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Synthesis and molecular modeling study of new trimeric quinoline derivatives

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ABSTRACT

Di- and trimeric quinoline derivatives have been recently described as potential modulators of Bcl-2 family protein interactions. However, only a few trimeric compounds have been described so far and an enlargement of the number of analogs of this class is needed to expand the structure–activity relationship study. Therefore, the synthesis of six new trimeric quinoline derivatives is reported. Moreover molecular modeling experiments were performed to study the conformational arrangement of compound **36** in Bak binding site of Bcl-x_L, showing that these compounds could be potential ligands for Bcl-x_L.

1. Introduction

Quinoline moiety is present in many classes of biologically active compounds such as antibacterial, antifungal, antitumor agents, HIV integrase inhibitors, histamine H_3 receptor antagonists, Bcl-2 inhibitors, anticonvulsants and kinase inhibitors [1–8].

In the course of our studies on new compounds of biological interest and given the great biological potential of quinoline-based scaffolds, we recently reported the synthesis and biological activities of new di- and trimeric quinoline derivatives (Fig. 1) [9–11].

Firstly, compounds **E**–**I** were studied for their antiproliferative activities toward a human fibroblast primary culture and two human solid cancer cell lines (MCF-7 and PA 1). The results obtained in this preliminary structure–activity relationship study have pointed out that in this series, the dimeric quinoline derivatives exhibited mild *in vitro* antiproliferative potencies, whereas trimeres were less active, possibly due to their lower solubility.

Subsequently, a new series of diversely substituted di- and trimeric quinoline derivatives **J**, **K** and **L** was prepared. These compounds, as well as their quinolin-2-one counterparts, were evaluated for their ability to modulate Bcl-2 family protein interactions. This study showed that, the 2-alkoxyquinoline derivatives were more potent modulators of the Bcl-2 family protein interactions compared to their quinolin-2-one analogs. This could be due to a better solubility of 2-alkoxy derivatives in contrast to their quinolin-2-one counterparts. Especially, compound **L**, that was designed to 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 whereas compound **K** inhibited Bcl-x_L/Bid interaction with IC_{50} value of 21 μM.

To get an insight into the substitution pattern required for the best biological profile in this series, we decided to prepare additional diversely substituted di- and trimeric 2-alkoxyquinolines bearing two or three isopropyl groups at the C-5 position, and alkoxy groups with different chain lengths at the C-2 position of the quinoline moieties. Previously, we have reported the preferential helical arrangement of trimeric analogs bearing methoxy, propoxy or butoxy side chains at the C-2 position of the quinoline moiety, but non-substituted on the carbocycle (compounds **G**–**I**, Fig. 1). Thus, to complete these preceding molecular modeling experiments, a theoretical study was undertaken to ascertain that the preferential conformational arrangement adopted by these new derivatives (substituted at the C-2 and C-5 positions of the quinoline moieties) was consistent with the establishment of noteworthy interactions with Bcl-x_L binding site.

2. Results and discussion

The key steps in the synthetic approach leading to polymeric quinoline derivatives are Suzuki cross-coupling reactions between a quinoline-3-boronic acid derivative and a 7-bromoquinoline monomer. The required monomeric moieties **2**, **3**, **6**, **7** and **16**–**19** were first prepared. Accordingly, compound **3** was prepared in 96% yield from 2-chloroquinoline as already described for compound **2** [10] whereas brominated analogs **6** and **7** were easily prepared in two steps from the 7-bromoquinolin-2(1*H*)-one **4** [10]. Compounds **16**–**19** were prepared from substituted quinolines **10** and **11** which were synthesized in six steps from 3-aminobenzoic acid **8** or 3-amino-5-bromobenzoic acid **9** as already described by our group (Scheme 1) [11]. 2-Chloroquinolines **10** and **11** were

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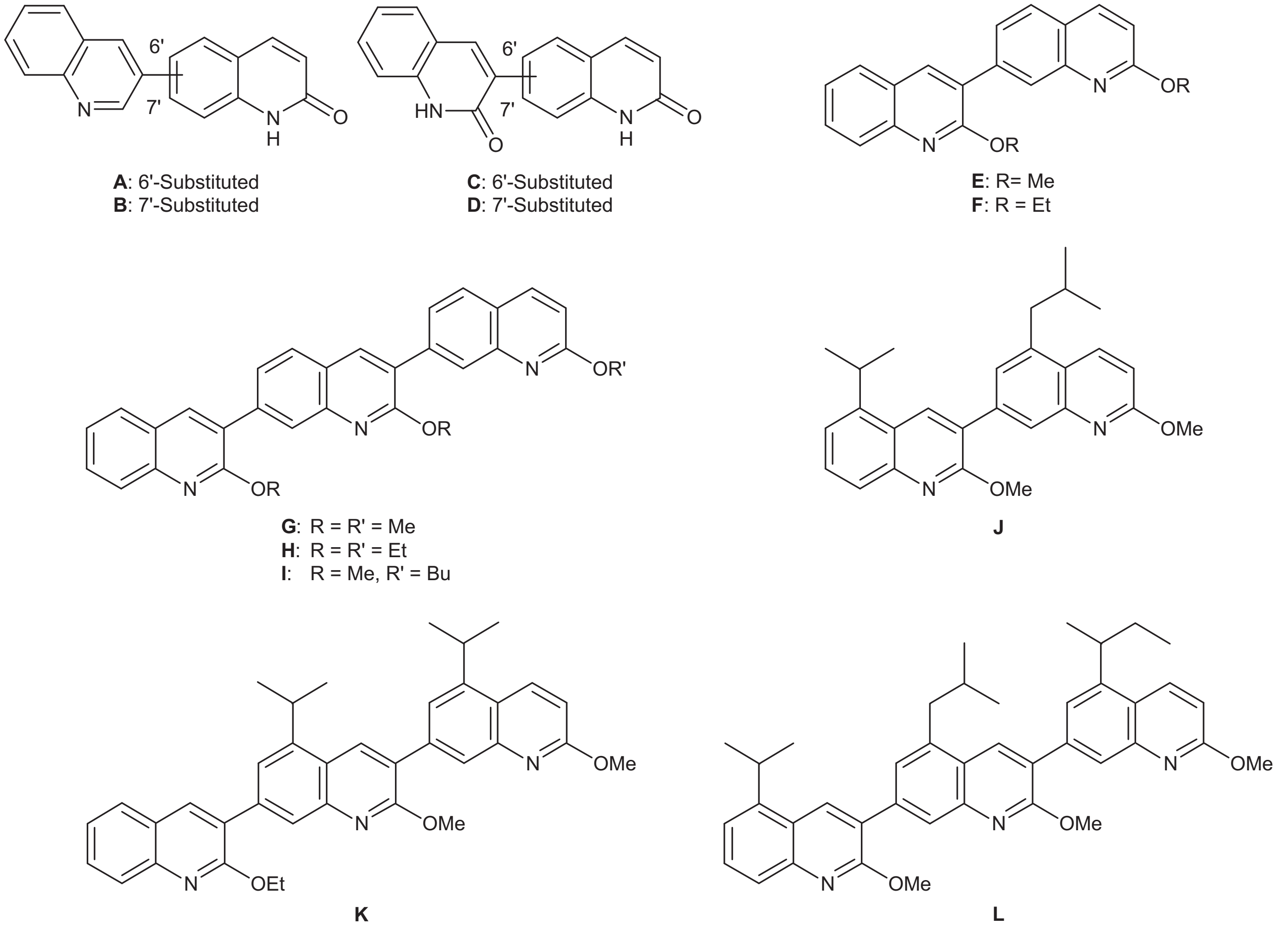


Fig. 1. Di- and trimeric quinoline derivatives published by our group.

firstly treated with sodium alkoxide to give compounds **12**–**15** in 86–99% yields. After hydrogenation of the propenyl group, quinoline derivatives **16**–**19** were isolated in 76–88% yields.

