg, 59 μmol) in EtOAc (5 mL) was hydrogenated for 15 h before filtration on Celite. After evaporation, the residue was purified by flash chromatography (cyclohexane/EtOAc 98:2) to give **33** (73.1 mg, 0.26 mmol, 87%) as a colourless oil.

IR (ATR): 1609, 1591, 1574, 1501, 1464, 1400, 1306, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (6H, d, J = 7.0 Hz), 3.51 (1H, hept, J = 7.0 Hz), 4.04 (3H, s), 6.88 (1H, d, J = 9.0 Hz), 7.38 (1H, d, J = 1.5 Hz), 7.91 (1H, d, J = 1.5 Hz), 8.14 (1H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 23.4 (2C), 28.6, 53.3 (CH_3, CH), 112.7, 123.5, 127.9, 134.3 (CH_{arom}), 121.6, 123.7, 146.8, 148.0, 162.4 (C_{arom}); HRMS (ESI+) calcd for $C_{13}H_{15}{}^{79}BrNO$ (M+H)$^+$ 280.0337, found 280.0353.

5.2.29. 2-Ethoxy-5′-isopropyl-2′-methoxy-3,7′-biquinoline (35)

To a solution of **33** (100 mg, 0.36 mmol) in THF (3 mL) were added $PdCl_2(PPh_3)_2$ (12.5 mg, 18 μmol), a 2 M aqueous Na_2CO_3 solution (0.89 mL, 1.78 mmol) and boronic acid **34** (155 mg, 0.71 mmol). The mixture was stirred under microwave irradiation (65 °C, 50 W, P_{atm}) for 20 min, poured into water and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 99:1) to give **35** (117 mg, 0.31 mmol, 88%) as a white solid.

Mp = 157 °C; IR (ATR): 1609, 1570, 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (6H, d, J = 7.0 Hz), 1.46 (3H, t, J = 7.0 Hz), 3.68 (1H, hept, J = 7.0 Hz), 4.11 (3H, s), 4.64 (2H, q, J = 7.0 Hz), 6.95 (1H, d, J = 9.0 Hz), 7.40 (1H, ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz), 7.64 (1H, ddd, J_1 = 8.5 Hz, J_2 = 7.0 Hz, J_3 = 1.5 Hz), 7.72 (1H, d, J = 1.5 Hz), 7.78 (1H, dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 7.90 (1H, d, J = 8.5 Hz), 7.98 (1H, s), 8.17 (1H, s), 8.32 (1H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.7, 23.8 (2C), 28.7, 53.5 (CH_3, CH), 62.2 (CH_2), 112.6, 122.1, 124.2, 125.7, 126.9, 127.6, 129.5, 134.4, 138.4 (CH_{arom}), 122.4, 125.6, 126.5, 138.3, 144.3, 146.1, 147.2, 159.5, 162.2 (C_{arom}); HRMS (ESI+) calcd for $C_{24}H_{25}N_2O_2$ (M+H)$^+$ 373.1916, found 373.1933.

5.2.30. 2-Ethoxy-5′,5″-diisopropyl-2′,2″-dimethoxy-3,7′:3,7″-terquinoline (37)

Step A. A solution of diisopropylamine (0.12 mL, 0.85 mmol) in THF (1 mL) was cooled to 0 °C before dropwise addition of *n*-BuLi (2.5 M in hexane, 0.32 mL, 0.80 mmol). The mixture was stirred for 1 h at 0 °C and was added dropwise to a solution, cooled to −78 °C, of **35** (80 mg, 0.21 mmol) and triisopropylborate (0.20 mL, 0.87 mmol) in THF (2 mL). After stirring for 4 h at −78 °C, the mixture was allowed to reach room temperature and was stirred for 15 h. After addition of a saturated aqueous NH_4Cl solution, the mixture was extracted with EtOAc and the assembled organic fractions were dried over $MgSO_4$ and evaporated to give **36** (89 mg) as a pale yellow solid.

