Controlling Helix Handedness in Water-Soluble Quinoline Oligoamide Foldamers

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For the purpose of biological applications, controlling the helix handedness of water soluble quinoline-based oligoamide foldamers has been investigated by the installation of chiral end groups at either the C- or N-terminus. This has resulted in the development of monomer units capable of unequivocally inducing helical sense without impacting on aqueous solubility.

Furthermore, we showed that very slow helix handedness inversion in water can be taken advantage of. The incorporation of a chiral moiety possessing no handedness induction properties was shown to allow chromatographic separation of *P* and *M* helices as diastereoisomers having a kinetically locked handedness.

The chirality of secondary structures such as helices is a property fundamental to the complex molecular interactions involved in cellular processes, for example at protein-protein interfaces. The importance of diastereomeric selectivity in biological target recognition highlights the need to investigate right-handed (*P*) or left-handed (*M*) conformers of helical foldamers as distinct entities, as such compounds are being considered as useful ligands for biopolymer recognition.^[1] By extension the ability to reliably induce helix handedness under biocompatible conditions is a must.

Induction of handedness in helical foldamers is an attractive concept, since it allows the display of functionality in a specific one-handed array along the face of the scaffold, and thus the potential ability to recognise a particular biological surface with high selectivity. Handedness induction is inherent in peptidic foldamers since chirality is imparted by the amino acid building blocks.^[2] Aromatic amide backbones do not possess stereogenic centres and form racemic mixtures of *P* and *M* helices in solution.^[3] In this case, it is therefore necessary to consider other methods for the control of handedness.

Helical aromatic oligoamide foldamers, such as those consisting of 8-amino-2-quinolinecarboxylic acid (Figure 1), feature properties which make them promising candidates for the recognition of protein and nucleic acid surfaces: they adopt well defined, predictable conformations, they are medium sized (0.5–5.0 kDa), they are resistant to proteolytic degradation, and have been shown to possess cell-penetrating properties.^[4] However the fact that they do not closely resemble the biological structures they mimic makes the challenge to design ligands for proteins and nucleic acids all the more difficult. One rapid method for screening quinoline oligoamides for activity against a given biological surface relies on the fact that without any stereogenic centre, short sequences

(< 5 units) exist as a mixture of interconverting P and M helical conformations. If binding to a target surface is helix sense dependent, then the equilibrium will be shifted towards the preferred conformer- a process which can be monitored by induced circular dichroism (ICD). Indeed, the P and M helices possess opposite sign CD bands that cancel each other. When equilibrium deviates from a 50:50 mixture, CD bands emerge. This technique has recently been used to screen short quinoline oligoamide sequences tethered to human carbonic anhydrase II (HCA) via a ligand (Figure 2), identifying a sequence which not only possessed affinity for the protein surface, but also induced the formation of a novel HCA dimer.^[5] Helix handedness induction has also been observed between a fully cationic side-chain functionalized tetramer and G-quadruplex DNA^[6] and between helical capsules and their chiral guests.^[7] In the former two cases, handedness induction is not required, because the biological target itself exerts control over helix sense.

Figure 1. Cationic octamer and camphanyl inducing groups.

However, it has also been shown that the kinetics of helix handedness inversion of 8-amino-2-quinolinecarboxylic acid oligoamides slow down as strand length increases.^[8] This effect is so pronounced in protic solvents that handedness becomes kinetically stable for octameric sequences,^[9] precluding the use of the biological target as a handedness inducer. An alternative is then to induce helix handedness in the oligomer via the incorporation of a chiral unit either at an end^[10] or middle^[11] of the sequence, or by the presence of chiral side chain functionality.^[12] Both enantiomers can then be assessed independently for binding affinity to the target.

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This approach has been used in the assessment of G-quadruplex DNA binding of quinoline oligoamide foldamers. SELEX (systematic evolution of ligands by exponential enrichment)^[13] was used to identify G-rich aptamers with affinity for fully-cationic side-chain functionalized octamer (**1**, Figure 1). The separate *P* and *M* helices of the octamer were then produced by installation of respectively the (1*S*)-(–)-camphanyl (**2**) or (1*R*)-(+)-camphanyl (**3**) group at the N-terminus,^[10i] and the aptamer candidates were then re-assessed for binding, with one example indicating preference for the *M* helix.^[14]

However, quantitative induction of helix handedness (*de* > 99%) is a challenging objective, and success is limited to a few cases.^[6,10i,15] While the camphanyl group is successful in inducing handedness in aromatic oligoamide foldamers, its bulky and hydrophobic nature may be problematic with respect to water solubility of the final compound and also to the functioning of the foldamer as an efficient ligand.^[14] It was therefore clear to us that there was a need to further develop methods for controlling the helix handedness of quinoline oligoamide foldamers for applications in water.

Presented here are two methods to allow the preparation of isolated *P* and *M* helices of water soluble quinoline oligoamides. Firstly we investigated the concept that, since longer (> 6 units) are essentially kinetically ‘locked’ into position in aqueous conditions, the incorporation of a chiral moiety possessing no handedness induction properties could potentially allow chromatographic separation of *P* and *M* helices as diastereoisomers. Secondly we studied the effect of appending a chiral moiety onto position 8 of a quinoline monomer unit (**Q_Y**, Figure 2) which could potentially allow it to act as an N-terminal handedness inducer.

Figure 2. (a) **Q^{xxx}** monomers; (b) HCA inhibitor structure; (c) **Q_Y** chiral monomers (d) Summary of foldamer sequences.

These units were deliberately designed to permit solubility in both organic and aqueous conditions, allowing us to incubate the

foldamer in organic solvents, taking advantage of the fast handedness inversion kinetics where equilibrium would be quickly reached, then subsequently ‘locking’ the handedness conformation in water.

Results and Discussion

Separation of diastereoisomers arising from helix handedness

Previously, the installation of a C-terminal phenylalanine group was found to be a poor method for controlling helix handedness in organic solvents.^[10b] However, it was noted that the resulting *P* and *M* diastereoisomers possessed strikingly different retardation factors on silica gel chromatography, allowing their separation at low temperatures. Re-equilibration of each isolated diastereoisomer to the racemic mixture then rapidly occurred at room temperature. We reasoned that if the same principle could be applied on reversed-phase chromatography using water-soluble oligomers, we could take advantage of the kinetic inertness in aqueous conditions to isolate diastereoisomers which would then not racemize, provided they were exposed only to aqueous solvent mixtures.