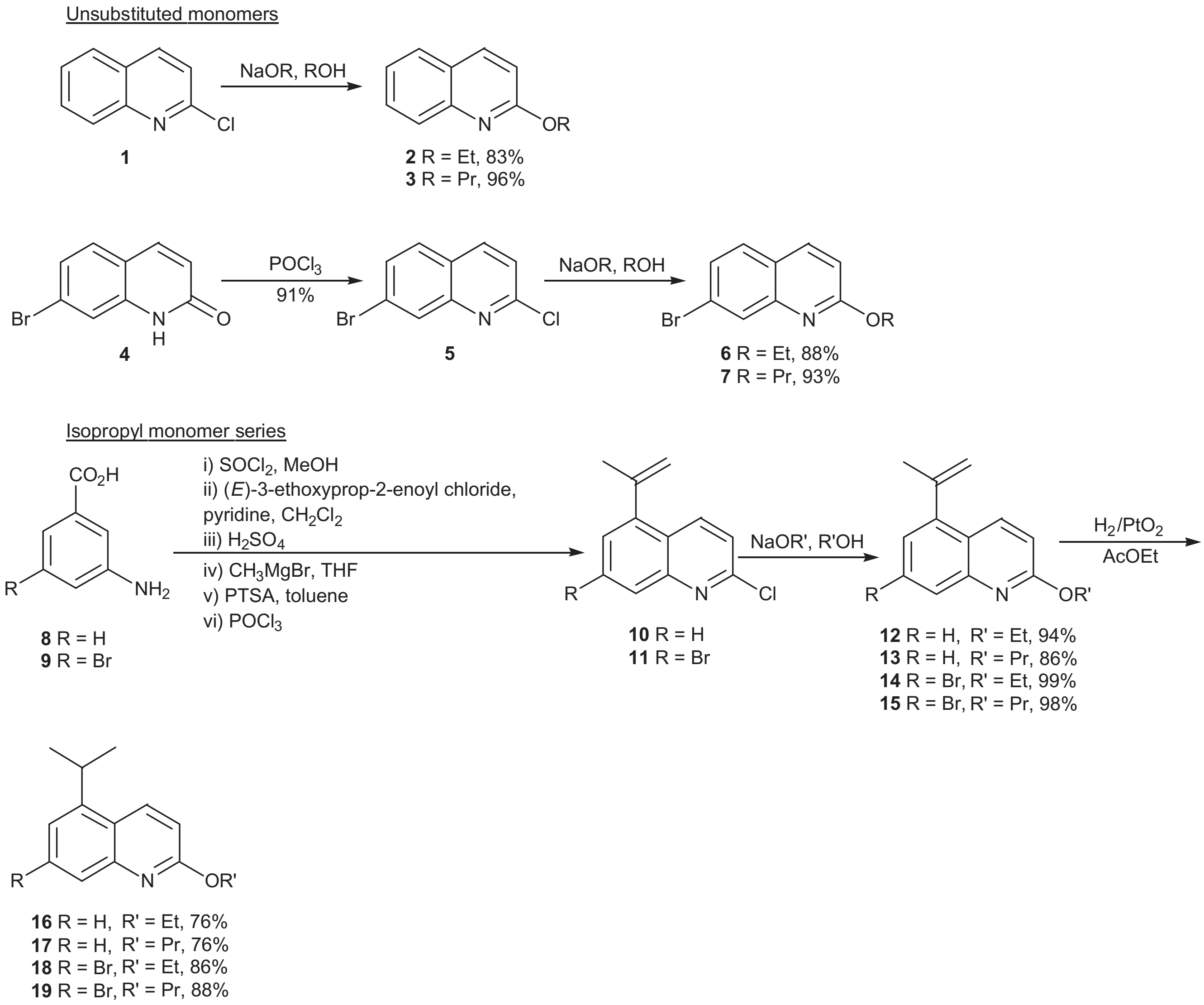
The dimeric quinoline moieties **24**–**27** were obtained by Suzuki cross-coupling between boronic acids **20**–**23** and bromoquinolines **18** or **19**. Boronic acids **20**–**23** were prepared by *ortho*-lithiation of compounds **2**, **3**, **16** or **17** in the presence of lithium diisopropylamide (LDA) and subsequent in situ borylation using triisopropylborate (Scheme 2) [11]. In order to prevent their degradation, compounds **20**–**23** were used without any further purification after their isolation from the reaction mixture. In this way, biquinolines **24**–**27** were obtained in yields ranging from 49% to 77%.

Finally, diversely substituted trimeric quinoline derivatives **32**–**37** were obtained using the same method as the one described for dimers **24**–**27**. Thus, Suzuki cross-coupling between bromoquinolines **6**, **7**, **18** or **19** and boronic acids **28**–**31**, produced from biquinolines **24**–**27** in the presence of LDA and triisopropylborate, provided terquinoline derivatives **32**–**37** in 50–93% yields (Scheme 2). As mentioned above, the coupling reaction was performed directly on the crude boronic acids.

3. Molecular modeling experiments

As mentioned earlier, di- and trimeric quinoline derivatives have been recently described as potential modulators of Bcl-2 family protein. Bcl-2 proteins regulation is mediated by protein–protein interactions between α-helical regions [11]. For example, Val74, Leu78, Ile81, and Ile85 residues of the α-helical BH3 domain of Bak, that correspond to the *i*, *i* + 4, *i* + 7, and *i* + 11 residues of the α-helix, have been identified as essential residues for its binding with Bcl-x_L. Thus, we decided to undertake molecular modeling experiments to study the conformational arrangement of polyquinoline derivatives. Dimeric analogs **26** and **27** bearing two isopropyl groups and substituted by either ethoxy or propoxy groups at the C-2 position of the quinoline moieties were taken as models. In order to evaluate the potential of **26** and **27** to easily undergo conformational changes, energy barriers for C4–C3–C7′–C8′ rotatable bond were evaluated, scanning the corresponding dihedral angles from 0 to 360 degrees in 10-degree steps. The C4–C3–C7′–C8′ dihedral angle scan calculations were performed using ab initio method (DFT/B3LYP/6-31G) in Gaussian03 program [12]. This method was chosen to take into account the π delocalization between the quinoline moieties, and the results were thoroughly analyzed. As shown in Fig. 2, the energy differences between lowest and highest energy conformers were found to be around 12–13 kJ mol^{-1} for both compounds. These results indicated that free rotations are allowed around the C3–C7′ bond linking the two quinoline moieties.

Since free rotations were allowed around the C3–C7′ bond of compounds **26** and **27**, we assumed that these rotations were also accepted for the trimeric analogs. Thus, an alignment between the structure of Bak peptide (taken from 1BXL PDB structure [13]) and triisopropylterquinoline **36** was made with Sybylx1.3 [14] using “similarity suite”. As shown in Fig. 3, the three isopropyl groups



Scheme 1. Preparation of monomers **2**, **3**, **6**, **7** and **16**–**19**.

of compound **36** and the hydrophobic side chains of Val74, Leu78 and Ile85 are distributed on the same side of the Bak peptide helix with an accurate superimposition. Moreover, the dihedral angles φ_1 (C_4–C_3–$C_{7'}$–$C_{8'}$) and φ_2 ($C_{4'}$–$C_{3'}$–$C_{7''}$–$C_{8''}$) were found in accordance with the conformational analysis study and consistent with the π–π interactions existing in this system.

