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Synthesis and preliminary evaluation of novel analogues of quindolines as potential stabilisers of telomeric G-quadruplex DNA

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Abstract—Telomeric DNA is a potential selective target for cancer therapy since the tumour-associated enzyme telomerase regulates telomere maintenance in most cancer cells. The 3′ single-stranded ends of telomeric DNA can be folded into quadruplex structures by appropriate small molecules. We describe the preparation of a new class of 2,7-disubstituted 10*H*-indolo[3,2-*b*]quinolines with enhanced selectivity for the stabilisation of quadruplex DNA compared to duplex DNA, and also the preparation of a key intermediate for the synthesis of trisubstituted quindolines.

1. Introduction

The enzyme telomerase is responsible for the synthesis of telomeric DNA to counteract its loss during replication,[1] and is expressed in >80% of cancer cells,[2] but not at significant levels in normal somatic cells. It has been shown that down-regulation of telomerase in cancer cells leads to their selective senescence and apoptosis.[3] The single-stranded 3′ ends[4] of human telomeric DNA are normally associated with the telomere-specific protein hPOT1 and the telomerase complex in cancer cells, which also plays a role in physically capping the 3′ ends of telomeric DNA.[5] However, these proteins can be displaced by a variety of small-molecule ligands, such as acridines, anthraquinones and porphyrins. These molecules induce the formation of stable G-quadruplex DNA (G4) higher-order structures, which do not bind these proteins, and which inhibit telomerase function.[6] The resulting quadruplex complexes in turn act as DNA damage response signals, leading to the selective and rapid apoptosis of cancer cells.[7] A number of these small molecules are thus being investigated as potential anticancer drugs targeting telomerase and/or G-quadruplex inhibition of telomere maintenance.[8] We have previously shown that appropriately substituted quindolines can act as G4 ligands, and that they also have significant telomerase inhibitory activity.[9] An attendant problem with such molecules is that many also show significant binding to duplex DNA, and thus they frequently show significant general cellular toxicity. This present work therefore describes the synthesis of novel quindolines using concise, reproducible chemistry, and with the overall goal of designing features that would enhance quadruplex affinity by diminishing duplex affinity. In addition, this report presents the synthesis of a quindoline building block bearing three different kinds of substituents that will enable the generation of small, focused libraries of quindolines, available for structure–activity relationship studies. Such a degree of structural versatility in quindoline substitution has not, to our knowledge, previously been attained.

2. Results and discussion

2.1. A novel synthetic route for 2,7-aminopropyl quindolines

We recently described[9] the synthesis of the 2,7-dibromoquindoline **1** and its conversion into 2,7-aminopropyl derivatives **2a**,**b** (Scheme 1), which possessed modest activity as stabilisers of telomeric G-quadruplex DNA. However, our synthetic route could not be used for the synthesis of the congener **2c** from *N*-methylpiperazine, owing to solubility problems linked to the physical properties of this ligand. An alternative route (Scheme 2) was developed, which had the advantage of being more concise than the previous route and also allowed access to a wider variety of aminopropyl analogues. This involved reaction of acryloyl chloride with *N*-methylpiperazine in DCM to produce the expected amide

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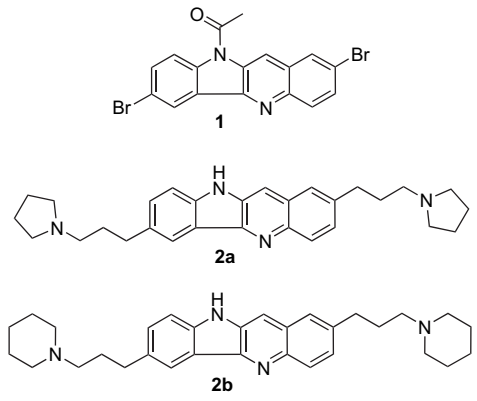
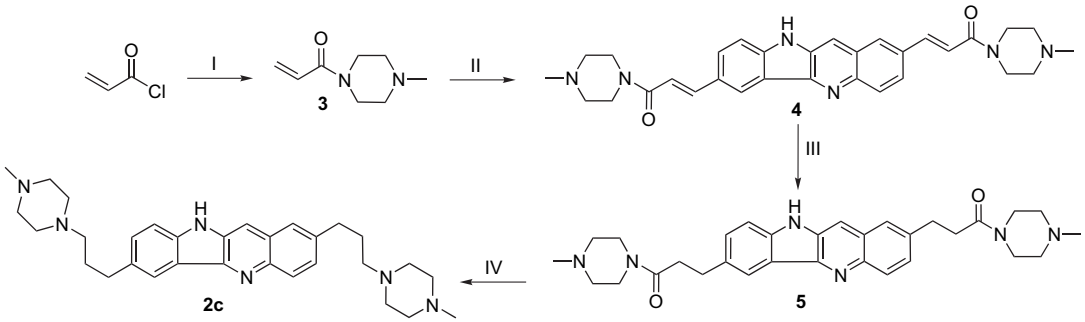


Scheme 1.

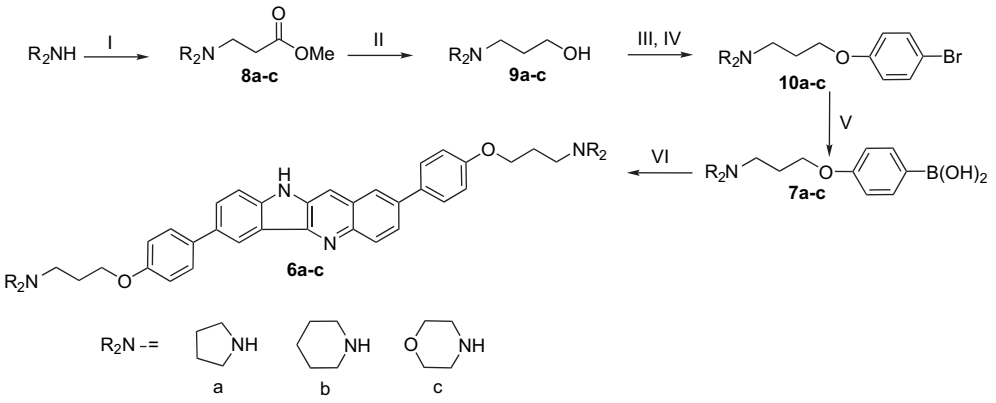
3, and this participated in a Heck reaction with dibromoquindoline **1** to provide the 2,7-disubstituted indolo[3,2-*b*]quinoline **4**. Attempted reduction of the double bonds with hydrogen and a number of catalysts was unsuccessful, but transfer hydrogenation using ammonium formate and palladium yielded the saturated amide **5** in excellent yield (97%), and thence the desired analogue **2c** after reduction with $LiAlH_4$.

2.2. Introduction of aromatic spacers via Suzuki coupling

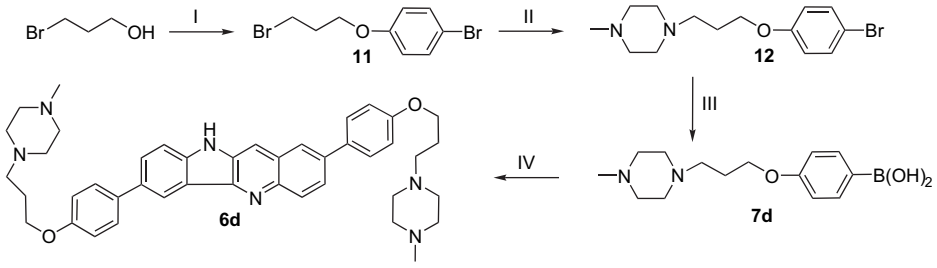
In an attempt to probe the importance of the proximity of the side-chain N-atoms to the main ring system, the novel compounds **6a–c** with a benzene spacer were prepared via the route shown in Scheme 3. The key step was a Suzuki coupling of the requisite boronic acids **7a–c** with dibromoquindoline **1**. Initial Michael addition of the three amines (pyrrolidine, piperidine and morpholine) to methyl acrylate provided the anticipated amino esters **8a–c**, which were reduced ($LiAlH_4$) to the alcohols **9a–c** before conversion into the corresponding chlorides. Reaction of these with 4-bromophenol with caesium carbonate as base produced the required aryl bromides **10a–c**. Finally, the requisite boronic acids **7a–c** were obtained via aryl lithiation and trapping with triisopropylborate. *This whole sequence could be carried out without the necessity for any chromatographic purification*. However, when this reaction sequence was attempted with *N*-methylpiperazine, the overall yield was very low. In consequence, an alternative sequence shown in Scheme 4 was employed. 3-Bromopropanol was reacted with 4-bromophenol under Mitsunobu conditions to give the precursor **11**, which underwent bromide displacement with *N*-methylpiperazine to give aryl bromide **12**. The requisite boronic acid **7d** was obtained via aryl lithiation and trapping with triisopropylborate. The Suzuki couplings were carried out using tetrakis triphenylphosphine palladium as catalyst with sodium carbonate as base, and provided the novel quindolines **6a–d** in yields ranging from 52 to 60%. It is worth noting that, although Heck reactions involving palladium chemistry have previously been performed in our laboratory, Suzuki reactions consisting of palladium couplings of a quindoline core with various boronic acids constitute a novel way of derivatising these sensitive systems. In addition, this



Scheme 2. (I) *N*-Methylpiperazine, DCM, 0 °C, 2 h, 44%; (II) **1**, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, NEt_3, DMF, reflux, 18 h, 65%; (III) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 24 h, 97%; (IV) $LiAlH_4$, THF, 1 h, reflux, 91%.