Scheme 1. SPS of fully-cationic side-chain octamer **4**. *Reagents and conditions*: (i) 20% v/v piperidine in DMF, rt, 10 min, repeat once; (ii) (a) Fmoc-Q^{Orn}-OH, 1-chloro-*N,N*,2-trimethyl-1-propenylamine, CH₂Cl₂, rt, 1 h; (b) Product from (a), *i*Pr₂EtN, THF, microwave 50 W, ramp to 50 °C, hold 50 °C for 15 min, repeat once; (iii) 20% v/v piperidine in DMF, rt, 10 min, repeat twice; (iv) Repeat steps (ii)–(iii); (v) Acetyl chloride, *i*Pr₂EtN, THF, microwave 50 W, ramp to 60 °C, hold 60 °C for 15 min, repeat once; (vi) TFA/*i*Pr₃SiH/H₂O (95:2.5:2.5), rt, 2 h.

Initial work focussed on the preparation of the all-cationic side-chain functionalized octamer (**4**, Figure 2). Low-loading Wang resin was functionalized with Fmoc-Phe-OH using the anhydride method well documented in the literature.^[16] Fmoc deprotection was then carried out using 20% v/v piperidine in DMF and the first Fmoc-Q^{Orn} unit installed via its acid chloride, formed using 1-chloro-*N,N*,2-trimethyl-1-propenylamine (Scheme 1).^[17] The oligoamide was then prepared using the microwave-assisted Fmoc strategy SPS previously reported by our group (see Experimental Section).^[18] Removal from the resin with concomitant side-chain Boc deprotection was subsequently carried out by treatment of the resin with 95/2.5/2.5 TFA/H₂O/*i*Pr₃SiH v/v/v. The crude material was analysed by RP-HPLC and indeed was found to consist of two well-separated main products (Figure 3) of approximate equal peak area; this was in concordance with ¹H-NMR analysis

demonstrating the presence of 14 amide signals, corresponding to two discrete octameric products (Figure 4a).

Figure 3. HPLC profile showing separation of diastereoisomers of compound 4.

Figure 4. Carboxamide region of ^1H -NMR for compound 4 and 5 in d_6 -DMSO: (a) Crude mixture of diastereoisomers of 4 after SPS (N. B. reflects ratio of diastereoisomers in TFA cleavage mixture); (b) *P*-4 (c) *M*-4 (d) Crude mixture of diastereoisomers of 5 after SPS; (e) *P*-5 (f) *M*-5.

Figure 5. CD spectra of separated *P* and *M* diastereoisomers of compounds 4 and 5, recorded using 50 – 60 μM solutions.

Purification of the crude mixture was carried out using preparative RP-HPLC and analysis of each product by ^1H -NMR and mass spectrometry confirmed identity as the expected octameric diastereoisomers. Analysis of the CD spectrum of each product was also important to confirm the separation of *P* and *M* helices. Although *P*-4 and *M*-4 helices are diastereoisomers and not enantiomers, the helical aromatic foldamer parts of their structures are mirror images and give rise virtually 'mirror-image' spectra of opposing sign. Indeed, CD experiments (Figure 5) showed the expected deflections at 390–410 nm, the absorption region of the quinoline chromophores. By analogy to previous work,^[10b] the first eluted diastereoisomer was determined to be the *P*-helix (positive band near 400 nm), and the second to be the *M*-helix (negative band).

The stability of the separate diastereoisomers of compound 4 in water was assessed by HPLC, which revealed no detectable interconversion between handedness forms over a period of five days at room temperature. Unlike peptidic α -helices which tend to be destabilised when consisting exclusively of positively charged residues,^[19] cationic aromatic oligoamide helices remain stable even when they possess multiple positive charges. This was in contrast to behaviour in DMSO, where a degree of racemization was observed after only two hours, and complete equilibration after 2–3 days (See Supporting Information). Interestingly, in DMSO it appears that the phenylalanine unit possesses a moderate ability to induce helix sense, with approximately 40% diastereomeric excess in favour of the *P*-helix.

The ability to separate *P* and *M* helices by using a C-terminal group allows the N-terminus to be left free for other purposes, i.e. incorporation of functionalities. This was of interest to us with respect to recent results concerning attachment of foldamers to HCA, via an N-terminal inhibitor moiety.^[5] We thus tested the separation of helix sense diastereoisomers in the context of HCA ligands and used SPS to prepare octamer 5 that includes an N-terminal HCA inhibitor moiety and a C-terminal Phe unit (Figure 2). Once again the crude HPLC demonstrated the presence of two major products assigned to the *P* and *M* helices. This was also reflected in the ^1H -NMR spectrum (Figure 4d). Separation of the two diastereoisomers by preparative HPLC was also found to be straightforward, and both could be obtained in reasonable purity, affording analogous CD profiles to compound 4 (Figure 5). Interestingly, the order of diastereoisomer elution was the same as previously, with the *P*-helix eluting first.

The stability of the separate diastereoisomers of 5 were also assessed in aqueous conditions, although for solubility reasons this required the addition of a small proportion (0.5 – 1%) of DMSO. Once again, no interconversion between handedness forms could be detected over a period of five days at room temperature (See Supporting Information).

Considering the diverse nature of the side-chains in comparison to the octamer 4, this data suggested to us that this method could potentially be applied to a greater range of sequences. In order to determine whether this method could be used to access pure diastereoisomers of longer foldamers, we prepared 12mer 6 (Figure 2). HPLC analysis again revealed the presence of the two distinct diastereoisomers, as confirmed by MS and ^1H -NMR, but baseline separation could not be afforded with a number of different gradients, and thus in this case preparative HPLC was not attempted.