Finally, the structure obtained for compound **36**, by alignment with Bak peptide, was used to model the interaction of **36** into Bcl-x_L binding site. For this purpose, we inserted compound **36** into Bcl-x_L binding site (PDB code: 1BXL [13]) after removing of the Bak peptide. After minimization without any constraint, as shown in Fig. 4, compound **36** remained in Bcl-x_L binding site. Interestingly, no steric conflict or electronic repulsion with the protein was noticed in this model. A similar result was obtained when a molecular dynamic was performed on **36** and side chains of Bcl-x_L residues using Sybyl. Compound **36** and Bcl-x_L binding site mainly interacted via hydrophobic interactions involving isopropyl groups of **36** and side chains of Phe97, Leu112, Val126, Leu130, Val141, Ala142, Phe146 and Leu162 hydrophobic residues of Bcl-x_L binding site. All together, these results pointed out that compound **36**, used as a representative model for this series of compounds, could display noteworthy interaction with Bcl-x_L binding site.

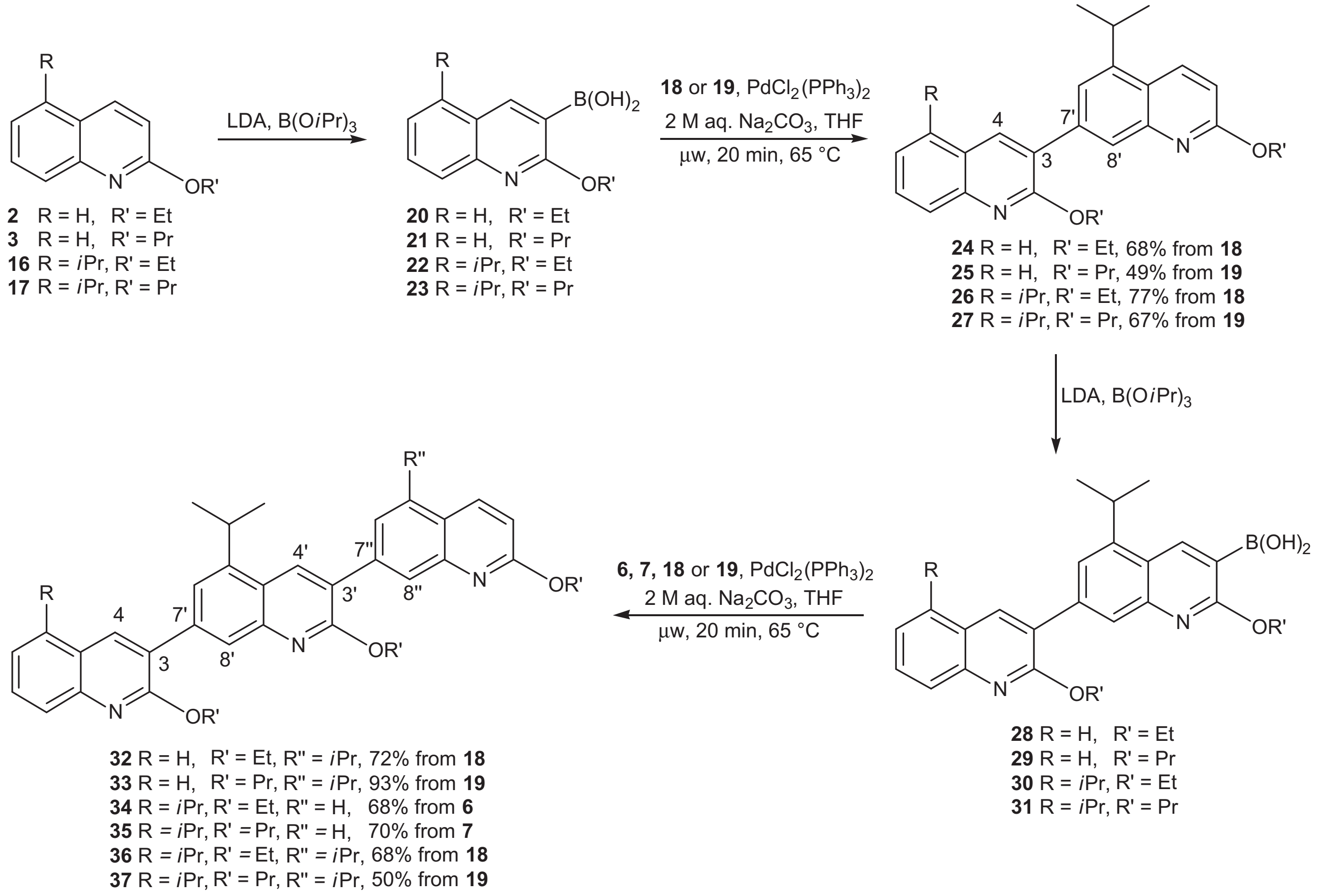
4. Conclusion

In conclusion, the synthesis of six new trimeric quinoline derivatives, substituted or not by an isopropyl group at the C-5 position of the quinoline moieties, and bearing alkoxy chains with various lengths at the C-2 position, was successfully completed. Molecular modeling experiments showed that these compounds could be potential ligand for Bcl-x_L. Moreover, the synthetic intermediates prepared during this work are useful building blocks for the synthesis of biologically active compounds and could be of interest for medicinal chemists. The biological activities of these compounds are currently under investigation.

5. Experimental

5.1. Chemistry

With the exception of compound **4** which was prepared according to reported procedures [9], all starting materials were obtained from commercial suppliers and used without further purification. Solvents and diisopropylamine were distilled prior to use. IR



Scheme 2. Synthesis of trimers **32**–**37**.

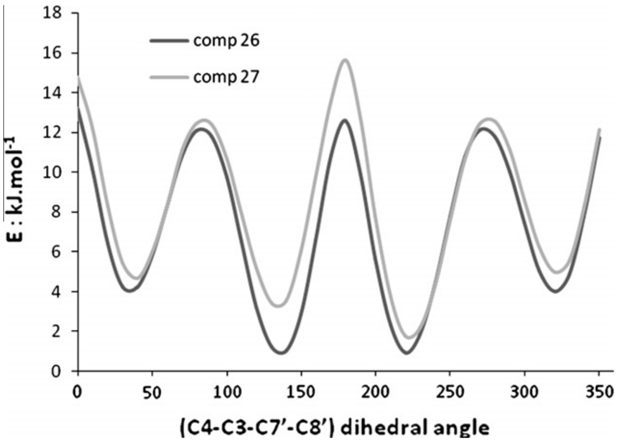


Fig. 2. Conformational analysis of compounds **26** and **27**.

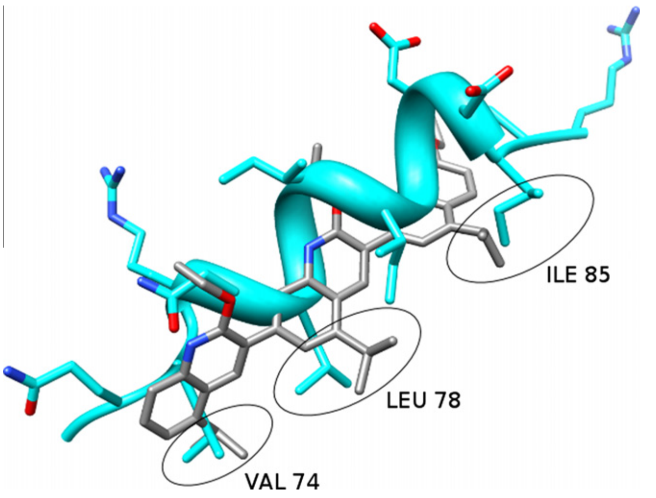


Fig. 3. Structure alignment of Bak peptide and compound **36** (picture designed using chimera software [15]).

spectra were recorded on a Shimadzu FTIR-8400S spectrometer ($\bar{\nu}$ in cm^{-1}). NMR spectra were performed on a Bruker AVANCE 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz); chemical shifts δ are indicated in parts per million (ppm) and the following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), sextet (sex), septet (sep), doublet of doublet (dd), multiplet (m). High resolution mass spectra (ESI+) were determined on a high-resolution Micro Q-Tof apparatus (CRMP, Université Blaise Pascal, Clermont-Ferrand, 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). Melting points were measured on a Reichert microscope and are uncorrected. Experiments under microwave irradiation were performed using a CEM Discover Benchmate apparatus.