Scheme 3. (I) Methyl acrylate, DCM, rt, 2 h, 84–99%; (II) $LiAlH_4$, Et_2O, rt, 2 h, 57–95%; (III) $SOCl_2$, DCM, rt, 2 h, 84–96%; (IV) 4-bromophenol, Cs_2CO_3, NaI, DMF, reflux, 18 h, 61–92%; (V) *n*-BuLi, $[(CH_3)_2CHO]_3B$, THF, −78 °C to rt, 18 h, 59–78%; (VI) $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH, reflux, 18 h, 57–60%.



Scheme 4. (I) 4-Bromophenol, PPh_3, DIAD, rt, 18 h, 62%; (II) *N*-methyl piperazine, DCM, rt, 4 h, 44%; (III) *n*-BuLi, $[(CH_3)_2CHO]_3B$, THF, −78 °C to rt, 18 h, 55%; (IV) **1**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH, reflux, 18 h, 52%.

highly convergent route minimises the number of steps involving relatively insoluble intermediates.

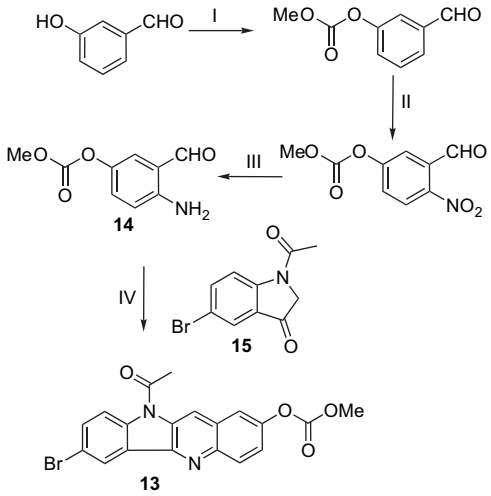
2.3. Structure–activity relationships

In preliminary studies carried out by our collaborators, the affinity of compounds **2a–c** and **6a–d** for the human telomeric quadruplex DNA sequence and for a duplex DNA sequence was assessed by the increase in DNA melting temperature, measured with a modified fluorescence resonance energy transfer assay (FRET[9]). The results show that compound **6a** produces the most stabilising effect of the four new aromatic ligands on the human intramolecular quadruplex, with **6b** only slightly less potent. The morpholino compound **6c** does not show any significant ability to stabilise the complex. Encouragingly, quindolines **2a** and **2b** lacking the phenyl ring in the side-chains, and quindolines **6a** and **6b** did not show significant stabilisation of duplex DNA.

These results are consistent with previous structural studies on ligand–quadruplex complexes where it was shown that, in each instance, the ligand has been shown to stack on the G-quadruplex surface, rather than intercalate between the G-quartets.[10] All ligands have an aromatic core, which is capable of stacking with the G-quadruplex surface. A larger aromatic system can moreover increase the selectivity for quadruplexes over duplex or triplex DNA. The aromatic core generally has substituents capable of forming interactions with the quadruplex grooves. Positive charges on the ligands, both in the aromatic core and the side-chains, appear to increase binding efficiency. These conclusions are borne out by the present study, which has shown that increasing the length of the side-chains enables the positively-charged termini to interact in the loops of the quadruplex.

2.4. Towards trisubstituted quindolines

In order to further probe these structural relationships, we have now prepared the key intermediate **13** via the route shown in Scheme 5. Thus 3-hydroxybenzaldehyde was initially protected using methyl chloroformate to give the corresponding carbonate in good yield (79%). The carbonate was then cautiously treated with a mixture of nitric acid and sulfuric acid to give the 4-nitro derivative as a single isomer. This was finally converted into 4-amino-3-formylphenyl methyl carbonate **14**[11,12] in excellent yield (88%), simply using iron and acetic acid. The amino aldehyde was rapidly isolated to avoid the formation of dimers in the reaction mixture. Initial attempts to condense **14** and 1-acetyl-5-bromo-1,2-dihydro-indol-3-one **15** (prepared as described in our earlier paper)[9] in toluene under reflux and using a Dean-Stark apparatus or by stirring both compounds at room temperature in the presence of molecular sieves failed to return the desired quindoline **13**. However, successful condensation was achieved by stirring the freshly prepared amino aldehyde **14** with **15** in DMF at 60 °C containing molecular sieves. It is expected that this intermediate **13** may be functionalised via palladium chemistry at the bromine position, Mitsunobu or alkylation chemistry at the phenolic position (after removal of the carbonate) and via organo lithium chemistry at the nitrogen position after deacetylation, hence leading to a large variety of novel, trisubstituted quindolines available for biological evaluation and additional structure–activity relationships. Full details of all of the biological studies and computer modelling will be reported in due course.



Scheme 5. (I) $ClCO_2Me$, Pyridine, 0 °C, 3 h, 79%; (II) H_2SO_4, HNO_3, −10 °C, 1 h, 74%; (III) Fe/AcOH, EtOH, 80 °C, 1 h, 88%; (IV), DMF, molecular sieves, 18 h, 60 °C, 43%.

3. Conclusion

The best compounds in the present series, **6a** and **6b**, are active as G-quadruplex stabilisers, but still markedly less active than the potent trisubstituted acridine BRACO-19.[13] However, **6a**,**b** have a greater selectivity for quadruplex DNA over duplex DNA, suggesting that if suitable modifications could be designed to enhance telomerase and quadruplex potency, then these could result in highly selective molecules. The new quindoline **13** is appropriately

substituted to produce a large array of analogues to probe further the structural requirements for selective G-quadruplex binding and telomerase inhibitory activity, and these studies are underway.

4. Experimental

4.1. General

^{1}H NMR spectra were obtained using a Bruker 300 NMR Avance DPX spectrometer or a Bruker DRX Avance spectrometer at 300 MHz and 500 MHz, respectively. ^{13}C NMR spectra were recorded at a frequency of 125 MHz on a Bruker Avance DRX spectrometer. ^{1}H–^{13}C NMR Correlation experiments were carried out on a Bruker Avance DRX spectrometer. Chemical shifts (δ) are given in part per million (ppm). Coupling constants (J) are given in hertz (Hz). Mass spectra were recorded on a VG Autospec instrument for chemical ionisation (CI) technique, and a VG Autospec instrument or a Micromass GCT Premier instrument for electron impact (EI). A VG Quattro spectrometer or a LCT Premier (Micromass) was used for the electrospray method. Infrared spectra were obtained on a Perkin–Elmer Spectrum RX I FTIR System instrument. Melting points were taken on a Gallenkamp® apparatus and are uncorrected.

4.1.1. 1-(4′-Methyl-piperazine)propenone 3. *N*-Methylpiperazine (10 mL, 90 mmol, 2.5 equiv) was added to DCM (55 mL) and the resulting solution lowered to 0 °C. Acryloyl chloride (2.92 mL, 36 mmol) was added drop-wise with care. The mixture was stirred at 0 °C for 2 h and the organic layer was then washed with water (2×50 mL), separated and dried. The solvent was evaporated to yield **3** as an orange oil (2.43 g, 44%). IR (film) ν: 2938 and 2793 (CH, alkene), 1649 (C═O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.27 (3H, s, –CH_3), 2.37 (4H, t, $J_{3'-2'}$ 5, H-3′), 3.52–3.66 (4H, br m, H-2′), 5.65 (1H, dd, $J_{Hb\text{-}2}$ 10.5, J_{b-a} 2, H-b), 6.24 (1H, dd, $J_{Ha\text{-}2}$ 16.5, J_{a-b} 2, H-a), 6.52 (1H, m, $J_{2\text{-}Ha}$ 16.5, $J_{2\text{-}Hb}$ 10.5, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.3 and 46.1 (2C, C-2′), 46.4 (–CH_3), 55.0 and 55.6 (2C, C-3′), 128.1 (2C, C-1 and C-2), 165.8 (C-3); *m*/*z* (EI): 154 (M+, 27%), 125 (13), 110 (15), 99 (63), 83 (30), 70 (100), 56 (77). HRMS (EI) found: 154.1102 ($C_8H_{14}N_2O$ requires: 154.1106).