In summary, the incorporation of a chiral centre at the C-terminus afforded separable helix sense diastereoisomers of two octameric sequences possessing diverse side-chain functionality. This way, both *P* and *M* helices could be afforded by a single synthesis. The separated diastereoisomers were observed to be kinetically inert in water over long periods (days). This is important with respect to their use for targeting protein surfaces

since each diastereoisomer could be assessed separately for binding via techniques such as surface plasmon resonance (SPR) without the risk of racemisation. Shorter sequences (≤ 5 units) can simply be presented to the target as a racemic mixture and interactions assessed via ICD, since this is permitted by their faster handedness inversion kinetics.

Induction of helix handedness via an N-terminal quinoline-based chiral building block

We sought to further enhance our toolkit for isolating discrete helix handedness forms and to develop a method that could be applied regardless of the sequence, in particular for longer oligomers that are not all amenable to diastereomer separation. This led us to reconsider the possibility of using a terminal functional group with the ability to induce handedness. Our experience with inducing groups positioned at the N- and C-termini demonstrated incomplete handedness induction, except in the case of the large and hydrophobic camphanyl group.^[10a-10c,10i] We speculated that bringing stereogenic centres as close as possible to the quinoline backbone might offer strong inducing properties, and decided to introduce a chiral centre directly connected to position 8 of an N-terminal quinoline unit. Furthermore, we chose groups which would potentially allow solubility in a range of solvents. This way, long foldamers could be designed to allow incubation in an organic solvent where inversion kinetics are relatively fast; once induction is complete, transfer to water would then lock the conformation.

Three designs were proposed, all accessible from a common ketone precursor **12** (Scheme 2), the synthesis of which has been previously described in the literature.^[20] The **Q_{Phen}** monomer (Figure 2) utilised a pendant phenoxy group as steric bulk to hinder one face of the monomer unit. This was also hoped to stabilize the preferred helix formation via stacking interactions.

Scheme 2. Synthesis of chiral quinoline monomers. *Reagents and conditions:* (i) Me_2SO_4 , K_2CO_3 , acetone, reflux, 1 h; (ii) NaBH_4 , $\text{C}_2\text{H}_4\text{Cl}_2$, 55 °C, 8 h; (iii) phenol, DBAD, PPh_3 , toluene, 80 °C, 3 h; (iv) morpholine, $\text{Na}(\text{OAc})_3\text{BH}$, $\text{C}_2\text{H}_4\text{Cl}_2$, 55 °C, 24 h; (v) 2-(1-piperazinyl)ethanol, $\text{Na}(\text{CN})\text{BH}_3$, AcOH , $\text{C}_2\text{H}_4\text{Cl}_2$, 55 °C, 3 h; (vi) $\text{LiOH}\cdot\text{H}_2\text{O}$, dioxane/ H_2O , 1 h; (vii) Ac_2O , DIEA, CHCl_3 , 4 h (carried out on **R-20**).

Scheme 3. Synthesis of pentamers bearing N-terminal handedness inducing groups from the tetramer amine precursor, **13**. *Reagents and conditions:* (i) (a) Chiral monomer unit, 1-chloro-*N,N*,2-trimethyl-1-propenylamine, CH_2Cl_2 , rt, 1 h; (b) Product from (a), $i\text{Pr}_2\text{EtN}$, CHCl_3 , rt, 20 h. (N.B. Configuration of **10** inferred from CD spectrum (i.e. the resulting induction of *M*-helix) and comparison between **Q_{Pip}** and **Q_{Morph}** CD spectra. See Supporting Information).

The remaining two designs incorporated either morpholine or piperazine via the amine functionality. While these would not be capable of stacking interactions with the aromatic foldamer backbone, they would be useful as solubilising groups. In addition, installation of a piperazine moiety might also allow further functionalization of the foldamer via the terminal amine group.

The starting quinolinone **12** was functionalised with a simple methoxy group in the 4-position to yield the common ketone precursor. This was then either reduced and subsequently treated with phenol under Mitsunobu conditions to yield the racemic **Q_{Phen}** monomer, or underwent direct reductive amination to incorporate the morpholine or piperazinyethanol moieties. Subsequent separation of each enantiomer from the racemic mixture by preparative chiral HPLC was followed by saponification yielding the free acids of the monomers. The terminal alcohol functionality of the **Q_{Pip}** monomer was then acetylated before activation as the acid chloride, to avoid the possibility of side-reactions at this position. The configurations of both enantiomers of the **Q_{Morph}** monomer were confirmed by their crystal structures. The remaining monomers proved difficult to crystallize. Their configurations were therefore inferred from their CD sign at 300 nm by comparison with that of the **Q_{Morph}** enantiomers (see Supporting Information).

In order to assess handedness induction by means of **Q_{Pip}**, **Q_{Morph}**, and **Q_{Phen}**, we initially designed a pentameric sequence with side-chain functionality compatible with a range of organic solvents. We have previously demonstrated that adjusting oligomer length and the solvents in which it was dissolved gave us an ability to ‘tune’ the rate of helix handedness inversion.^[8,9] In this case, a pentameric sequence in a non-polar solvent such as chloroform would possess slow enough handedness inversion kinetics on an NMR timescale that the separate diastereoisomers could be visualised as a distinct set of resonances. However, this behaviour would still be sufficiently fast that equilibration between handedness forms would be complete after minutes, and thus the degree of handedness induction could be accurately assessed. Quantitative induction could therefore be initially determined by analysis of the ^1H -NMR spectrum, which should show a single set of resonances. Analysis by CD would then confirm the induction of a single helix handedness form, indicated by a deflection at the quinoline chromophore absorption region, discounting the possibility that separate diastereoisomers possessed exactly overlapping NMR resonances.

The tetramer amine **13** (Scheme 3) was synthesised using the procedures previously reported by our group^[21] and functionalized with a terminal chiral building block via the acid chloride. It was found that the tertiary amine present on the **Q_{Morph}** and **Q_{Pip}** units could interfere with the activation. Prior protonation of these amines allowed the clean activation of acid functions into acid chlorides. No such problems were associated with the **Q_{Phen}** building block.