5.1.1. 2-Propoxyquinoline ***3***

2-Chloroquinoline **1** (500 mg, 3.06 mmol) was added to a solution of sodium *n*-propoxide (10.1 mmol prepared from 232 mg of

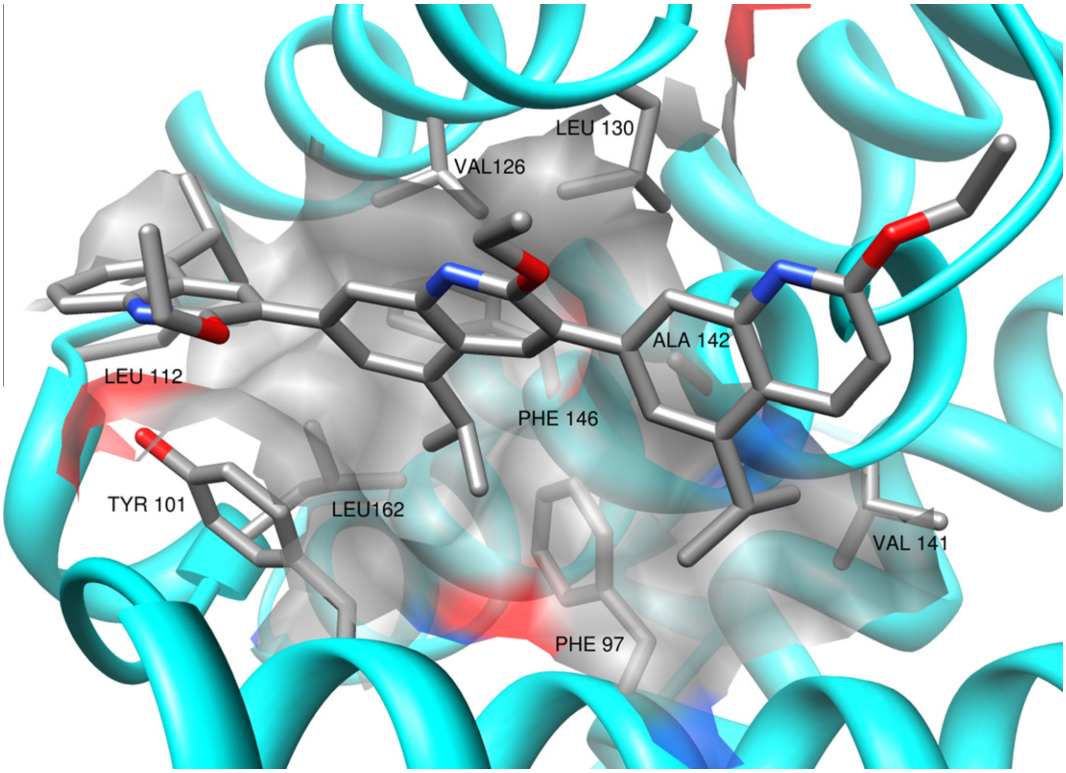


Fig. 4. Model of compound **36** into the binding site of Bcl-x_L (picture designed using chimera software [15]).

Na) in *n*PrOH (10 mL). The mixture was refluxed for 4 h. The solvent was removed, water was added and the mixture was extracted with EtOAc. After drying over $MgSO_4$, the solvent was removed to give compound **3** (551 mg, 2.94 mmol, 96%) as a colorless oil.

IR (ATR): $\bar{\nu}$ 1618, 1606, 1428, 1313, 1276, 1259, 1238 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 1.01 (3H, t, J = 7.5 Hz), 1.79 (2H, sex, J = 7 Hz), 4.36 (2H, t, J = 6.5 Hz), 7.00 (1H, d, J = 9 Hz), 7.41 (1H, t, J = 7.5 Hz), 7.65 (1H, t, J = 7.5 Hz), 7.87 (1H, d, J = 8 Hz), 7.75 (1H, d, J = 8 Hz), 8.22 (1H, d, J = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 10.5 (CH_3), 21.8, 66.9 (CH_2), 113.0, 124.0, 126.7, 127.7, 129.7, 139.2 (CH_{arom}), 124.7, 145.9, 161.7 (C_{arom}).

HRMS (ESI+): m/z calcd for $C_{12}H_{14}NO$ $(M+H)^+$ 188.1075. Found 188.1077.

5.1.2. 7-Bromo-2-propoxyquinoline *7*

Compound **5** (150 mg, 0.62 mmol) was added to a solution of sodium *n*-propoxide (3.09 mmol prepared from 71 mg of Na) in *n*PrOH (4.5 mL). The mixture was refluxed for 15 h. The solvent was removed, water was added and the mixture was extracted with EtOAc. After drying over $MgSO_4$, the solvent was removed to give compound **7** (153 mg, 0.57 mmol, 93%) as a white solid.

Mp = 54–59 °C.

IR (ATR): $\bar{\nu}$ 1614, 1496, 1446, 1336, 1301, 1253, 1124 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 1.00 (3H, t, J = 7.5 Hz), 1.78 (2H, sex, J = 7 Hz), 4.35 (2H, t, J = 6.5 Hz), 7.04 (1H, d, J = 9 Hz), 7.57 (1H, d, J = 8.5 Hz), 7.84 (1H, d, J = 8.5 Hz), 7.93 (1H, s), 8.25 (1H, d, J = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 10.4 (CH_3), 21.7, 67.2 (CH_2), 113.7, 127.1, 128.6, 129.6, 139.2 (CH_{arom}), 122.9, 123.6, 146.8, 162.4 (C_{arom}).

HRMS (ESI+): m/z calcd for $C_{12}H_{13}{}^{79}BrNO$ $(M+H)^+$ 266.0181. Found 266.0183.

5.1.3. 5-(Propen-2-yl)-2-ethoxyquinoline *12*

Compound **10** (728 mg, 3.57 mmol) was added to a solution of sodium ethoxide (17.8 mmol prepared from 410 mg of Na) in ethanol (40 mL). The mixture was refluxed for 15 h. The solvent was removed, water was added and the mixture was extracted with EtOAc. After drying over $MgSO_4$, the solvent was removed to give compound **12** (720 mg, 3.38 mmol, 94%) as a colorless oil.

IR (ATR): $\bar{\nu}$ 1609, 1412, 1314, 1260, 1042 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 1.38 (3H, t, J = 7 Hz), 2.15 (3H, s), 4.46 (2H, q, J = 7 Hz), 4.97 (1H, s), 5.45 (1H, s), 6.99 (1H, d, J = 9 Hz), 7.27 (1H, d, J = 7 Hz), 7.61 (1H, t, J = 7.5 Hz), 7.67 (1H, d, J = 8 Hz), 8.25 (1H, d, J = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 24.9 (CH_3), 61.2 (CH_2), 112.9, 122.4, 125.9, 129.2, 136.7 (CH_{arom}), 116.8, 121.8, 141.8, 142.9, 146.4, 161.3 ($=CH_2$, C).