4.1.2. 2,7-Bis[2′-*N*-(7′-methyl-piperazine)carbonylvinyl]-10*H*-indolo[3,2-*b*]quinoline 4. 10-Acetyl-2,7-bis-(bromo)-indolo[3,2-*b*]quinoline **1** (1 g, 2.4 mmol), tri-(*o*-tolyl)-phosphine (0.22 g, 0.72 mmol, 0.3 equiv), 1-(4′-methyl-piperazine)propenone **3** (1.1 g, 7.2 mmol, 3 equiv), palladium acetate (75 mg, 0.24 mmol, 0.1 equiv) and triethylamine (2 mL) were added to DMF (20 mL). The mixture was set to reflux overnight and then cooled to room temperature. The mixture was then filtered on Celite to remove the palladium residue. Ethyl acetate was added (100 mL) and the organic layer washed with water (2×100 mL) and brine (100 mL). It was then separated and dried. The solvent was evaporated yielding a residue, which was purified by column chromatography (DCM/MeOH/TEA, 50:50:1) and then recrystallised from ethyl acetate to yield **4** as a yellow amorphous solid (0.81 g, 65%). IR (KBr disk) ν: 3420 (N–H), 1643 (C═O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (6H, s, –CH_3), 2.50 (8H, br s, H-6′), 3.75–3.82 (8H, br m, H-5′ and H-5″), 7.05 (2H, m, $J_{2'-1'}$=$J_{2''-1''}$ 15.5, H-2′ and H-2″), 7.47 (1H, d, J_{9-8} 8, H-9), 7.73 (1H, dd, J_{8-9} 8, J_{8-6} 1.5, H-8), 7.87–7.91 (3H, m, H-1′, H-1″ and H-3), 7.96 (1H, s, H-1), 8.07 (1H, s, H-1), 8.28 (1H, d, J_{4-3} 8, H-4), 8.75 (1H, s, H-6), 8.76 (1H, s, N–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.6 and 46.2 (4C, C-6′ and C-6″), 46.4 (2C, –CH_3), 55.2 and 55.7 (4C, C-5′ and C-5″), 111.8 (C-9), 114.6 (C-11), 115.7 (2C, C-2′ and C-2″), 117.9, 120.9 (C-6), 124.6 (C-1′ and C-1″ or C-3), 127.5, 128.5, 129.6 (C-1), 130.3 (C-4), 131.6 (C-6), 132.8, 133.7, 142.9, 143.6 (C-1′ and C-1″ or C-3), 144.9, 147.0, 165.9 and 166.2 (C-3′ and C-3″); *m*/*z* (FAB): 523 (M+1, 95%), 423 (100), 396 (15), 295 (20), 267 (14), 154 (47), 136 (40), 127 (21). HRMS (FAB) found: 523.2829 ($C_{31}H_{34}N_6O_2$ requires: 523.2822).

4.1.3. 2,7-Bis-[2′,2″-*N*-(7′,7″-methyl-piperazinyl)carbonylethyl]-10*H*-indolo[3,2-*b*]quinoline 5. 2,7-Bis[2′-*N*-(7′-methyl-piperazine)carbonylvinyl]-10*H*-indolo[3,2-*b*]quinoline **4** (0.25 g, 0.47 mmol) was added to methanol together with ammonium formate (0.6 g, 9.5 mmol, 20 mol %) and 10% palladium on carbon (50 mg, 20% by weight). The mixture was refluxed overnight and then cooled to room temperature. The reaction mixture was filtered and the filtrate treated with chloroform to precipitate the excess ammonium formate. The mixture was filtered once more and the solvent evaporated to yield a yellow residue, which was purified by column chromatography (DCM/MeOH/Et_3N, 50:50:1) to give 2,7-bis-[2′,2″-*N*-(7′,7″-methyl-piperazinyl)carbonylethyl]-10*H*-indolo[3,2-*b*]quinoline **5** as a yellow waxy oil (0.24 g, 97%). IR (KBr disk) ν: 3436 (N–H), 1644 (C═O), 1455 (–CH_2–); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 (3H, s, H-8′ or H-8″), 2.25 (3H, s, H-8′ or H-8″), 2.29–2.37 (8H, m, H-6′ and H-6″), 2.74–2.77 (4H, m, H-1′ and H-1″), 3.15–3.21 (4H, m, H-2′ and H-2″), 3.41–3.44 (4H, m, H-5$_b$′ and H-5$_b$″), 3.65–3.68 (4H, m, H-5a′ and H-5a″), 7.37 (1H, d, J_{9-8} 8.5, H-9), 7.46 (1H, dd, J_{8-9} 8.5, J_{8-6} 2, H-8), 7.51 (1H, dd, J_{3-4} 8.5, J_{3-1} 2, H-3), 7.72 (1H, d, J_{1-3} 2, H-1), 7.93 (1H, s, H-11), 8.22 (1H, d, J_{4-3} 8.5, H-4), 8.34 (1H, d, J_{6-8} 2, H-6), 8.44 (1H, s, N–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.8 and 32.1 (2C, C-2′ and C-2″), 35.2 and 36.0 (2C, C-1′ and C-1″), 42.0 (2C, C-5$_a$′ and C-5$_a$″), 45.9 (2C, C-5$_b$′ and C-5$_b$″), 46.3 (2C, C-8′ and C-8″), 55.1 and 55.4 (4C, C-6′ and C-6″), 111.4 (C-9), 113.2 (C-11), 121.5 (C-6), 122.7, 126.3 (C-1), 127.5, 128.2 (C-3), 129.7 (C-4), 131.1 (C-8), 133.5, 133.6, 138.6, 142.7, 143.7, 146.4, 171.0 and 171.2 (2C, C-3′ and C-3″); *m*/*z* (FAB): 527 (M+1, 100%), 456 (15), 399 (17), 271 (15), 257 (20), 133 (49). HRMS (FAB) found: 527.3143 ($C_{31}H_{38}N_6O_2$ requires: 527.3135).

4.1.4. 2,7-Bis-[3′,3″-*N*-(7′,7″-methyl-piperazinyl)propyl]-10*H*-indolo[3,2-*b*]quinoline 2c. 2,7-Bis-[2′,2″-*N*-(7′,7″-methyl-piperazinyl)carbonylethyl]-10*H*-indolo[3,2-*b*]quinoline **5** (0.23 g, 0.44 mmol) was dissolved in THF (2.5 mL). A solution of lithium aluminium hydride (1 M in THF, 4.4 mL, 4.4 mmol) was added carefully at 0 °C and the mixture was then refluxed for 30 min. The reaction mixture was quenched with water (0.17 mL), then with a solution of 15% aqueous sodium hydroxide solution (0.17 mL) and finally with more water (0.51 mL). THF (2 mL) was added and the mixture refluxed for a further 20 min. After a hot filtration of the precipitate, the filtrate was evaporated to give 2,7-bis-[3′,3″-*N*-(7′,7″-methyl-piperazinyl)propyl]-10*H*-indolo[3,2-*b*]quinoline

2c as a yellow amorphous solid (0.2 g, 91%). IR (KBr disk) ν: 3414 (N–H), 2937 and 2803 (–CH_2–), 1488 (–CH_2–); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.90–1.98 (4H, m, H-2′ and H-2″), 2.29 (6H, s, 2×N–CH_3), 2.41–2.46 (20H, m, H-3′, H-3″, H-5′, H-5″, H-6′ and H-6″), 2.82–2.87 (4H, m, H-1′ and H-1″), 7.34 (1H, d, J_{9-8} 8, H-9), 7.40 (1H, dd, J_{8-9} 8, J_{8-6} 1.5, H-8), 7.50 (1H, dd, J_{3-4} 8, J_{3-1} 1.5, H-3), 7.67 (1H, s, H-1), 7.91 (1H, s, H-11), 8.17 (1H, s, NH), 8.22 (1H, d, J_{4-3} 8, H-4), 8.33 (1H, s, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.9 and 29.7 (2C, C-2′ and C-2″), 34.1 and 34.2 (2C, C-1′ and C-1″), 46.5 (2C, 2×N–CH_3), 53.6 and 55.6 (8C, 2×C-5′, 2×C-5″, 2×C-6′ and 2×C-6″), 58.4 (2C, C-3′ and C-3″), 111.9 (C-9), 113.0 (C-11), 121.7 (C-6), 122.8, 125.8 (C-1), 127.4, 128.6 (C-3), 129.5 (C-4), 130.7 (C-8), 133.4, 134.7, 139.6, 142.3, 143.7, 146.4; *m/z* (FAB): 499 (M+1, 100%), 455 (7), 385 (15), 372 (17), 307 (28), 147 (10), 136 (17). HRMS (FAB) found: 499.3538 ($C_{31}H_{43}N_6$ requires: 499.3549).