¹H-NMR analysis of pentamer **7** indicated the presence of both *P* and *M* diastereoisomers in an almost 1:1 ratio, as demonstrated by the eight carboxamide resonances between 11 and 12 ppm (Figure 6). This was confirmed by CD experiments (Figure 7) which showed negligible deflection at 390–410 nm. In contrast, pentamers **8** and **9** possessing respectively the *R* and *S* enantiomers of the **Q_{Morph}** monomer were each found to afford an identical single set of ¹H-NMR signals, indicating quantitative handedness induction. This was also observed in *d*₃-MeCN/CDCl₃ (3:1), *d*₃-MeOH and in *d*₆-DMSO. Compound **8** was found to remain as one set of NMR signals in *d*₆-DMSO for over four weeks at room temperature, and even after heating to 50 °C for 24 hours.

Figure 6. Carboxamide region of ¹H-NMR spectra in CDCl₃ for: (a) compound **7**; (b) Unprotonated form of compound **8** (* shows minor set of peaks); (c) Hydrochloride salt of compound **8**.

Figure 7. CD spectra of compounds **7–11**, recorded using 50 – 60 μM solutions.

Analysis by CD confirmed single helix handedness, with intense bands at 390–410 nm. Again, by analogy to previous work, the negative sign of these bands indicate a preferred *M* handedness for compound **8**, possessing the (*R*)-**Q_{Morph}** monomer, and the inverse

for compound **9** (possessing the (*S*)-**Q_{Morph}** monomer) indicating a preferred *P* handedness. Interestingly, the protonation state of the morpholine unit appeared to slightly enhance handedness induction efficiency- the ¹H-NMR spectrum of the unprotonated form of **8** showed the presence of minor amide resonances (Figure 6), thought to be those of the unfavoured *P* diastereoisomer, which were eliminated on conversion to the hydrochloride salt. CD experiments (See Supporting Information) supported this, showing a small reduction in intensity in the unprotonated form, perhaps indicating a slight decrease in induction efficiency.

The **Q_{Pip}** monomer also demonstrated an ability to quantitatively induce helix handedness, with compound **10** showing a negative CD deflection of approximately the same magnitude as that of compound **8** at 390–410 nm. This indicates the monomer is of the *R*-configuration and supports our earlier inference from comparison of the **Q_{Pip}** CD spectra with those of **Q_{Morph}**. As with the morpholine functionalised monomer, the protonation state appeared to slightly affect induction efficiency (see Supporting Information).

In order to assess handedness induction efficiency in water, we returned to the solid phase synthesis methodology for the production of a simple pentameric sequence consisting of an N-terminal (*R*)-**Q_{Morph}** monomer plus four **Q^{Om}** residues. Including the morpholine functionality, this sequence would be a pentacationic species after deprotection, and thus was anticipated to be highly water-soluble at neutral pH or below. In addition, this pentameric sequence would also possess handedness inversion kinetics fast enough in water to permit racemization, and thus assess handedness induction in this medium.

Low loading Wang bromide resin was prepared using the procedure of Morales and co-workers^[22] and functionalized with the first quinoline monomer in the presence of Cs₂CO₃.

Scheme 4. SPS of water soluble pentamer with N-terminal helix sense inducing group. *Reagents and conditions*: (i) Fmoc-**Q^{Om}**(Boc)-OH, Cs₂CO₃, *i*Pr₂EtN, DMF, microwave 50 W, ramp to 50 °C, hold 50 °C for 5 min, repeat once; (ii) 20% *v/v* piperidine in DMF, rt, 10 min, repeat twice; (iii) (a) Fmoc-**Q^{Om}**(Boc)-OH, 1-chloro-*N,N*,2-trimethyl-1-propenylamine, CH₂Cl₂, rt, 1 h; (b) Product from (a), *i*Pr₂EtN, THF, microwave 50 W, ramp to 50 °C, hold 50 °C for 15 min, repeat once; (iv) Repeat steps (ii)-(iii); (v) (a) (*R*)-**Q_{Morph}**, 1-chloro-*N,N*,2-trimethyl-1-propenylamine, CH₂Cl₂, rt, 1 h; (b) Product from (a), *i*Pr₂EtN, CHCl₃, microwave 50 W, ramp to 50 °C, hold 50 °C for 30 min, then repeat at rt, 20 h.

The Fmoc group was deprotected and SPS continued using the methodology previously detailed in the literature (Scheme 4). Activation of the (**R**)-**Q**_{Morph} unit was preceded by protonation of its tertiary amine group, in order for efficient coupling to be carried out. The crude foldamer was removed from the resin with 50/48/2 TFA/CH₂Cl₂/iPr₃SiH v/v/v and purified by RP-HPLC. ¹H-NMR analysis in both D₂O and *d*₆-DMSO revealed the presence of a single set of signals, indicating quantitative handedness induction, and this was confirmed by CD experiments which showed the expected negative deflection (Figure 7). Compound **11** was found to remain as one set of NMR signals in D₂O even after heating at 40 °C for 48 hours.

Conclusions

Two methods for the isolation of separate *P* and *M* helices of quinoline oligoamides have been assessed. Incorporation of a phenylalanine residue at the C-terminus of two diversely-functionalized water-soluble octamers was in both cases found to afford a mixture of the *P* and *M* diastereoisomers with strikingly different retention times. RP-HPLC separation of the diastereoisomers was found to be straightforward, with each demonstrating a marked stability in water, indicating extremely slow kinetics of handedness inversion under these conditions, regardless of side chain composition, and even in the case of the multicationic species. The facility of this method and the availability of the N-terminus for further functionalization make it attractive in instances where foldamer length (and therefore the resulting slow kinetics of handedness inversion) preclude the use of ICD to determine chirality-dependent interactions with biological targets such as protein surfaces.

Two chiral quinoline monomers were found to offer quantitative induction of helix handedness in both organic and aqueous conditions when installed at the N-terminus of pentameric sequences. These units should provide solubility in a greater range of solvents than the camphanyl group, and due to their smaller steric bulk, may be less likely to disrupt potential foldamer-biomolecule interactions. In addition, the piperazine moiety provides the opportunity for further functionalization of the foldamer after the chiral unit, for example tethering fluorescent probes or small molecule enzyme inhibitors.

These methods for handedness control will serve not only to aid investigation into the chirality-dependence of foldamer-target interactions, but also to facilitate the isolation of discrete, stable handedness forms of a foldamer sequence for use in biological and biophysical assays.