HMRS (ESI+): m/z calcd for $C_{14}H_{16}NO$ $(M+H)^+$ 214.1232. Found 214.1230.

5.1.4. 5-(Propen-2-yl)-2-propoxyquinoline *13*

Compound **10** (625 mg, 3.07 mmol) was added to a solution of sodium *n*-propoxide (15.4 mmol prepared from 353 mg of Na) in *n*PrOH (33 mL). The mixture was refluxed for 15 h. The solvent was removed, water was added and the mixture was extracted with EtOAc. After drying over $MgSO_4$, the solvent was removed to give compound **13** (597 mg, 2.63 mmol, 86%) as a colorless oil.

IR (ATR): $\bar{\nu}$ 1610, 1411, 1315, 1265 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 1.00 (3H, t, J = 7.5 Hz), 1.79 (2H, sex, J = 7 Hz), 2.15 (3H, s), 4.37 (2H, t, J = 6.5 Hz), 4.97 (1H, s), 5.45 (1H, s), 7.00 (1H, d, J = 9 Hz), 7.27 (1H, dd, J_1 = 7 Hz, J_2 = 1 Hz), 7.61 (1H, t, J = 7.5 Hz), 7.67 (1H, d, J = 8.5 Hz), 8.25 (1H, d, J = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 10.5, 24.9 (CH_3), 21.8, 67.0 (CH_2), 112.9, 122.4, 125.9, 129.2, 136.8 (CH_{arom}), 116.8, 121.9, 141.8, 143.0, 146.4, 161.5 ($=CH_2$, C).

HRMS (ESI+): *m/z* calcd for $C_{15}H_{18}NO$ $(M+H)^+$ 228.1388. Found 228.1383.

5.1.5. *7-Bromo-2-ethoxy-5-(propen-2-yl)quinoline* ***14***

Compound **11** (350 mg, 1.24 mmol) was added to a solution of sodium ethoxide (5.57 mmol prepared from 128 mg of Na) in ethanol (10 mL). The mixture was refluxed for 2 h. The solvent was removed, water was added and the mixture was extracted with EtOAc. After drying over $MgSO_4$, the solvent was removed to give compound **14** (357 mg, 1.22 mmol, 99%) as a white solid.

Mp = 34–37 °C.

IR (ATR): $\bar{\nu}$ 1607, 1312, 1275, 1248, 1128, 1043 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (3H, t, *J* = 7 Hz), 2.15 (3H, m), 4.45 (2H, q, *J* = 7 Hz), 5.01 (1H, m), 5.48 (1H, m), 7.03 (1H, d, *J* = 9 Hz), 7.43 (1H, d, *J* = 2 Hz), 7.86 (1H, dd, J_1 = 2 Hz, J_2 = 0.5 Hz), 8.23 (1H, dd, J_1 = 9 Hz, J_2 = 0.5 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 24.6 (CH_3), 61.6 (CH_2), 113.6, 125.2, 127.8, 136.9 (CH_{arom}), 117.8, 120.9, 122.4, 141.7, 143.8, 147.3, 162.1 ($=CH_2$, C).

HRMS (ESI+): *m/z* calcd for $C_{14}H_{15}{}^{79}BrNO$ $(M+H)^+$ 292.0337. Found 292.0331.

5.1.6. *7-Bromo-5-(propen-2-yl)-2-propoxyquinoline* ***15***

Compound **11** (500 mg, 1.77 mmol) was added to a solution of sodium *n*-propoxide (8.0 mmol prepared from 183 mg of Na) in *n*PrOH (14.5 mL). The mixture was refluxed for 2 h. The solvent was removed, water was added and the mixture was extracted with EtOAc. After drying over $MgSO_4$, the solvent was removed to give compound **15** (530 mg, 1.73 mmol, 98%) as a white solid.

Mp = 30–32 °C.

IR (ATR): $\bar{\nu}$ 1607, 1406, 1313, 1274, 1127 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (3H, t, *J* = 7.5 Hz), 1.78 (2H, sex, *J* = 7 Hz), 2.15 (3H, s), 4.36 (2H, t, *J* = 6.5 Hz), 5.02 (1H, s), 5.49 (1H, s), 7.05 (1H, d, *J* = 9 Hz), 7.42 (1H, d, *J* = 2 Hz), 7.87 (1H, d, *J* = 1.5 Hz), 8.23 (1H, d, *J* = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 10.4, 24.6 (CH_3), 21.7, 67.3 (CH_2), 113.5, 125.2, 127.8, 137.0 (CH_{arom}), 117.8, 120.9, 122.4, 141.7, 143.8, 147.3, 162.3 ($=CH_2$, C).

HRMS (ESI+): *m/z* calcd for $C_{15}H_{17}{}^{79}BrNO$ $(M+H)^+$ 306.0494. Found 306.0492.

5.1.7. *2-Ethoxy 5-isopropylquinoline* ***16***

A mixture of **12** (26 mg, 0.12 mmol) and PtO_2 (5.5 mg, 0.024 mmol) in EtOAc (1 mL) was hydrogenated at room temperature for 4 h before filtration through Celite. After evaporation, the residue was purified by flash chromatography (cyclohexane/EtOAc, 98:2) to give **16** (20 mg, 0.093 mmol, 76%) as a colorless oil.

IR (ATR): $\bar{\nu}$ 1606, 1412, 1387, 1305, 1290, 1264, 1241, 1043 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (6H, d, *J* = 7 Hz), 1.37 (3H, t, *J* = 7 Hz), 3.67 (1H, sep, *J* = 7 Hz), 4.45 (2H, q, *J* = 7 Hz), 7.00 (1H, d, *J* = 9 Hz), 7.31–7.37 (1H, m), 7.57–7.64 (2H, m), 8.46 (1H, d, *J* = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 23.6 (2C), 27.8 (CH_3, CH), 61.1 (CH_2), 112.5, 119.9, 125.0, 129.5, 135.1 (CH_{arom}), 122.5, 145.1, 146.5, 161.0 (C_{arom}).

HRMS (ES+): *m/z* calcd for $C_{14}H_{18}NO$ $(M+H)^+$ 216.1388. Found 216.1393.

5.1.8. *5-Isopropyl-2-propoxyquinoline* ***17***

Similar procedure to that described for the synthesis of **16**; from **13** (552 mg, 2.43 mmol), compound **17** (422 mg, 1.84 mmol, 76%) was obtained as a colorless oil.

IR (ATR): $\bar{\nu}$ 1606, 1412, 1306, 1289, 1267, 1240 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (3H, t, *J* = 7.5 Hz), 1.31 (6H, d, *J* = 7 Hz), 1.79 (2H, sex, *J* = 7 Hz), 3.67 (1H, sep, *J* = 7 Hz), 4.35 (2H, t, *J* = 6.5 Hz), 7.01 (1H, d, *J* = 9 Hz), 7.31–7.37 (1H, m), 7.56–7.64 (2H, m), 8.46 (1H, d, *J* = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 10.5, 23.6 (2C), 27.8 (CH_3, CH), 21.8, 66.8 (CH_2), 112.4, 119.9, 124.9, 129.5, 135.1 (CH_{arom}), 122.5, 145.1, 146.5, 161.2 (C_{arom}).

HRMS (ESI+): *m/z* calcd for $C_{15}H_{20}NO$ $(M+H)^+$ 230.1545. Found 230.1545.