4.1.5. 3-Pyrrolidinyl-methyl-propanoate 8a. Methyl acrylate (12.1 g, 12.6 mL, 141 mmol) was added to DCM (150 mL). The solution was brought to 0 °C. Pyrrolidine (10 g, 11.7 mL, 141 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to yield **8a** as a yellow oil (21.95 g, 99%). IR (film) ν: 2958 (–CH_2–), 1741 (C═O), 1203 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78 (4H, t, J_{b-a} 5.2, H-b), 2.52 (6H, m, H-3, H-a), 2.78 (2H, t, J_{2-3} 7.4, H-2), 3.69 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.5 (2C, C-b), 34.0 (C-3), 54.0 (2C, C-a), 52.1 (C-2), 52.2 (OCH_3), 173.0 (C═O); *m/z* (EI): 157 (M+, 9%), 84 (100), 82 (7), 70 (6), 55 (11). HRMS (EI) found: 157.1109 ($C_8H_{15}O_2N$ requires: 157.1103).

4.1.6. 3-Piperidinyl-methyl-propanoate 8b. Methyl acrylate (5.06 g, 5.29 mL, 58.7 mmol) was added to DCM (80 mL). The solution was brought to 0 °C. Piperidine (5 g, 5.81 mL, 58.7 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to yield **8b** as a yellow oil (8.95 g, 98%). IR (film) ν: 2936 (–CH_2–), 1741 (C═O), 1155 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41–1.43 (2H, m, J_{c-b} 5.5, H-c), 1.55–1.59 (4H, m, J_{b-c}=J_{b-a} 5.5, H-b), 2.39 (4H, br s, H-a), 2.49–2.52 (2H, t, J_{2-3} 7, H-2), 2.64–2.74 (2H, t, J_{3-2} 7, H-3), 3.67 (3H, s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9 (C-c), 26.1 (2C, C-b), 31.9 (C-2), 51.5 (OCH_3), 54.3 (3C, C-a and C-3), 173.1 (C═O); *m/z* (EI): 171 (M+, 8%), 98 (100), 96 (12), 84 (12), 68 (10), 57 (10). HRMS (EI) found: 171.1258 ($C_9H_{17}O_2N$ requires: 171.1259).

4.1.7. 3-Morpholinyl-methyl-propanoate 8c. Methyl acrylate (4.94 g, 5.17 mL, 57.4 mmol) was added to DCM (80 mL). The solution was brought to 0 °C. Morpholine (5 g, 5.01 mL, 57.4 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to yield **8c** as a yellow oil (8.24 g, 84%). IR (film) ν: 2954 (–CH_2–), 1739 (C═O), 1182 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.44–2.46 (4H, t, J_{a-b} 4.5, H-a), 2.49–2.52 (2H, t, J_{2-3} 7, H-2), 2.67–2.70 (2H, t, J_{3-2} 7, H-3), 3.68–3.70 (7H, m, H-b and OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.9 (C-2), 51.6 (2C, C-b), 53.4 (2C, C-a), 54.0 (C-3), 66.9 (OCH_3), 172.8 (C-1); *m/z* (EI): 173 (M+, 7%), 124 (5), 109 (5) 100 (100), 98 (13), 86 (6), 69 (8), 54 (26). HRMS (EI) found: 173.1055 ($C_8H_{15}O_3N$ requires: 173.1052).

4.1.8. 3-Pyrrolidinyl-propan-1-ol 9a. 3-Pyrrolidinyl-methyl-propanoate **8a** (21 g, 134 mmol) was added to dry diethyl ether (150 mL) and the solution brought to 0 °C. A solution of lithium aluminium hydride (5.08 g, 134 mmol, 1 equiv) in dry diethyl ether (80 mL) was slowly added. The reaction mixture was left stirring at room temperature for 2 h. The mixture was quenched with water (5.08 mL), then a solution of 15% aqueous sodium hydroxide (5.08 mL) and finally more water (15 mL). Dichloromethane was added (90 mL) and the mixture stirred until the formation of a white precipitate. The precipitate was filtered off and the filtrate evaporated to give **9a** as a yellow oil (16.4 g, 95%). IR (film) ν: 3367 (–OH), 2952 (–CH_2–), 1136 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.71–1.76 (6H, m, H-2, H-b), 2.55 (4H, t, J_{a-b} 5.5, H-a), 2.72 (2H, t, J_{3-2} 5.9, H-3), 3.80 (2H, t, J_{1-2} 5.3, H-1), 5.30 (1H, s, –OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.4 (2C, C-b), 29.3 (C-2), 54.2 (2C, C-a), 56.2 (C-3), 64.7 (C-1); *m/z* (EI): 129 (M+, 7%), 111 (6). 85 (6), 84 (100), 70 (12), 68 (6), 57 (14), 55 (22). HRMS (EI) found: 129.1155 ($C_7H_{15}NO$ requires: 129.1154).

4.1.9. 3-Piperidinyl-propan-1-ol 9b. 3-Piperidinyl-methyl-propanoate **8b** (7 g, 41.4 mmol) was added to dry diethyl ether (50 mL) and the solution brought to 0 °C. A solution of lithium aluminium hydride (1.57 g, 41.4 mmol, 1 equiv) in dry diethyl ether (27 mL) was slowly added. The reaction mixture was left stirring at room temperature for 2 h. The mixture was quenched with water (1.57 mL), then a solution of 15% aqueous sodium hydroxide (1.57 mL) and finally more water (4.71 mL). Dichloromethane was added (30 mL) and the mixture stirred until the formation of a white precipitate. The precipitate was filtered off and the filtrate evaporated to yield **9b** as a yellow oil (4.76 g, 80%). IR (film) ν: 3369 (–OH), 2934 (–CH_2–), 1120 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44–1.46 (2H, m, H-c), 1.55–1.59 (4H, m, J_{b-c}=J_{b-a} 5.5, H-b), 1.68–1.72 (2H, m, J_{2-3}=J_{2-1} 5.5, H-2), 2.45 (4H, br s, H-a), 2.54–2.56 (2H, t, J_{3-2} 5.5, H-3), 3.77–3.79 (2H, t, J_{1-2} 5.5, H-1), 5.92 (1H, s, –OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.6 (C-c), 46.3 (C-2), 53.6 (2C, C-b), 55.4 (2C, C-a), 58.9 (C-3), 64.6 (C-1); *m/z* (EI): 143 (M+, 6%), 124 (4), 110 (4), 98 (100), 84 (9), 69 (7), 54 (6). HRMS (EI) found: 143.1306 ($C_8H_{17}ON$ requires: 143.1310).

4.1.10. 3-Morpholinyl-propan-1-ol 9c. 3-Morpholinyl-methyl-propanoate **8c** (7.3 g, 42.2 mmol) was added to dry diethyl ether (50 mL) and the solution brought to 0 °C. A solution of lithium aluminium hydride (1.61 g, 42.2 mmol, 1 equiv) in dry diethyl ether (25 mL) was slowly added. The reaction mixture was left stirring at room temperature for 2 h. The mixture was quenched with water (1.61 mL), then a solution of 15% aqueous sodium hydroxide (1.61 mL) and finally more water (4.83 mL). Dichloromethane was added (30 mL) and the mixture stirred until the formation of a white precipitate. The precipitate was filtered off and the filtrate evaporated to leave **9c** as a yellow oil (3.46 g, 57%). IR (film) ν: 3401 (–OH), 2954 (–CH_2–), 1118 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.71–1.75 (2H, m, J_{2-3}=J_{2-1} 5.5, H-2), 2.53 (4H, br s, H-a), 2.60–2.63 (2H, t, J_{3-2} 5.5, H-3), 3.70–3.72 (4H, m, H-b), 3.79–3.82 (2H, t, J_{1-2} 5.5, H-1); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.3 (C-2),

54.2 (2C, C-a), 57.4 (C-3), 64.9 (C-1), 67.3 (2C, C-b); *m/z* (EI): 145 (M+, 7%), 100 (100), 86 (9), 71 (6), 69 (21), 56 (9), 54 (56). HRMS (EI) found: 145.1099 ($C_7H_{15}NO_2$ requires: 145.1103).