Experimental Section

General Methods. Low loading Wang resin was purchased from Novabiochem. Ghosez reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine) was purchased from Sigma Aldrich. *N,N*-diisopropylethylamine was distilled over calcium hydride. Analytical grade organic solvents were used for solid phase synthesis. Anhydrous THF and CHCl₃ for solution and solid phase synthesis were dispensed from an MBRAUN SPS-800 solvent purification system. RP-HPLC-quality acetonitrile and MilliQ water were used for RP-HPLC analyses and purification. Reactions requiring anhydrous conditions were performed under nitrogen. ¹H-NMR spectra were measured at 300, 400 or 500 MHz and ¹³C-NMR spectra were measured at 75, 100 or 125 MHz. Chemical shifts are reported in ppm and are calibrated against residual solvent signals of CDCl₃ (δ 7.26, 77.2), DMSO-*d*₆ (δ 2.50, 39.4), or D₂O (δ 4.79). All coupling constants are reported in hertz (Hz). Signals were abbreviated as s, singlet; brs, broad singlet; d,

doublet; t, triplet; q, quartet; m, multiplet, dd, doublet of doublets. Silica gel chromatography was performed using Merck Kieselgel Si 60. Thin layer chromatography was performed using Merck Kieselgel Si 60 F254 plates. Chiral preparative HPLC was performed using a Daicel Chiralpak AD column with isocratic ethanol/heptane mixtures as the eluent running at either 100 mL min⁻¹ (**Q**_{Phen} synthesis) or 50 mL min⁻¹ (**Q**_{Morph} and **Q**_{Pip} syntheses). RP-HPLC analyses were performed at 1.5 mL min⁻¹ using a Machery-Nagel Nucleodur C18 or C8 Gravity column (4.6 x 100 mm, 3 μm). The mobile phase was composed of 0.1% (v/v) TFA-H₂O (Solvent A) and 0.1% TFA-CH₃CN (Solvent B) running the following gradients: 5–30% B over 13 min, then 30–100% B over 5 min (System A), 5–100% B over 13 min then 100% B for 5 min (System B), or 20–60% B over 25 min then 60–100% B for 5 min (System C). Monitoring by UV detection was carried out at 214 nm, 254 nm and 300 nm using a diode array detector. Semi-preparative purifications of oligomers were performed at 4 mL min⁻¹ on a semipreparative HPLC using a Machery-Nagel Nucleodur C18 HTEC column (21 mm x 125 mm, 5 μm). The mobile phase was the same as for the analytic system, running the following gradients: 5–26% B over 40 minutes (System D), 5–40% B over 20 minutes (System E) or 20–55% B over 35 minutes (System F). Monitoring by UV detection was carried out at 254 nm and 300 nm using a diode array detector. High resolution electrospray ionization time of flight (ESI-TOF) mass spectra were measured in the positive ion mode on a Waters/Micromass Q-ToF Ultima. X-ray diffraction experiments were carried out on a high flux RIGAKU FRX rotating anode at the Cu Kα wavelength.

Monomer synthesis. Fmoc-Q^{Hyd}, Fmoc-Q^{Ala}, Fmoc-Q^{Leu}, Fmoc-Q^{Asp} and Fmoc-Q^{Orn} were synthesized using the methods previously reported.^[4,17] Fmoc-Q^{TEG} was provided by the Servier Research Institute of Medicinal Chemistry, Hungary.

Methyl 8-acetyl-4-methoxy-quinoline-2-carboxylate 13. 491 mg of methyl 8-acetyl-4-hydroxy-quinoline-2-carboxylate^[20] (2.00 mmol) was dissolved in 10 mL acetone, then 553 mg potassium carbonate (4.00 mmol) and 182 μL dimethyl sulfate (2.00 mmol) were added. The mixture was stirred at reflux for 1 hour, then cooled to rt. Water was added and the resulting precipitate was filtered, washed with water to afford the title compound as a white solid (424 mg, 82%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ = 8.30 (dd, 1H, *J* = 8.3, 1.5), 7.93 (dd, 1H, *J* = 7.1, 1.5), 7.73 (dd, 1H, *J* = 8.3, 7.1), 7.57 (s, 1H), 4.13 (s, 3H), 3.96 (s, 3H), 2.88 (s, 3H). ¹³C-NMR (100 MHz, DMSO-*d*₆): δ = 202.9, 165.6, 163.5, 149.3, 145.2, 139.9, 130.6, 127.9, 125.2, 121.8, 101.1, 57.1, 53.4, 33.2. HRMS calculated for C₁₄H₁₃NO₄: 259.0845; found 260.0916, [M + H]⁺.

Methyl 8-(1-hydroxyethyl)-4-methoxy-quinoline-2-carboxylate 14. 7.519 g of methyl 8-acetyl-4-methoxy-quinoline-2-carboxylate (29.00 mmol) was dissolved in 200 mL dry 1,2-dichloroethane, then 3.292 g sodium borohydride (87.00 mmol) was added. The mixture was stirred at 55 °C for 8 hours, then cooled to rt. The mixture was diluted with 100 mL methylene chloride, and acetic acid was added to quench. The mixture was then washed with water and brine and extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (heptane/EtOAc) to afford the title compound as a white solid (5.096 g, 67%). ¹H-NMR (500 MHz, DMSO-*d*₆): δ = 8.07 (dd, 1H, *J* = 8.3, 1.4), 7.94 (d, 1H, *J* = 7.0), 7.68 (dd, 1H, *J* = 8.1, 7.3), 7.55 (s, 1H), 5.84 (m, 1H), 5.36 (d, 1H, *J* = 4.7), 4.12 (s, 3H), 3.96 (s, 3H), 1.45 (d, 3H, *J* = 6.4). ¹³C-NMR (125 MHz, DMSO-*d*₆): δ = 166.0, 163.4, 148.4, 146.5, 145.1, 128.2, 126.9, 121.6, 120.2, 100.5, 64.5, 56.9, 53.3, 26.2. HRMS calculated for C₁₄H₁₅NO₄: 261.1001; found 262.1072, [M + H]⁺.