5.1.9. *7-Bromo-2-ethoxy-5-isopropylquinoline* ***18***

Similar procedure to that described for the synthesis of **16**; from **14** (356 mg, 1.22 mmol), compound **18** (309 mg, 1.05 mmol, 86%) was obtained as a colorless oil.

IR (ATR): $\bar{\nu}$ 1609, 1303, 1290, 1253, 1041 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, *J* = 7 Hz), 1.37 (3H, t, *J* = 7 Hz), 3.67 (1H, sep, *J* = 7 Hz), 4.45 (2H, q, *J* = 7 Hz), 7.04 (1H, d, *J* = 9 Hz), 7.43 (1H, s), 7.79 (1H, s), 8.47 (1H, d, *J* = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 23.3 (2C), 27.9 (CH_3, CH), 61.5 (CH_2), 113.2, 121.4, 126.9, 135.4 (CH_{arom}), 123.1, 123.2, 147.4, 147.7, 161.8 (C_{arom}).

HRMS (ESI+): *m/z* calcd for $C_{14}H_{17}{}^{79}BrNO$ $(M+H)^+$ 294.0494. Found 294.0494.

5.1.10. *7-Bromo-5-isopropyl-2-propoxyquinoline* ***19***

Similar procedure to that described for the synthesis of **16**; from **15** (426 mg, 1.39 mmol), compound **19** (376 mg, 1.22 mmol, 88%) was obtained as a white solid.

Mp = 39–41 °C.

IR (ATR): $\bar{\nu}$ 1605, 1312, 1287, 1256 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (3H, t, *J* = 7.5 Hz), 1.30 (6H, d, *J* = 7 Hz), 1.78 (2H, sex, *J* = 7 Hz), 3.67 (1H, sep, *J* = 7 Hz), 4.35 (2H, t, *J* = 6.5 Hz), 7.05 (1H, d, *J* = 9 Hz), 7.42 (1H, d, *J* = 1.5 Hz), 7.79 (1H, d, *J* = 1.5 Hz), 8.47 (1H, d, *J* = 9 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 10.4, 23.3 (2C), 28.0 (CH_3, CH), 21.7, 67.2 (CH_2), 113.1, 123.2, 126.9, 135.4 (CH_{arom}), 121.4, 123.1, 147.4, 147.7, 162.0 (C_{arom}).

HRMS (ESI+): *m/z* calcd for $C_{15}H_{19}{}^{79}BrNO$ $(M+H)^+$ 308.0650. Found 308.0639.

5.1.11. *2,2′-Diethoxy-5′-isopropyl-3,7′-biquinoline* ***24***

Step A. A solution of diisopropylamine (2.24 mL, 15.9 mmol) in THF (6.5 mL) was cooled to −5 °C before dropwise addition of *n*-BuLi (2.2 M in hexane, 6.68 mL, 14.7 mmol). The mixture was stirred at −5 °C for 1 h and was added dropwise to a solution, cooled to −78 °C, of **2** (687 mg, 3.97 mmol) and triisopropylborate (3.67 mL, 15.9 mmol) in THF (6.5 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 **20** (890 mg).

Step B. To a solution of **18** (88 mg, 0.30 mmol) in THF (2.5 mL) were added $PdCl_2(PPh_3)_2$ (10.5 mg, 15 µmol), a 2 M aqueous Na_2CO_3 solution (0.73 mL, 1.46 mmol) and boronic acid **20** from step A (130 mg). The mixture was stirred under microwave irradiation (65 °C, P_{max} = 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 **24** (79 mg, 0.20 mmol, 68%) as a white solid.

Mp = 85–87 °C.

IR (ATR): $\bar{\nu}$ 1604, 1409, 1342, 1294, 1264, 1255, 1047 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.40–1.46 (12H, m), 3.78 (1H, sep, *J* = 7 Hz), 4.53 (2H, q, *J* = 7 Hz), 4.60 (2H, q, *J* = 7 Hz), 6.99 (1H, d, *J* = 9 Hz), 7.46 (1H, t, *J* = 7.5 Hz), 7.68 (1H, t, *J* = 7.5 Hz), 7.77 (1H, s), 7.84 (1H, d, *J* = 8.5 Hz), 7.92 (1H, s), 7.96 (1H, d, *J* = 8 Hz), 8.35 (1H, s), 8.49 (1H, d, *J* = 9 Hz).

^{13}C NMR (100 MHz, acetone-d_6): δ 14.85, 14.87, 24.0 (2C) (CH$_3$), 62.0, 62.6 (CH$_2$), 29.2 (CH), 113.5, 122.7, 125.1, 126.5, 127.5, 128.7, 130.3, 135.4, 139.2 (CH$_{\text{arom}}$), 123.1, 126.5, 127.1, 138.9, 145.4, 146.9, 148.2, 160.1, 162.7 (C$_{\text{arom}}$).

HRMS (ESI+): *m/z* calcd for $C_{25}H_{27}N_2O_2$ (M+H)$^+$ 387.2073. Found 387.2061.

5.1.12. 5′-Isopropyl-2,2′-dipropoxy-3,7′-biquinoline **25**

Similar procedure to that described for the synthesis of **24**; from **19** (164 mg, 0.53 mmol), compound **25** (109 mg, 0.26 mmol, 49%) was obtained as a white gum.

IR (ATR): $\tilde{\nu}$ 1607, 1409, 1289, 1262, 1255 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.06 (6H, t, J = 7.5 Hz), 1.43 (6H, d, J = 6.5 Hz), 1.80–1.91 (4H, m), 3.79 (1H, sep, J = 7 Hz), 4.44 (2H, t, J = 6.5 Hz), 4.51 (2H, t, J = 6.5 Hz), 7.01 (1H, d, J = 9 Hz), 7.46 (1H, t, J = 7.5 Hz), 7.69 (1H, t, J = 7.5 Hz), 7.76 (1H, s), 7.85 (1H, d, J = 8.5 Hz), 7.93 (1H, s), 7.97 (1H, d, J = 8 Hz), 8.36 (1H, s), 8.50 (1H, d, J = 9 Hz).

^{13}C NMR (100 MHz, acetone-d_6): δ 10.8, 11.2, 24.0 (2C) (CH$_3$), 22.97, 22.99, 67.9, 68.5 (CH$_2$), 29.2 (CH), 113.5, 122.6, 125.1, 126.7, 127.5, 128.7, 130.3, 135.4, 139.2 (CH$_{\text{arom}}$), 123.1, 126.5, 127.1, 138.9, 145.4, 146.9, 148.2, 160.3, 162.8 (C$_{\text{arom}}$).

HRMS (ESI+): *m/z* calcd for $C_{27}H_{31}N_2O_2$ (M+H)$^+$ 415.2386. Found 415.2391.

5.1.13. 2,2′-Diethoxy-5,5′-diisopropyl-3,7′-biquinoline **26**

Similar procedure to that described for the synthesis of **24**; from **18** (148 mg, 0.50 mmol), compound **26** (165 mg, 0.39 mmol, 77%) was obtained as a white solid.

Mp = 122–125 °C.

IR (ATR): $\tilde{\nu}$ 1608, 1261, 1254, 1046 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.39–1.45 (18H, m), 3.79 (1H, sep, J = 7 Hz), 3.87 (1H, sep, J = 7 Hz), 4.54 (2H, q, J = 7 Hz), 4.59 (2H, q, J = 7 Hz), 6.99 (1H, d, J = 9 Hz), 7.41 (1H, d, J = 7 Hz), 7.64 (1H, t, J = 8 Hz), 7.70 (1H, d, J = 8 Hz), 7.77 (1H, s), 7.91 (1H, s), 8.50 (1H, d, J = 9 Hz), 8.56 (1H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 14.87, 14.88, 23.98 (2C), 24.03 (2C) (CH$_3$), 62.1, 62.4 (CH$_2$), 29.0, 29.2 (CH), 113.5, 121.0, 122.9, 125.8, 126.6, 130.3, 135.1, 135.4 (CH$_{\text{arom}}$), 123.1, 124.2, 126.5, 139.3, 145.2, 146.4, 147.5, 148.2, 159.6, 162.7 (C$_{\text{arom}}$).