4.1.11. 1-Bromo-4-(3′-pyrrolidinyl-propoxy)-benzene 10a. 3-Pyrrolidinyl-propan-1-ol **9a** (5 g, 39 mmol) was added to DCM (53 mL) and the solution lowered to 0 °C. Thionyl chloride (5.65 mL, 78 mmol, 2 equiv) was added slowly and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to yield 3-pyrrolidinyl-1-chloropropane (6 g, 85%) as a yellow oil. 4-Bromo-phenol (5 g, 27.2 mmol, 1 equiv), caesium carbonate (26.6 g, 81.5 mmol, 3 equiv), sodium iodide (4.08 g, 27.2 mmol, 1 equiv) and the chloro intermediate (5 g, 27.2 mmol) were added to dry DMF (35 mL). The reaction mixture was heated to reflux overnight and then cooled to room temperature. The precipitate was filtered off and the organic layer was washed with brine (100 mL) and 2 M sodium hydroxide solution (100 mL), then separated and dried. The solvent was evaporated to yield **10a** as a brown solid (7.08 g, 92%). Mp 39–40 °C; IR (KBr disk) *ν*: 2966 (–CH_2–), 2779 (–CH_2–), 1246 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 1.79–1.80 (4H, m, H-b), 1.98–2.02 (2H, m, H-2′), 2.51–2.53 (4H, m, H-a), 2.59–2.62 (2H, t, $J_{3'-2'}$ 7.5, H-3′), 3.98–4.00 (2H, t, $J_{1'-2'}$ 6.5, H-1′), 6.77–6.79 (2H, d, J_{3-2} 7, H-3), 7.34–7.36 (2H, d, J_{2-3} 7, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 23.5 (2C, C-b), 28.8 (C-2′), 53.1 (C-3′), 54.3 (2C, C-a), 66.7 (C-1′), 112.7 (C-1), 116.4 (2C, C-3), 132.2 (2C, C-2), 158.2 (C-4); *m/z* (EI): 285 (M+, 97%), 283 (100), 185 (22), 172 (15), 157 (31), 145 (42), 119 (11), 110 (33), 99 (16). HRMS (EI) found: 283.0573 (^{79}Br, $C_{13}H_{18}NOBr$ requires: 283.0572).

4.1.12. 1-Bromo-4-(3′-piperidinyl-propoxy)-benzene 10b. 3-Piperidinyl-propan-1-ol **9b** (4.2 g, 24.9 mmol) was added to DCM (40 mL) and the solution brought to 0 °C. Thionyl chloride (4.28 mL, 58.8 mmol, 2 equiv) was added slowly and reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to yield 3-piperidinyl-1-chloropropane (4.5 g, 91%) as a yellow oil. 4-Bromo-phenol (3.49 g, 20.22 mmol, 1 equiv), caesium carbonate (19.76 g, 60.6 mmol, 3 equiv), sodium iodide (3.03 g, 20.2 mmol, 1 equiv) and the chloro intermediate (4 g, 20.2 mmol) were added to dry DMF (25 mL). The reaction mixture was heated to reflux overnight and the mixture was then cooled to room temperature. The precipitate was filtered off and the organic layer was washed with brine (100 mL) and 2 M sodium hydroxide solution (100 mL), then separated and dried. The solvent was evaporated to yield **10b** as a brown solid (5.21 g, 87%). Mp 40–42 °C; IR (KBr disk) *ν*: 2938 and 2763 (–CH_2–), 1246 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 1.44–1.45 (2H, m, H-c), 1.56–1.60 (4H, m, J_{b-a}=J_{b-c} 5.5, H-b), 1.93–1.98 (2H, m, $J_{2'-3'}$=$J_{2'-1'}$ 6.5, H-2′), 2.39 (4H, br s, H-a), 2.44–2.47 (2H, t, $J_{3'-2'}$ 6.5, H-3′), 3.96–3.98 (2H, t, $J_{1'-2'}$ 6.5, H-1′), 6.77–6.79 (2H, d, J_{3-2} 9, H-3), 7.34–7.36 (2H, J_{2-3} 9, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 24.5 (C-c), 26.0 (2C, C-b), 26.8 (C-2′), 54.7 (2C, C-a), 55.9 (C-3′), 66.8 (C-1′), 112.7 (C-1), 116.4 (2C, C-3), 132.2 (2C, C-2), 158.2 (C-4); *m/z* (EI): 299 (M+, 4%), 297 (5), 143 (5), 124 (5), 98 (100), 85 (12), 69 (12). HRMS (EI) found: 297.0743 (^{79}Br, $C_{14}H_{20}NOBr$ requires: 297.0728).

4.1.13. 1-Bromo-4-(3′-morpholinyl-propoxy)-benzene 10c. 3-Morpholinyl-propan-1-ol **9c** (3.25 g, 22.4 mmol) was added to DCM (30 mL) and the solution brought to 0 °C. Thionyl chloride (3.27 mL, 44.8 mmol, 2 equiv) was added slowly and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to yield 3-morpholinyl-1-chloropropane (4.3 g, 96%) as a yellow oil. 4-Bromo-phenol (3.68 g, 21.25 mmol, 1 equiv), caesium carbonate (20.78 g, 63.75 mmol, 3 equiv), sodium iodide (3.19 g, 21.25 mmol, 1 equiv) and the chloro intermediate (4.25 g, 21.25 mmol) were added to dry DMF (25 mL). The reaction mixture was heated to reflux and left overnight. The mixture was then cooled to room temperature. The precipitate was filtered off and the organic layer was washed with brine (100 mL) and 2 M sodium hydroxide solution (100 mL), then separated and dried. The solvent was evaporated to yield **10c** as a brown solid (3.89 g, 61%). Mp 57–58 °C; IR (KBr disk) *ν*: 2939 and 2815 (–CH_2–), 1245 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 1.93–1.99 (2H, m, $J_{2'-3'}$=$J_{2'-1'}$ 7.5, H-2′), 2.46 (4H, br s, H-a), 2.49–2.52 (2H, t, $J_{3'-2'}$ 7.5, H-3′), 3.71–3.73 (4H, t, J_{b-a} 4.5, H-b), 3.98–4.00 (2H, t, $J_{1'-2'}$ 7.5, H-1′), 6.77–6.79 (2H, d, J_{3-2} 8.5, H-3), 7.35–7.37 (2H, d, J_{2-3} 8.5, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 26.4 (C-2′), 53.8 (2C, C-a), 55.5 (C-3′), 66.4 (C-1′), 67.0 (2C, C-b), 112.8 (C-1), 116.3 (C-3), 132.2 (C-2), 158.1 (C-4); *m/z* (EI): 301 (M+, 32%), 299 (28), 172 (5), 157 (9), 143 (11), 128 (11), 100 (100), 98 (21), 87 (13), 70 (56), 63 (15), 57 (7). HRMS (EI) found: 299.0527 (^{79}Br, $C_{13}H_{18}NO_2Br$ requires: 299.0521).

4.1.14. 4-(3′-Pyrrolidinyl-propoxy)phenyl-boronic acid 7a. 1-Bromo-4-(3′-pyrrolidinyl-propoxy)-benzene **10a** (4.7 g, 16.5 mmol) was added to dry THF (75 mL). The solution was lowered to −78 °C using a dry ice bath. Butyl lithium solution (2.5 M) in hexane (9.96 mL, 24.8 mmol, 1.5 equiv) was added and the reaction mixture stirred for 45 min. Triisopropylborate (11.47 mmol, 49.6 mmol, 3 equiv) was added and the solution was allowed to warm to room temperature overnight. Saturated ammonium chloride solution (150 mL) was added, followed by ethyl acetate (150 mL). The aqueous layer was further extracted with ethyl acetate (2×100 mL) and the organic layer was separated and dried. The solvent was evaporated to yield a clear residue. The residue was washed with diethyl ether to yield a white precipitate, which was filtered to give **7a** as a white solid (2.82 g, 68%). Mp 58–60 °C (decomp.); IR (KBr disk) *ν*: 3435 (–OH), 1602 (CH aromatic), 1238 (C–O); ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 1.73–1.75 (4H, m, H-b), 1.92–1.95 (2H, m, H-2′), 2.61–2.63 (4H, m, H-a), 2.67–2.71 (2H, t, $J_{3'-2'}$ 7.5, H-3′), 4.02–4.04 (2H, t, $J_{1'-2'}$ 6, H-1′), 6.87–6.89 (2H, d, J_{3-2} 8.5, H-3), 7.72–7.74 (2H, d, J_{2-3} 8.5, H-2); ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 23.4 (2C, C-b), 28.0 (C-2′), 52.4 (C-3′), 53.9 (2C, C-a), 65.7 (C-1′), 113.8 (2C, C-3), 114.8 (C-1), 136.2 (2C, C-2), 158.3 (C-4); *m/z* (electrospray): 264.4 (M+15, 78%), 250.4 (M+1, 100), 206.4 (16), 137.2 (12), 116.2 (15), 103.1 (8).