1R and 1S methyl 4-methoxy-8-[1-phenoxyethyl]quinoline-2-carboxylate 15. 4.734 g of methyl 8-(1-hydroxyethyl)-4-methoxyquinoline-2-carboxylate (18.12 mmol), 2.555 g phenol (27.15 mmol) and 8.335 g di-*tert*-butylazodicarboxylate (36.20 mmol) were dissolved in 400 mL dry toluene, then 12.067 g of polymer-bound triphenylphosphine (36.20 mmol, 3 mmol/g) was added and the mixture was stirred at 80 °C under nitrogen atmosphere for 3 hours. It was then filtered, washed with ethyl acetate and the filtrate was concentrated under reduced pressure. The crude product was purified via silica gel chromatography (heptane/EtOAc) to afford racemic methyl 4-methoxy-8-[1-phenoxyethyl]quinoline-2-carboxylate (3.388 g, 55%). The enantiomers were then separated by chiral chromatography (ethanol/heptane 15:85) to obtain each enantiomer in ee ≥ 99.8%. The absolute configuration of the enantiomers was not determined, however comparison of the CD spectrum of the **Q_{Phen}** monomer precursors with those of the **Q_{Morph}** monomers (See Supporting Information) indicated that the first eluting enantiomer was 4-methoxy-8-[(1S)-1-phenoxyethyl]quinoline-2-carboxylate and the second eluting enantiomer was 4-methoxy-8-[(1R)-1-phenoxyethyl]quinoline-2-carboxylate. ¹H-NMR (400 MHz, DMSO-*d*₆): δ = 8.11 (dd, 1H, *J* = 8.3, 1.4), 7.83 (dd, 1H, *J* = 7.2, 1.2), 7.65 (dd, 1H, *J* = 8.3, 7.3), 7.62 (s, 1H), 7.14 (m, 2H), 6.84–6.78 (m, 3H), 6.61 (q, 1H, *J* = 6.3), 4.14 (s, 3H), 3.99 (s, 3H), 1.68 (d, 3H, *J* = 6.3). ¹³C-NMR (100 MHz, DMSO-*d*₆): δ = 165.5, 163.1, 157.4, 148.5, 144.6, 141.4, 129.5, 127.9, 126.7, 121.3, 120.8, 120.5, 115.3, 100.6, 70.0, 56.5, 52.9, 23.6. HRMS calculated for C₂₀H₁₉NO₄: 337.1314; found 338.1389, [M + H]⁺ for first eluting enantiomer and 338.1396 [M + H]⁺ for second eluting enantiomer.

1R and 1S methyl 4-methoxy-8-(1-morpholinoethyl)quinoline-2-carboxylate 16. 1.919 g of methyl 8-acetyl-4-methoxyquinoline-2-carboxylate (7.40 mmol) was dissolved in 110 mL dry 1,2-dichloroethane, then 3.87 mL morpholine (44.40 mmol) and 4.705 g sodium triacetoxyborohydride (22.20 mmol) were added and the mixture was stirred at 55 °C for 24 hours. It was then diluted with 150 mL water and extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (heptane/EtOAc) to afford racemic methyl 4-methoxy-8-(1-morpholinoethyl)quinoline-2-carboxylate (1.847 g, 76%). The enantiomers were then separated by chiral chromatography (ethanol/heptane 15:85 with 0.05% *v/v* diethylamine). The first eluting enantiomer was determined by X-ray diffraction (See Supporting Information) as methyl 4-methoxy-8-[(1S)-1-morpholinoethyl]quinoline-2-carboxylate (CCDC 990871), and the second eluting enantiomer was determined also by X-ray diffraction (See Supporting Information) as methyl 4-methoxy-8-[(1R)-1-morpholinoethyl]quinoline-2-carboxylate (CCDC 990870). ¹H-NMR (500 MHz, DMSO-*d*₆): δ = 8.10 (dd, 1H, *J* = 8.3, 1.4), 7.93 (dd, 1H, *J* = 7.2, 1.3), 7.70 (dd, 1H, *J* = 8.1, 7.5), 7.55 (s, 1H), 4.95 (q, 1H, *J* = 6.8), 4.12 (s, 3H), 3.96 (s, 3H), 3.56 (m, 4H), 2.48 (m, 2H), 2.29 (m, 2H), 1.33 (d, 3H, *J* = 6.8). ¹³C-NMR (125 MHz, DMSO-*d*₆): δ = 166.1, 163.4, 148.4, 146.3, 143.0, 128.6, 128.1, 121.8, 120.3, 100.5, 67.0, 56.9, 56.8, 53.3, 51.4, 20.5. HRMS (of racemate) calculated for C₁₈H₂₂N₂O₄: 330.1580; found 331.1639, [M + H]⁺.

1R and 1S methyl 8-(1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)-4-methoxyquinoline-2-carboxylate 17. 3.370 g of methyl 8-acetyl-4-methoxyquinoline-2-carboxylate (13.00 mmol) was dissolved in 200 mL anhydrous 1,2-dichloroethane, then 14.36 mL 2-(1-piperazinyl)ethanol (117.00 mmol), 2 mL glacial acetic acid (35 mmol) and 2.042 g sodium cyanoborohydride (32.50 mmol) were added to the solution. The mixture was stirred at 55 °C for 3 hours, then diluted with 200 mL saturated NaCl and extracted

with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified via silica gel chromatography, (CH₂Cl₂/MeOH) to afford racemic methyl 8-(1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)-4-methoxyquinoline-2-carboxylate (2.631 g, 54%). The enantiomers were separated by chiral chromatography (ethanol/heptane 15:85 with 0.05% *v/v* diethylamine) to obtain the first eluting enantiomer in ee = 99.8% and the second eluting enantiomer in ee = 94.4%. The absolute configuration of the enantiomers was not determined, however comparison of the CD spectrum of the **Q_{Pip}** monomer precursors with those of the **Q_{Morph}** monomers (See Supporting Information) indicated that the first eluting enantiomer was methyl 8-[(1R)-1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl]-4-methoxyquinoline-2-carboxylate and the second eluting enantiomer was methyl 8-[(1S)-1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl]-4-methoxyquinoline-2-carboxylate. ¹H-NMR (400 MHz, DMSO-*d*₆): δ = 8.08 (dd, 1H, *J* = 8.3, 1.4), 7.91 (dd, 1H, *J* = 7.2, 1.4), 7.69 (dd, 1H, *J* = 8.2, 7.4), 7.55 (s, 1H), 4.95 (q, 1H, *J* = 6.7), 4.31 (t, 1H, *J* = 5.4), 4.12 (s, 3H), 3.96 (s, 3H), 3.42 (m, 2H), 2.38 (br s, 4H), 2.32 (m, 2H), 2.30 (br s, 4H), 1.33 (d, 3H, *J* = 6.7). ¹³C-NMR (100 MHz, DMSO-*d*₆): δ = 166.1, 163.4, 148.3, 146.3, 143.4, 128.5, 128.1, 121.8, 120.2, 100.4, 60.8, 58.9, 56.9, 56.4, 55.4, 54.1, 53.3, 50.6, 20.8. HRMS calculated for C₂₀H₂₇N₃O₄: 373.2002; found 374.2064 [M + H]⁺ for first eluting enantiomer and 374.2053 [M + H]⁺ for second eluting enantiomer.