HRMS (ESI+): *m/z* calcd for $C_{28}H_{33}N_2O_2$ (M+H)$^+$ 429.2542. Found 429.2539.

5.1.14. 5,5′-Diisopropyl-2,2′-dipropoxy-3,7′-biquinoline **27**

Similar procedure to that described for the synthesis of **24**; from **19** (89 mg, 0.29 mmol), compound **27** (88 mg, 0.19 mmol, 67%) was obtained as a white solid.

Mp = 110–116 °C.

IR (ATR): $\tilde{\nu}$ 1607, 1409, 1265, 1252 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.05 (3H, t, J = 7.5 Hz), 1.06 (3H, t, J = 7.5 Hz), 1.41 (6H, d, J = 7 Hz), 1.43 (6H, d, J = 7 Hz), 1.79–1.91 (4H, m), 3.79 (1H, sep, J = 7 Hz), 3.87 (1H, sep, J = 7 Hz), 4.45 (2H, t, J = 6.5 Hz), 4.50 (2H, t, J = 6.5 Hz), 7.01 (1H, d, J = 9 Hz), 7.41 (1H, d, J = 7 Hz), 7.64 (1H, t, J = 8 Hz), 7.71 (1H, d, J = 8 Hz), 7.75 (1H, s), 7.92 (1H, s), 8.51 (1H, d, J = 9 Hz), 8.55 (1H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 10.8, 11.2, 23.95 (2C), 24.03 (2C) (CH$_3$), 22.98, 23.00, 67.9, 68.3 (CH$_2$), 29.0, 29.2 (CH), 113.5, 121.0, 122.8, 125.8, 126.7, 130.3, 135.1, 135.5 (CH$_{\text{arom}}$), 123.1, 124.1, 126.6, 139.4, 145.3, 146.4, 147.5, 148.2, 159.7, 162.8 (C$_{\text{arom}}$).

HRMS (ESI+): *m/z* calcd for $C_{30}H_{37}N_2O_2$ (M+H)$^+$ 457.2855. Found 457.2845.

5.1.15. 2,2′,2″-Triethoxy 5′,5″-diisopropyl-3,7′:3,7″-terquinoline **32**

Similar procedure to that described for the synthesis of **24**; from **18** (21 mg, 0.071 mmol), compound **32** (31 mg, 0.052 mmol, 72%) was obtained as a white solid.

Mp = 90–92 °C.

IR (ATR): $\tilde{\nu}$ 1608, 1253, 1047 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.41–1.50 (21H, m), 3.80 (1H, sep, J = 7 Hz), 3.94 (1H, sep, J = 7 Hz), 4.55 (2H, q, J = 7 Hz), 4.63 (4H, q, J = 7 Hz), 7.00 (1H, d, J = 9 Hz), 7.47 (1H, t, J = 7.5 Hz), 7.70 (1H, t, J = 7.5 Hz), 7.81 (1H, s), 7.84 (1H, s), 7.86 (1H, d, J = 8.5 Hz), 7.95 (1H, s), 7.97–8.01 (2H, m), 8.40 (1H, s), 8.51 (1H, d, J = 9 Hz), 8.60 (1H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 14.89 (2C), 14.91, 24.0 (2C), 24.1 (2C) (CH$_3$), 62.1, 62.5, 62.6 (CH$_2$), 29.1, 29.2 (CH), 113.5, 122.9, 123.0, 125.1, 126.1, 126.6, 127.6, 128.8, 130.4, 134.9, 135.4, 139.2 (CH$_{\text{arom}}$), 123.1, 123.6, 126.5, 126.7, 127.1, 138.9, 139.3, 145.3, 145.7, 147.0, 147.6, 148.2, 159.9, 160.1, 162.7 (C$_{\text{arom}}$).

HRMS (ESI+): *m/z* calcd for $C_{39}H_{42}N_3O_3$ (M+H)$^+$ 600.3226. Found 600.3231.

5.1.16. 5′,5″-Diisopropyl-2,2′,2″-tripropoxy-3,7′:3,7″-terquinoline **33**

Similar procedure to that described for the synthesis of **24**; from **19** (18.5 mg, 0.060 mmol), compound **33** (36 mg, 0.056 mmol, 93%) was obtained as a white solid.

Mp = 79–84 °C.

IR (ATR): $\tilde{\nu}$ 1608, 1257, 1241 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.04–1.11 (9H, m), 1.45 (6H, d, J = 7 Hz), 1.48 (6H, d, J = 7 Hz), 1.82–1.93 (6H, m), 3.80 (1H, sep, J = 7 Hz), 3.95 (1H, sep, J = 7 Hz), 4.46 (2H, t, J = 6.5 Hz), 4.54 (4H, t, J = 6.5 Hz), 7.02 (1H, d, J = 9 Hz), 7.47 (1H, t, J = 7.5 Hz), 7.70 (1H, t, J = 7.5 Hz), 7.79 (1H, s), 7.82 (1H, s), 7.86 (1H, d, J = 8.5 Hz), 7.96 (1H, s), 7.99 (1H, d, J = 8 Hz), 8.02 (1H, s), 8.40 (1H, s), 8.52 (1H, d, J = 9 Hz), 8.59 (1H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 10.8, 11.19, 11.23, 24.0 (2C), 24.1 (2C) (CH$_3$), 22.98, 23.00 (2C), 67.9, 68.4, 68.5 (CH$_2$), 29.19, 29.25 (CH), 113.5, 122.8, 122.9, 125.1, 126.3, 126.7, 127.5, 128.7, 130.3, 135.0, 135.5, 139.2 (CH$_{\text{arom}}$), 123.1, 123.5, 126.5, 126.8, 127.1, 138.9, 139.3, 145.3, 145.7, 146.9, 147.6, 148.2, 160.0, 160.3, 162.8 (C$_{\text{arom}}$).

HRMS (ESI+): *m/z* calcd for $C_{42}H_{48}N_3O_3$ (M+H)$^+$ 642.3696. Found 642.3713.

5.1.17. 5,5′-Diisopropyl-2,2′,2″-triethoxy-3,7′:3,7″-terquinoline **34**

Similar procedure to that described for the synthesis of **24**; from **6** (23 mg, 0.091 mmol), compound **34** (37 mg, 0.062 mmol, 68%) was obtained as a white solid.

Mp = 72–76 °C.

IR (ATR): $\tilde{\nu}$ 1609, 1448, 1301, 1252, 1242, 1045 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.39–1.51 (21H, m), 3.83–4.00 (2H, m), 4.55 (2H, q, J = 7 Hz), 4.62 (2H, q, J = 7 Hz), 4.64 (2H, q, J = 7 Hz), 6.99 (1H, d, J = 8.5 Hz), 7.42 (1H, d, J = 7.5 Hz), 7.65 (1H, t, J = 7.5 Hz), 7.72 (1H, d, J = 8.5 Hz), 7.80–7.84 (1H, m), 7.83 (1H, s), 7.93 (1H, d, J = 8.5 Hz), 7.99 (1H, s), 8.11 (1H, s), 8.23 (1H, d, J = 8.5 Hz), 8.60 (2H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 14.83, 14.85, 14.92, 24.0 (2C), 24.1 (2C) (CH$_3$), 62.2, 62.5, 62.6 (CH$_2$), 29.07, 29.13 (CH), 114.2, 121.0, 123.3, 125.9, 126.2, 126.7, 127.9, 128.5, 130.3, 135.1, 135.2, 139.5 (CH$_{\text{arom}}$), 123.5, 124.2, 125.3, 126.4, 126.5, 139.49, 139.55, 145.6, 146.4, 147.5, 147.6, 147.7, 159.6, 159.8, 163.3 (C$_{\text{arom}}$).