4.1.15. 4-(3′-Piperidinyl-propoxy)phenyl-boronic acid 7b. 1-Bromo-4-(3′-piperidinyl-propoxy)-benzene **10b** (4.5 g, 15.1 mmol) was added to dry THF (70 mL). The solution was lowered to −78 °C using a dry ice bath. Butyl lithium solution (2.5 M) in hexane (9.06 mL, 15.1 mmol, 1.5 equiv) was added and the reaction mixture stirred for 45 min.

Triisopropylborate (10.6 mL, 45.3 mmol, 3 equiv) was added and the solution was allowed to warm to room temperature overnight. Saturated ammonium chloride solution (150 mL) was added, followed by ethyl acetate (150 mL). The aqueous layer was further extracted with ethyl acetate (2×100 mL) and the organic layer was separated and dried. The solvent was evaporated to yield a clear residue. The residue was washed with diethyl ether to yield a white precipitate, which was filtered to give **7b** as a white solid (2.35 g, 59%). Mp 82–84 °C (decomp.); IR (KBr disk) *ν*: 3410 (–OH), 1602 (CH aromatic), 1238 (C–O); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.39–1.40 (2H, m, H-c), 1.49–1.53 (4H, m, J_{b-a}=J_{b-c} 5.5, H-b), 1.84–1.90 (2H, m, $J_{2'-3'}$=$J_{2'-1'}$ 6.5, H-2′), 2.37–2.43 (6H, m, H-a and H-3′), 4.00–4.02 (2H, t, $J_{1'-2'}$ 6.5, H-1′), 6.87–6.89 (2H, d, J_{3-2} 9, H-3), 7.71–7.73 (2H, d, J_{2-3} 9, H-2), 7.87 (2H, s, –O*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.4 (C-c), 25.8 (2C, C-b), 26.5 (C-2′), 54.4 (2C, C-a), 55.5 (C-3′), 65.9 (C-1′), 113.7 (C-1), 113.8 (2C, C-3), 136.2 (2C, C-2), 160.7 (C-4); *m*/*z* (electrospray): 278.4 (M+15, 80%), 264 (100), 220 (7), 137 (3), 105 (3).

4.1.16. 4-(3′-Morpholinyl-propoxy)phenyl-boronic acid 7c. 1-Bromo-4-(3′-morpholinyl-propoxy)-benzene **10c** (3.5 g, 11.7 mmol) was added to dry THF (56 mL). The solution was lowered to −78 °C using a dry ice bath. Butyl lithium solution (2.5 M) in hexane (7 mL, 17.5 mmol, 1.5 equiv) was added and the reaction mixture stirred for 45 min. Triisopropylborate (8.19 mL, 35 mmol, 3 equiv) was added and the solution was allowed to warm to room temperature overnight. Saturated ammonium chloride solution (150 mL) was added, followed by ethyl acetate (150 mL). The aqueous layer was further extracted with ethyl acetate (2×100 mL) and the organic layer was separated and dried. The solvent was evaporated to yield a clear residue. The residue was washed with diethyl ether to yield a white precipitate, which was filtered to give **7c** as a white solid (2.42 g, 78%). Mp 62–63 °C (decomp.); IR (KBr disk) *ν*: 3427 (–OH), 1602 (CH aromatic), 1239 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.87–1.89 (2H, m, H-2′), 2.40–2.43 (6H, m, H-a and H-3′), 3.59 (4H, br s, H-b), 4.01–4.03 (2H, t, $J_{1'-2'}$ 6, H-1′) 6.87–6.89 (2H, d, J_{3-2} 8.5, H-3), 7.72–7.73 (2H, d, J_{2-3} 8.5, H-2), 7.85 (2H, s, –OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.1 (C-2′), 53.7 (2C, C-a), 55.2 (C-3′), 65.8 (C-1′), 66.5 (2C, C-b), 113.7 (C-1), 113.8 (C-3), 136.2 (C-2), 160.7 (C-4); *m*/*z* (electrospray): 280.5 (M+15, 30%), 266.5 (M+1, 80), 238.5 (17), 222.5 (100), 211.3 (12).

4.1.17. 1-Bromo-4-(3′-bromo-propoxy)-benzene 11. 4-Bromo-phenol (4 g, 23.1 mmol) and triphenylphosphine (6.74 g, 25.4 mmol, 1.1 equiv) were added to dry THF (96 mL). Diisopropylazodicarboxylate (5.14 g, 5.01 mL, 25.4 mmol, 1.1 equiv) was added drop-wise with care. The mixture was stirred at room temperature for 15 min then 3-bromopropanol (3.22 g, 2.09 mL, 25.4 mmol, 1 equiv) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated to yield a crude product, which was purified by column chromatography (petroleum ether, 100%) to yield **11** as a white solid (5.29 g, 62%). Mp 58–59 °C; IR (KBr disk) *ν*: 2958 and 2930 (–CH_2), 1489 (–CH_2–), 1241 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36–2.40 (2H, m, $J_{2'-3'}$=$J_{2'-1'}$ 6, H-2′), 3.66–3.69 (2H, t, $J_{3'-2'}$ 6, H-3′), 4.13–4.16 (2H, t, $J_{1'-2'}$ 6, H-1′), 6.87 (2H, d, J_{3-2} 9, H-3), 7.46 (2H, d, J_{2-3} 9, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.3 (C-3′), 30.7 (C-2′), 64.1 (C-1′), 111.6 (C-1), 114.8 (2C, C-3), 130.8 (2C, C-2), 156.3 (C-4); *m*/*z* (EI): 296 (M+, 45%), 294 (80), 174 (97), 172 (100), 143 (20), 121 (17), 93 (21), 76 (19), 63 (43). HRMS (EI) found: 291.9095 (^{79}Br, $C_9H_{10}Br_2O$ requires: 291.9098).

4.1.18. 1-Bromo-4-[3′-(4″-methyl-piperazinyl)-propoxy]-benzene 12. 1-Bromo-4-(3′-bromo-propoxy)-benzene **11** (4.5 g, 15.3 mmol) was added to dry DCM (90 mL). 4-Methyl-piperazine (1.84 g, 2.04 mL, 18.4 mmol, 1.2 equiv) was added. The mixture was stirred at room temperature for 4 h and the reaction mixture was then washed with water (2×100 mL). The solvent was evaporated to yield a brown solid, which was purified by column chromatography to yield **12** as a brown amorphous solid (2.1 g, 44%). IR (KBr disk) *ν*: 2938 and 2795 (–CH_2–), 1489 (–CH_2–), 1245 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.94–1.97 (2H, m, $J_{2'-1'}$=$J_{2'-3'}$ 7.5, H-2′), 2.29 (3H, s, N–C*H*$_3$), 2.42 (8H, br s, H-2″ and H-3″), 2.50–2.53 (2H, t, $J_{3'-2'}$ 7.5, H-3′), 3.96–3.99 (2H, t, $J_{1'-2'}$ 7.5, H-1′), 6.77 (2H, d, J_{3-2} 9, H-3), 7.36 (2H, d, J_{2-3} 9, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.1 (C-2′), 44.5 (N*C*H$_3$), 51.7 and 53.6 (C-2″ and C-3″), 53.5 (C-3′), 111.1 (C-1), 114.8 (2C, C-3), 130.6 (2C, C-2), 156.6 (C-4); *m*/*z* (EI): 314 (M+, 66%), 312 (68), 185 (6), 157 (6), 113 (100), 85 (11), 70 (38), 58 (8). HRMS (EI) found: 312.0839 (^{79}Br, $C_{14}H_{21}N_2OBr$ requires: 312.0837).