General method for **Q_V** monomer precursor saponification.

The corresponding ester was dissolved in dioxane-water 5:1 (10 mL/mmol) and 3 eq. lithium hydroxide monohydrate was added. The mixture was stirred at rt until no further conversion was observed by TLC. The mixture was then neutralized with 1.25 M HCl in ethanol (3 equiv) and concentrated under reduced pressure. The crude product was purified via preparative reversed phase chromatography using an Armen Spot Liquid Chromatography system with a Gemini-NX[®] 10 μM C18, 250 mm × 50 mm i.d. column from Phenomenex, running at a flow rate of 118 mL min⁻¹ with UV diode array detection (210 – 400 nm) using 5 mM aqueous ammonium formate solution and acetonitrile or water and acetonitrile as eluents.

R/S-Q_{Phen} 18. ¹H-NMR (500 MHz, DMSO-*d*₆): δ = 13.33 (br s, 1H), 8.10 (dd, 1H, *J* = 8.3, 1.5), 7.73 (dd, 1H, *J* = 7.2, 1.2), 7.63 (dd, 1H, *J* = 8.3, 7.2), 7.63 (s, 1H), 7.14 (m, 2H), 6.86 (m, 2H), 6.80 (m, 1H), 6.77 (q, 1H, *J* = 6.3), 4.13 (s, 3H), 1.65 (d, 3H, *J* = 6.3). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 166.3, 163.2, 157.4, 149.1, 144.4, 141.6, 129.4, 127.8, 126.6, 121.3, 120.7, 120.4, 115.3, 100.2, 70.0, 56.5, 23.7. HRMS calculated for C₁₉H₁₇NO₄: 323.1158; found 324.1229 [M + H]⁺ and 324.1228 [M + H]⁺.

R/S-Q_{Morph} 19. ¹H-NMR (500 MHz, DMSO-*d*₆): δ = 8.11 (dd, 1H, *J* = 8.4, 1.4), 7.92 (dd, 1H, *J* = 7.2, 1.3), 7.70 (dd, 1H, *J* = 8.3, 7.3), 7.59 (s, 1H), 4.91 (q, 1H, *J* = 6.7), 4.15 (s, 3H), 3.61 (m, 4H), 2.55 (m, 2H), 2.35 (m, 2H), 1.36 (d, 3H, *J* = 6.7). ¹³C-NMR (125 MHz, DMSO-*d*₆): δ = 165.4, 163.9, 149.9, 144.2, 140.7, 128.9, 127.5, 121.2, 120.2, 100.0, 66.2, 57.5, 56.7, 50.7, 19.5. HRMS calculated for C₁₇H₂₀N₂O₄: 316.1423; found 317.1502 [M + H]⁺ (**S-Q_{Morph}**) and 317.1506 [M + H]⁺ (**R-Q_{Morph}**).

1R and 1S 8-(1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)-4-methoxyquinoline-2-carboxylic acid 20. ¹H-NMR (500 MHz, DMSO-*d*₆): 8.09 (dd, 1H, *J* = 8.3, 1.4), 7.88 (dd, 1H, *J* = 7.3, 1.3), 7.66 (dd, 1H, *J* = 8.2, 7.3), 7.56 (s, 1H), 4.94 (q, 1H, *J* = 6.7), 4.12 (s, 3H), 3.48 (t, 2H, *J* = 6.2), 2.58 (br s, 4H), 2.49–2.23 (m, 6H), 1.38 (d, 3H, *J* = 6.7). ¹³C-NMR (125 MHz, DMSO-*d*₆): δ = 166.2, 163.5, 151.9, 144.4, 140.3, 128.5, 127.0, 121.0, 120.2, 100.0, 59.8, 58.0, 57.5, 56.5, 52.8, 49.4, 19.6. HRMS calculated for C₁₉H₂₅N₃O₄: 359.1845; found 360.1931 [M + H]⁺ and 360.1937 [M + H]⁺.

R-Q_{Pip} 21. 300 mg of 8-((1*R*)-1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)-4-methoxy-quinoline-2-carboxylic acid was dissolved in CHCl₃ and stirred at rt under N₂. 0.872 mL *i*Pr₂EtN (5.00 mmol, 6 equiv) was then added, followed by 0.237 mL Ac₂O (2.50 mmol, 3 equiv) and the mixture stirred at rt for 4 h under N₂. Solvents were evaporated under reduced pressure, the crude residue dissolved in 6.0 mL THF/H₂O (1:1) and stirred for 3 h at rt. 1 M HCl was then added dropwise to bring the mixture to pH 2 and solvents evaporated under reduced pressure. The crude residue was purified by silica gel chromatography (100% CH₂Cl₂ to CH₂Cl₂/MeOH 85:5) to yield the title compound as a white foam (225 mg, 67%). ¹H-NMR (300 MHz, CDCl₃): δ = 8.30 (dd, 1H, *J* = 8.4, 1.3), 7.99 (s, 1H), 7.80 (m, 1H), 7.70 (dd, 1H, *J* = 8.3, 7.4), 4.32 (s, 3H), 4.29 (m, 1H), 4.21 (t, 2H, *J* = 5.8), 2.94–2.84 (m, 6H), 2.76 (m, 2H), 2.70 (m, 2H), 2.07 (s, 3H), 1.61 (d, 3H, *J* = 6.8). ¹³C-NMR (75 MHz, DMSO-*d*₆): δ = 171.0, 168.4, 153.0, 138.1, 134.1, 132.2, 128.0, 122.5, 101.2, 64.0, 61.7, 57.8, 56.2, 52.2, 21.0, 18.2. HRMS calculated for C₂₁H₂₇N₃O₅: 401.1951; found 402.2041 [M + H]⁺.