HRMS (ESI+): *m/z* calcd for $C_{39}H_{42}N_3O_3$ (M+H)$^+$ 600.3226. Found 600.3223.

5.1.18. 5,5′-Diisopropyl-2,2′,2″-tripropoxy-3,7′:3,7″-terquinoline **35**

Similar procedure to that described for the synthesis of **24**; from **7** (31 mg, 0.12 mmol), compound **35** (52 mg, 0.081 mmol, 70%) was obtained as a white solid.

Mp = 71–73 °C.

IR (ATR): $\tilde{\nu}$ 1609, 1449, 1262, 1241 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.02–1.11 (9H, m), 1.42 (6H, d, J = 6 Hz), 1.47 (6H, d, J = 6.5 Hz), 1.80–1.92 (6H, m), 3.83–4.00 (2H, m), 4.46 (2H, t, J = 6.5 Hz), 4.52 (2H, t, J = 7 Hz), 4.54 (2H, t, J = 7 Hz), 7.00 (1H, d, J = 9 Hz), 7.42 (1H, d, J = 7 Hz), 7.65 (1H, t, J = 7.5 Hz), 7.72 (1H, d, J = 8 Hz), 7.81 (1H, s), 7.80–7.84 (1H, m), 7.93 (1H, d, J = 8 Hz), 7.99 (1H, s), 8.13 (1H, s), 8.23 (1H, d, J = 8.5 Hz), 8.59 (1H, s), 8.60 (1H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 10.8, 11.1, 11.2, 24.04 (2C), 24.06 (2C) (CH_3), 22.95 (2C), 23.03, 68.1, 68.37, 68.42 (CH_2), 29.1, 29.2 (CH), 114.2, 121.0, 123.1, 125.9, 126.3, 126.6, 127.8, 128.6, 130.3, 135.1 (2C), 139.5 (CH_{arom}), 123.5, 124.2, 125.3, 126.4, 126.6, 139.48, 139.49, 145.6, 146.4, 147.5, 147.6, 147.7, 159.7, 160.0, 163.4 (C_{arom}).

HRMS (ESI+): m/z calcd for $C_{42}H_{48}N_3O_3$ $(M+H)^+$ 642.3696. Found 642.3707.

5.1.19. *2,2′,2″-Triethoxy-5,5′,5″-triisopropyl-3,7′:3,7″-terquinoline* ***36***

Similar procedure to that described for the synthesis of **24**; from **18** (23 mg, 0.078 mmol), compound **36** (34 mg, 0.053 mmol, 68%) was obtained as a white solid.

Mp = 98–104 °C.

IR (ATR): $\bar{\nu}$ 1609, 1251, 1047 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.39–1.50 (27H, m), 3.79 (1H, sep, J = 7 Hz), 3.88 (1H, sep, J = 7 Hz), 3.94 (1H, sep, J = 7 Hz), 4.55 (2H, q, J = 7 Hz), 4.58–4.67 (4H, m), 7.00 (1H, d, J = 9 Hz), 7.41 (1H, d, J = 7.5 Hz), 7.64 (1H, t, J = 8 Hz), 7.72 (1H, d, J = 8.5 Hz), 7.81 (1H, s), 7.83 (1H, s), 7.95 (1H, s), 7.99 (1H, s), 8.50 (1H, d, J = 9 Hz), 8.60 (2H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 14.88, 14.90, 14.92, 24.00 (2C), 24.04 (2C), 24.1 (2C) (CH_3), 62.1, 62.5, 62.6 (CH_2), 29.05, 29.14, 29.2 (CH), 113.5, 121.0, 122.9, 123.2, 125.8, 126.2, 126.6, 130.3, 134.9, 135.1, 135.4 (CH_{arom}), 123.1, 123.5, 124.2, 126.5, 126.7, 139.3, 139.4, 145.3, 145.6, 146.4, 147.56, 147.62, 148.2, 159.6, 159.9, 162.7 (C_{arom}).

HRMS (ESI+): m/z calcd for $C_{42}H_{48}N_3O_3$ $(M+H)^+$ 642.3696. Found 642.3679.

5.1.20. *5,5′,5″-Triisopropyl-2,2′,2″-tripropoxy-3,7′:3,7″-terquinoline* ***37***

Similar procedure to that described for the synthesis of **24**; from **19** (29 mg, 0.094 mmol), compound **37** (32 mg, 0.047 mmol, 50%) was obtained as a white solid.

Mp = 89–91 °C.

IR (ATR): $\bar{\nu}$ 1609, 1559, 1506, 1456, 1258 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ 1.04–1.11 (9H, m), 1.41–1.50 (18H, m), 1.82–1.92 (6H, m), 3.81 (1H, sep, J = 7 Hz), 3.89 (1H, sep, J = 7 Hz), 3.95 (1H, sep, J = 7 Hz), 4.46 (2H, t, J = 6.5 Hz), 4.52 (2H, t, J = 6.5 Hz), 4.55 (2H, t, J = 6.5 Hz), 7.02 (1H, d, J = 9 Hz), 7.42 (1H, d, J = 7 Hz), 7.65 (1H, t, J = 7.5 Hz), 7.72 (1H, d, J = 8 Hz), 7.79 (1H, s), 7.82 (1H, s), 7.96 (1H, s), 8.00 (1H, s), 8.52 (1H, d, J = 9 Hz), 8.60 (2H, s).

^{13}C NMR (100 MHz, acetone-d_6): δ 10.8, 11.20, 11.21, 23.96 (2C), 24.04 (2C), 24.1 (2C) (CH_3), 22.98, 23.01, 23.03, 67.9, 68.37, 68.44 (CH_2), 29.1, 29.2, 29.3 (CH), 113.5, 121.0, 122.8, 123.1, 125.8, 126.3, 126.7, 130.3, 135.0, 135.1, 135.5 (CH_{arom}), 123.1, 123.5, 124.2, 126.6, 126.8, 139.3, 139.4, 145.3, 145.6, 146.4, 147.57, 147.63, 148.2, 159.7, 160.0, 162.9 (C_{arom}).

HRMS (ESI+): m/z calcd for $C_{45}H_{54}N_3O_3$ $(M+H)^+$ 684.4165. Found 684.4173.

5.2. *Molecular modeling experiments*

Superimposition of **36** and Bak was performed using the similarity suite of sybylx1.3 with topomersearch-Rgroup (default parameters) as similarity mode and Bak as template. All the conformations of C3–C7′ and C3′–C7″ bonds that were not an energy minimum, regarding the energy function (Fig. 2), were discarded. The best result was next superimposed with the Bak ligand in 1BXL PDB structure. Bak was then removed before adding hydrogen atoms to this new Bcl-x_L/**36** system that was minimized without any constraint using Tripos force field, Gasteiger–Hückel charges and conjugate gradient method. Molecular dynamic experiments were performed on the minimized state, at 300° K, with NTV ensemble on 50,000 integration steps of 1 fs. In order to study only the interaction between **36** and Bcl-x_L, for these experiments, all Bcl-x_L backbone atoms were frozen.

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