4.1.19. 4-[3′-(4″-Methyl-piperazinyl)-propoxy]phenyl-boronic acid 7d. 1-Bromo-4-[3′-(4″-methyl-piperazinyl)-propoxy]-benzene **12** (1.46 g, 4.7 mmol) was added to dry THF (25 mL). The solution was lowered to −78 °C using a dry ice bath. *n*-Butyl lithium solution (2.5 M) in hexane (2.8 mL, 6.99 mmol, 1.5 equiv) was added and the reaction mixture stirred for 45 min. Triisopropylborate (3.27 mL, 14 mmol, 3 equiv) was added and the solution was allowed to warm to room temperature overnight. Saturated ammonium chloride solution (50 mL) was added, followed by ethyl acetate (100 mL). The aqueous layer was further extracted with ethyl acetate (2×50 mL) and the organic layer was separated and dried. The solvent was evaporated to yield a clear residue. The residue was washed with diethyl ether to yield a white precipitate, which was filtered to give **7d** as a white solid (0.71 g, 55%). Mp 62–64 °C (decomp.); IR (KBr disk) *ν*: 3411 (–OH), 1602 (CH aromatic), 1241 (C–O); ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.90–1.93 (2H, m, $J_{2'-3'}$=$J_{2'-1'}$ 6.5, H-2′), 2.27 (3H, s, N*C*H$_3$), 2.47–2.50 (10H, m, H-3′, H-2″ and H-3″), 4.03–4.09 (2H, m, $J_{1'-2'}$ 6.5, H-1′), 6.92 (2H, d, J_{3-2} 8.5, H-3), 7.77 (2H, d, J_{2-3} 8.5, H-2), 7.91 (2H, s, –OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.1 (C-2′), 44.3 (N*C*H$_3$), 51.2 and 53.3 (C-2″ and C-3″), 64.4 (C-1′), 112.3 (C-1), 134.8 (4C, C-2 and C-3), 159.2 (C-4); *m*/*z* (electrospray): 293 (M+15, 45%), 279.1 (M+, 95), 235.1 (100), 195 (50), 181 (35), 165 (30).

4.1.20. 2,7-Bis[4′-(3″-*N*-pyrrolidinyl-propoxy)phenyl]-10*H*-indolo[3,2-*b*]quinoline 6a. 10-Acetyl-2,7-bis-(bromo)-indolo[3,2-*b*]quinoline **1** (0.1 g, 0.24 mmol) was added to DME (3 mL) together with tetrakis(triphenylphosphine)-palladium(0) (17 mg, 14.4 mmol, 0.06 equiv) and 4-(3′-pyrrolidinyl-propoxy)phenyl-boronic acid **7a** (0.18 g, 0.72 mmol). Aqueous sodium carbonate solution (2 M, 0.6 mL,

1.2 mmol, 5 equiv) and ethanol (2 mL) were then added. The reaction mixture was heated at reflux for 18 h then cooled to room temperature. Ethyl acetate (50 mL) was added and the organic layer was washed with water (2×100 mL), separated and dried. The solvent was evaporated yielding a yellow solid, which was purified by column chromatography (DCM/MeOH/TEA, 50:50:1) to give **6a** as a yellow solid (86 mg, 57%). Mp 237–238 °C (decomp.); IR (KBr disk) ν: 3436 (N–H), 2936 (–CH_2–), 1607 (CH aromatic) 1477 (–CH_2–), 1244 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82–1.84 (8H, m, H-b), 2.04–2.10 (4H, m, H-2″), 2.61–2.62 (8H, m, H-a), 2.70–2.72 (4H, m, H-3″), 4.07–4.08 (4H, m, H-1″), 6.97–7.01 (4H, m, $J_{3'-2'}$ 8.5, H-3′), 7.46 (1H, d, J_{9-8} 8.5, H-9), 7.63–7.67 (4H, m, $J_{2'-3'}$ 8.5, H-2′), 7.77 (1H, dd, J_{8-9} 8.5, J_{8-6} 1.5, H-8), 7.90 (1H, dd, J_{3-4} 9, J_{3-1} 2, H-3), 8.02 (2H, br s, H-1 and H-11), 8.36 (1H, d, J_{4-3} 9, H-4), 8.57 (1H, s, N–H), 8.71 (1H, d, J_{6-8} 1.5, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.5 (4C, C-a), 28.7 (2C, C-2″), 53.2 (2C, C-3″), 54.2 (4C, C-a), 66.4 (2C, C-1′), 111.2 (C-9), 113.3 (C-1 or C-11), 115.0 (4C, C-3′), 119.8 (C-6), 122.8, 124.0 (C-1 or C-11), 126.3 (C-3), 127.4, 128.4 (4C, C-2′), 129.5 (C-4), 133.3, 133.5 (2C, C-1′), 133.8, 137.6, 142.7, 143.6, 146.4, 158.2 (2C, C-4′); *m*/*z* (CI): 625.4 (M+1, 100%), 554 (2), 441 (3), 338 (5), 222 (7). HRMS (CI) found: 625.3520 ($C_{41}H_{44}N_4O_2$ requires: 625.3543).

4.1.21. 2,7-Bis[4′-(3″-*N*-piperidinyl-propoxy)phenyl]-10*H*-indolo[3,2-*b*]quinoline 6b. 10-Acetyl-2,7-bis-(bromo)-indolo[3,2-*b*]quinoline **1** (0.1 g, 0.24 mmol) was added to DME (3 mL) together with tetrakis(triphenylphosphine)-palladium(0) (17 mg, 14.4 μmol, 0.06 equiv) and 4-(3′-piperidinyl-propoxy)phenyl-boronic acid **7b** (0.19 g, 0.72 mmol, 3 equiv). Aqueous sodium carbonate solution (2 M, 0.6 mL, 1.2 mmol, 5 equiv) and ethanol (2 mL) were then added. The reaction mixture was heated at reflux for 18 h then cooled to room temperature. Ethyl acetate (50 mL) was added and the organic layer was washed with water (2×100 mL), separated and dried. The solvent was evaporated to yield a yellow solid, which was purified by column chromatography (DCM/MeOH/TEA, 50:50:1) to give **6b** as a yellow solid (94.2 mg, 60%). Mp 210–212 °C (decomp.); IR (KBr disk) ν: 3430 (N–H), 2932 (–CH_2–), 1608 (CH aromatic), 1477(–CH_2–), 1244 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (4H, br s, H-c), 1.69–1.70 (8H, m, H-b), 2.10 (4H, m, H-2″), 2.54–2.63 (12H, m, H-a and H-3″), 4.07–4.10 (4H, m, H-1″), 6.99–7.04 (4H, m, $J_{3'-2'}$ 8.5, H-3′), 7.51 (1H, d, J_{9-8} 8.5, H-9), 7.66–7.69 (4H, m, $J_{2'-3'}$ 8.5, H-2′), 7.81 (1H, dd, J_{8-9} 8.5, J_{8-6} 1.5, H-8), 7.92 (1H, dd, J_{3-4} 9, J_{3-1} 2, H-3), 8.06 (1H, d, J_{1-3} 2, H-1), 8.07 (1H, s, H-11), 8.22 (1H, s, N–H), 8.37 (1H, d, J_{4-3} 9, H-4), 8.72 (1H, s, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.5 (2C, C-c), 26.0 (4C, C-b), 26.9 (2C, C-2″), 54.7 (4C, C-a), 56.0 (2C, C-3″), 66.7 (2C, C-1″), 111.2 (C-9), 113.3 (C-11), 114.9 (4C, C-3′), 119.8 (C-6), 124.0 (C-1), 126.4 (C-3), 127.4, 127.7, 128.3 (4C, C-3′), 128.8 (C-8), 129.6 (C-4), 133.4 (2C, C-1′), 133.8, 137.6, 142.6, 143.7, 146.5, 158.3 (2C, C-4′), 158.9; *m*/*z* (CI): 653.5 (M+1, 100%), 467 (9), 438 (11), 338 (17), 279 (6), 236 (9). HRMS (CI) found: 653.3856 ($C_{43}H_{48}N_4O_2$ requires: 653.3856).