Step B. To a solution of **33** (20 mg, 71 μmol) in THF (2 mL) were added $PdCl_2(PPh_3)_2$ (2.5 mg, 3.6 μmol), a 2 M aqueous Na_2CO_3 solution (0.18 mL, 0.36 mmol) and boronic acid **36** from step A (89 mg). The mixture was stirred under microwave irradiation (65 °C, 50 W, P_{atm}) for 20 min, poured into water and extracted with EtOAc. The assembled organic fractions were dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (cyclohexane/EtOAc 99:1) to give **37** (31 mg, 54 μmol, 75%) as a white solid.

Mp = 109 °C; IR (ATR): 1609, 1568, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.46 (6H, d, J = 7.0 Hz), 1.47 (6H, d, J = 7.0 Hz), 1.48 (3H, t, J = 7.0 Hz), 3.70 (1H, hept, J = 7.0 Hz), 3.78 (1H, hept, J = 7.0 Hz), 4.13 (3H, s), 4.16 (3H, s), 4.66 (2H, q, J = 7.0 Hz), 6.97 (1H, d, J = 9.0 Hz), 7.42 (1H, ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz), 7.62–7.68 (2H, m), 7.76 (1H, d, J = 1.5 Hz), 7.81 (1H, dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 7.90 (1H, d, J = 8.5 Hz), 8.00 (1H, d, J = 1.5 Hz), 8.03 (1H, d, J = 1.5 Hz), 8.21 (1H, s), 8.34 (1H, d, J = 9.0 Hz), 8.44 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 14.7, 23.8 (2C), 23.9 (2C), 28.7, 28.8, 53.5, 53.8 (CH_3, CH), 62.2 (CH_2), 112.7, 122.1, 122.3, 124.3, 125.4, 125.8, 126.9, 127.6, 129.5, 134.2, 134.5, 138.3 (CH_{arom}), 122.5, 122.9, 125.6, 126.1, 126.6, 138.2, 138.6, 144.6, 144.7, 146.1, 146.8, 147.3, 159.6 (2C), 162.3 (C_{arom}); HRMS (ESI+) calcd for $C_{37}H_{38}N_3O_3$ $(M+H)^+$ 572.2913, found 572.2906.

Acknowledgements

The French Ministère de l'Enseignement Supérieur et de la Recherche is greatly acknowledged for financial support (S.B.). This work was also supported by grants INSERM and UCB Lyon 1 and additional supports from the Ligue contre le Cancer (07 and 26) to N.B.B. The authors are grateful to Bertrand Légeret for mass spectra analysis.