4.1.22. 2,7-Bis[4′-(3″-*N*-morpholinyl-propoxy)phenyl]-10*H*-indolo[3,2-*b*]quinoline 6c. 10-Acetyl-2,7-bis-(bromo)-indolo[3,2-*b*]quinoline **1** (0.2 g, 0.48 mmol) was added to DME (6 mL) together with tetrakis(triphenylphosphine)-palladium(0) (0.034 g, 0.0288 mmol, 0.06 equiv) and 4-(3′-morpholinyl-propoxy)phenyl-boronic acid **7c** (0.38 g, 1.44 mmol, 3 equiv). Aqueous sodium carbonate solution (2 M, 1.2 mL, 2.4 mmol, 5 equiv) and ethanol (4 mL) were then added. The reaction mixture was heated at reflux for 18 h then cooled to room temperature. Ethyl acetate (50 mL) was added and the organic layer was washed with water (2×100 mL), separated and dried. The solvent was evaporated to a yellow solid, which was purified by column chromatography (DCM/MeOH, 50:50) to give **6c** as a yellow solid (0.18 g, 57%). Mp 180–182 °C (decomp.); IR (KBr disk) ν: 3408 (N–H), 2927 and 2852 (–CH_2–), 1606 (CH aromatic), 1242 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06–2.08 (4H, m, H-2″), 2.60 (8H, br s, H-a), 2.64–2.65 (4H, m, H-3″), 3.79–3.81 (8H, m, H-b), 4.07–4.08 (4H, m, H-1″), 6.97–7.02 (4H, m, $J_{3'-2'}$ 8.5, H-3′), 7.48 (1H, d, J_{9-8} 9, H-9), 7.64–7.69 (4H, m, $J_{2'-3'}$ 8.5, H-2′), 7.78 (1H, dd, J_{8-9} 9, J_{8-6} 2, H-8), 7.92 (1H, dd, J_{3-4} 9, J_{3-1} 2, H-3), 8.02 (1H, d, J_{1-3} 2, H-1), 8.05 (1H, s, H-11), 8.38 (1H, d, J_{4-3} 9, H-4), 8.46 (1H, s, N–H), 8.71 (1H, d, J_{6-8} 2, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5 (2C, C-2″), 53.9 (4C, C-a), 56.1 (2C, C-3″), 66.4 (2C, C-1″), 67.0 (4C, C-b), 111.7 (C-9), 113.9 (C-11), 115.3 (2C, C-3′), 120.3 (C-6), 124.4 (C-1), 126.9 (C-3), 127.7, 128.1, 128.6 (2C, C-2′), 129.3 (C-8), 129.8 (C-4), 133.7 (2C, C-1′), 138.0, 143.0, 143.9, 146.7, 158.5 (2C, C-4′), 159.1; *m*/*z* (CI): 657.4 (M+1, 100%), 540 (27), 442 (61), 295 (12), 238 (10), 222 (5). HRMS (CI) found: 657.3437 ($C_{41}H_{44}N_4O_4$ requires: 657.3441).

4.1.23. 2,7-Bis{4′-[3″-*N*-(4‴-methyl-piperazinyl)-propoxy]-phenyl}-10*H*-indolo[3,2-*b*]quinoline 6d. 10-Acetyl-2,7-bis-(bromo)-indolo[3,2-*b*]quinoline **1** (100 mg, 0.24 mmol) was added to DME (3 mL) together with tetrakis(triphenylphosphine)palladium(0) (17 mg, 14.4 μmol, 0.06 equiv) and 4-[3′-(4″-methyl-piperazinyl)-propoxy]phenyl-boronic acid **7d** (200 g, 0.72 mmol, 3 equiv). Aqueous sodium carbonate solution (2 M, 0.6 mL, 1.2 mmol, 5 equiv) and ethanol (2 mL) were then added. The reaction mixture was heated at reflux for 18 h then cooled to room temperature. Ethyl acetate (50 mL) was added and the organic layer was washed with water (2×100 mL), separated and dried. The solvent was evaporated to yield a yellow solid, which was purified by column chromatography (DCM/MeOH, 50:50) to give **6d** as a yellow solid (85 mg, 52%). Mp 238–240 °C (decomp.); IR (KBr disk) ν: 3430 (N–H), 2932 and 2797 (–CH_2–), 1606 (CH aromatic), 1242 (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01–2.04 (4H, m, H-2″), 2.31 (6H, s, N–CH_3), 2.56–2.59 (20H, m, H-3″, H-2‴ and H-3‴), 4.08–4.10 (4H, m, H-1″), 6.99–7.04 (4H, m, $J_{3'-2'}$ 9, H-3′), 7.48 (1H, d, J_{9-8} 8.5, H-9), 7.65–7.70 (4H, m, $J_{2'-3'}$ 9, H-2′), 7.79–7.81 (1H, d, J_{8-9} 8.5, H-8), 7.92 (1H, J_{3-4} 8.5, H-3), 8.04 (1H, s, H-11), 8.05 (1H, br s, H-1), 8.31 (1H, s, N–H), 8.37 (1H, d, J_{4-3} 8.5, H-4), 8.72 (1H, br s, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.3 (2C, C-2″), 44.5 (2C, NCH_3), 51.7 (8C, C-2‴ and C-3‴), 53.6 (2C, C-3″), 64.8 (2C, C-1″), 109.5 (C-9), 111.6 (C-11), 113.4 (4C, C-3′), 118.2 (C-6), 122.4 (C-1), 124.8 (C-3), 125.8, 126.1, 126.9 (4C, C-2′), 127.2 (C-8), 128.0 (C-4), 131.7 (2C, C-1′), 132.2, 136.1, 140.1, 142.1, 144.9, 156.7 (2C, C-4′), 157.2; *m*/*z* (CI): 683.5 (M+1, 56%), 468 (100). HRMS (CI) found: 683.4055 ($C_{43}H_{50}N_6O_2$ requires: 683.40734).

4.1.24. 4-Amino-3-formylphenyl methyl carbonate 14. A solution of methyl 3-formyl-4-nitrophenyl carbonate[11,12] (1 g, 4.44 mmol) in ethanol (30 mL) was treated with reduced iron (1.2 g, 21.5 mmol) and 20% aqueous acetic acid (3.5 mL). The reaction mixture was heated to 80 °C for 1 h. It was then poured in a mixture of ice, salt and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layer was washed with saturated bicarbonate solution (100 mL) followed by brine (100 mL). It was dried over magnesium sulfate and evaporated to give the title compound as a yellow foamy solid (761 mg, 88%). Compound **14** was used without prior purification in the next step. Mp 72–74 °C; IR (KBr disk) *ν*: 3466, 3355, 2958, 1760, 1666, 1218; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 3.89 (3H, s, CH_3), 6.11 (2H, br s, NH_2), 6.62 (1H, d, *J* 9, 5-H), 7.12 (1H, dd, *J* 9, 3, 4-H), 7.29 (1H, d, *J* 3), 9.73 (1H, s, CHO); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 55.8, 117.4, 118.5, 126.8, 129.1, 141.6, 148.5, 155.1, 193.4; *m*/*z* (EI): 195.0538 (M+1, 12%), 85.1021 (68), 71.0859 (100). HRMS (EI) found: 195.0538 ($C_9H_9NO_4$ requires: 195.0532).

4.1.25. 10-Acetyl-7-bromo-10*H*-indolo[3,2-*b*]quinolin-2-yl methyl carbonate 13. Molecular sieves (4 Å) were added to a solution of indole **15** (326 mg, 1.28 mmol) and amino aldehyde **14** (250 mg, 1.28 mmol) in dry DMF (5 mL), and the solution was heated to 60 °C for 18 h. The solvent was co-evaporated with toluene, and the resulting crude product was purified by filtration though a plug of silica gel, followed by two recrystallisation from ethanol, toluene and petroleum ether (40:60). The desired quindoline was obtained as a pale tan solid (227 mg, 43%). Mp 148–150 °C; IR (KBr disk) *ν*: 2958, 1764, 1262; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 2.87 (3H, s, CH_3CO), 3.98 (3H, s, CH_3OCO), 7.56 (1H, dd, *J* 9, 2.5, H-8), 7.68 (1H, dd, *J* 8.5, 2, H-3), 7.75 (1H, d, *J* 2.5, H-6), 7.99 (1H, d, *J* 8.5, H-4), 8.19 (1H, d, *J* 9, H-9), 8.49 (1H, d, *J* 2, H-1), 8.73 (1H, s, H-11); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 27.8, 59.0, 117.8, 118.3, 118.8, 121.2, 123.9, 125.1, 127.6, 127.9, 131.0, 132.0, 133.7, 140.5, 144.4, 146.5, 149.3, 154.6, 169.7; *m*/*z* (ES): 413.0142/415.0117 $(M+1)^+$, HRMS (ES) found: 413.0142 (^{79}Br, $C_{19}H_{14}N_2O_4Br$ requires: 413.0137).

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