References and notes

1. Kroemer, G. *Nat. Med.* **1997**, *3*, 614.
2. Adams, J. M.; Cory, S. *Science* **1998**, *281*, 1322.
3. Szegezdi, E.; MacDonald, D. C.; Chonghaile, T. N.; Gupta, S.; Samali, A. *Am. J. Physiol. Cell Physiol.* **2009**, *296*, 941.
4. Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. *Tetrahedron Lett.* **2000**, *41*, 6993.
5. 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.* **2000**, *97*, 7124.
6. Enyedy, I. J.; Ling, Y.; Nacro, K.; Tomita, Y.; Wu, X.; Cao, Y.; Guo, R.; Li, B.; Zhu, X.; Huang, Y.; Long, Y.-Q.; Roller, P. P.; Yang, D.; Wang, S. *J. Med. Chem.* **2001**, *44*, 4313.
7. Degterev, A.; Lugovskoy, A.; Cardone, M.; Mulley, B.; Wagner, G.; Mitchison, T.; Yuan, J. *Nat. Cell Biol.* **2001**, *3*, 173.
8. Tzung, S.-P.; Kim, K. M.; Basañez, G.; Giedt, C. D.; Simon, J.; Zimmerberg, J.; Zhang, K. Y. J.; Hockenbery, D. M. *Nat. Cell Biol.* **2001**, *3*, 183.
9. Kim, K. M.; Giedt, C. D.; Basañez, G.; O'Neill, J. W.; Hill, J. J.; Han, Y.-H.; Tzung, S.-P.; Zimmerberg, J.; Hockenbery, D. M.; Zhang, K. Y. J. *Biochemistry* **2001**, *40*, 4911.
10. Kaneko, M.; Nakashima, T.; Uosaki, Y.; Hara, M.; Ikeda, S.-I.; Kanda, Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 887.
11. Vogler, M.; Dinsdale, D.; Dyer, M. J. S.; Cohen, G. M. *Cell Death Differ.* **2009**, *16*, 360.
12. Bernardo, P. H.; Wan, K.-F.; Sivaraman, T.; Xu, J.; Moore, F. K.; Hung, A. W.; Mok, H. Y. K.; Yu, V. C.; Chai, C. L. L. *J. Med. Chem.* **2008**, *51*, 6699.
13. Prakesch, M.; Denisov, A. Y.; Naim, M.; Gehring, K.; Arya, P. *Bioorg. Med. Chem.* **2008**, *16*, 7443.
14. Janssen, C. O.; Lim, S.; Lo, E. P.; Wan, K. F.; Yu, V. C.; Lee, M. A.; Ng, S. B.; Everett, M. J.; Buss, A. D.; Lane, D. P.; Boyce, R. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5771.
15. Wang, L.; Kong, F.; Kokoski, C. L.; Andrews, D. W.; Xing, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 236.
16. Rodriguez, J. M.; Nevola, L.; Ross, N. T.; Lee, G.-I.; Hamilton, A. D. *ChemBioChem* **2009**, *10*, 829.
17. Orzáez, M.; Mondragón, L.; García-Jareño, A.; Mosulén, S.; Pineda-Lucena, A.; Pérez-Payá, E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1592.
18. Oltersdorf, T.; Elmore, S. W.; Shoemaker, A. R.; Armstrong, R. C.; Augeri, D. J.; Belli, B. A.; Bruncko, M.; Deckwerth, T. L.; Dinges, J.; Hajduk, P. J.; Joseph, M. K.; Kitada, S.; Korsmeyer, S. J.; Kunzer, A. R.; Letai, A.; Li, C.; Mitten, M. J.; Nettesheim, D. G.; Ng, S.; Nimmer, P. M.; O'Connor, J. M.; Oleksijew, A.; Petros, A. M.; Reed, J. C.; Shen, W.; Tahir, S. K.; Thompson, C. B.; Tomaselli, K. J.; Wang, B.; Wendt, M. D.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H. *Nature* **2005**, *435*, 677.
19. Sturla, S. J.; Irwin, J. J.; Loeppky, R. N.; Mulvihill, M. J.; Searcey, M. *Cancer Res.* **2007**, *67*, 6539.
20. Sattler, M.; Liang, H.; Nettesheim, D.; Meadows, R. P.; Harlan, J. E.; Eberstadt, M.; Yoon, H. S.; Shuker, S. B.; Chang, B. S.; Minn, A. J.; Thompson, C. B.; Fesik, S. W. *Science* **1997**, *275*, 983.
21. Broch, S.; Aboab, B.; Anizon, F.; Moreau, P. *Eur. J. Med. Chem.* **2010**, *45*, 1657.
22. Broch, S.; Anizon, F.; Moreau, P. *Synthesis* **2008**, 2039.
23. Tominaga, M.; Yo, E.; Ogawa, H.; Yamashita, S.; Yabuuchi, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1986**, *34*, 682.
24. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
25. Zhai, D.; Ziwei, H.; Jin, C.; Huang, Z.; Satterthwait, A. C.; Reed, J. C. *J. Biol. Chem.* **2008**, *283*, 9580.
26. Certo, M.; Del Gaizo Moore, V.; Nishino, M.; Wei, G.; Korsmeyer, S.; Amstrong, S. A.; Letai, A. *Cancer Cell* **2006**, *9*, 351.
27. Moreau, E.; Fortin, S.; Lacroix, J.; Patenaude, A.; Rousseau, J. L. C.; Gaudreault, R. C. G. *Bioorg. Med. Chem.* **2008**, *16*, 1206.
28. Inglis, S. R.; Zervosen, A.; Woon, E. C. Y.; Gerards, T.; Teller, N.; Fischer, D. S.; Luxen, A.; Schofield, C. J. *J. Med. Chem.* **2009**, *52*, 6097.