Compound 4. Synthesized on a 0.022 mmol (50 mg Wang resin loading 0.44 mmol g⁻¹) scale, using the general methods previously reported.^[18] The crude mixture of diastereoisomers was purified by RP-HPLC (System D) to yield each pure diastereoisomer as a yellow solid. **P-4:** (corresponding to first analytical peak, 5.0 mg, 21%). RP-HPLC (C18, System A) *R*_t = 9.83 min. ¹H-NMR (300 MHz, DMSO-*d*₆): δ = 11.51 (s, 1H), 11.30 (s, 1H), 11.08 (s, 1H), 10.99 (s, 1H), 10.94 (s, 1H), 10.87 (s, 1H), 8.49 (s, 1H), 7.95–8.29 (m, CHAr), 7.34–7.89 (m, 13H), 7.08–7.23 (m, 3H), 6.99 (s, 1H), 6.87 (s, 1H), 6.78 (m, 1H), 6.46–6.65 (m, 9H), 6.34 (s, 1H), 6.25 (m, 2H), 5.97 (s, 1H), 3.78–4.49 (m, 16H), 3.03–3.17 (m, 16H). HRMS calculated for C₁₁₅H₁₁₇N₂₅O₁₉: 2151.8958; found 2152.9098 [M + H]⁺. **M-4:** (corresponding to second analytical peak, 4.5 mg, 19%). RP-HPLC (C18, System A): *R*_t = 10.11 min. ¹H-NMR (300 MHz, DMSO-*d*₆): δ = 11.27 (s, 1H), 11.14 (s, 1H), 11.06 (s, 1H), 11.00 (s, 1H), 10.90 (s, 1H), 10.84 (s, 1H), 8.47 (s, 1H), 7.96–8.22 (m, CHAr), 7.34–7.82 (m, 13H), 7.06–7.23 (m, 3H), 6.97 (s, 1H), 6.86 (s, 1H), 6.76 (m, 3H), 6.51 (s, 1H), 6.39 (m, 3H), 6.31 (s, 1H), 6.20 (s, 1H), 5.96 (s, 1H), 4.07–4.46 (m, 16H), 3.11 (m, 16H), 2.22 (m, 16H). HRMS calculated for C₁₁₅H₁₁₇N₂₅O₁₉: 2151.8958; found 2152.9098 [M + H]⁺.

Compound 5. Synthesized on a 0.019 mmol (50 mg Wang resin loading 0.38 mmol g⁻¹) scale, using the general methods previously reported.^[5,18] The crude mixture of diastereoisomers was purified by RP-HPLC (System F) to yield each pure diastereoisomer as a pale yellow solid. **P-5:** (corresponding to first analytical peak) 2.2 mg (9%). RP-HPLC (C18, System C) *R*_t = 14.37 min. ¹H-NMR (300 MHz, DMSO-*d*₆): δ = 11.61 (s, 1H), 11.54 (s, 1H), 11.44 (s, 1H), 11.20 (s, 1H), 11.02 (s, 1H), 10.98 (s, 1H), 10.87 (s, 1H), 10.77 (s, 1H), 9.14 (t, 1H, *J* = 6.1), 8.13–7.33 (m, 25H), 7.22–7.06 (m, 4H), 6.93 (m, 2H), 6.85–6.63 (m, 6H), 6.46 (m, 3H), 6.17 (m, 3H), 5.99 (s, 1H), 5.95 (brs, 1H), 5.05–4.61 (m, 7H), 4.40 (m, 2H), 4.32–4.15 (m, 5H), 3.94 (m, 3H), 3.68 (m, 3H), 1.37–1.27 (m, 8H), 1.21–1.16 (m, 6H), 1.06 (m, 4H). HRMS calculated for C₁₂₆H₁₁₄N₂₂O₂₇S: 2398.7945; found 2398.7935 [M]⁺. **M-5:** (corresponding to second analytical peak) 2.8 mg (11%). RP-HPLC (C18, System C) *R*_t = 14.53 min. ¹H-NMR (300 MHz, DMSO-*d*₆): δ = 11.58 (s, 1H), 11.45 (s, 1H), 11.16 (s, 1H), 11.03 (s, 1H), 10.99 (s, 1H), 10.88 (s, 1H), 10.80 (s, 1H), 10.72 (s, 1H), 9.13 (t, 1H, *J* = 5.9), 8.05–7.31 (m, 27H), 7.20–7.05 (m, 5H), 6.91 (s, 1H), 6.84–6.62 (m, 6H), 6.58 (s, 1H), 6.55 (s, 1H), 6.36 (m, 3H), 6.14 (s, 1H), 6.12 (s, 1H), 5.99 (s, 1H), 5.92 (brs, 1H), 4.98–4.69 (m, 7H), 4.39 (m, 2H), 4.23–4.11 (m, 5H), 3.93 (m, 3H), 3.65 (m, 3H), 1.35–1.26 (m, 8H), 1.20–1.16 (m, 6H), 1.05 (m, 4H). HRMS calculated for C₁₂₆H₁₁₄N₂₂O₂₇S: 2398.7945; found 2398.7971 [M]⁺.

Compound 6. Synthesized on a 0.022 mmol (50 mg Wang resin loading 0.44 mmol g⁻¹) scale, using the general methods previously reported^[18] to yield 55 mg crude material (67% crude yield) as a

yellow solid. RP-HPLC (C8, System B): Major peaks at: *R*_t = 6.82 min, 6.91 min. ¹H-NMR (300 MHz, DMSO-*d*₆): Approximate 1:1 ratio of diastereoisomers: δ = 11.11 (s, 1H), 10.93 (s, 2H), 10.83 (s, 1H), 10.77 (s, 2H), 10.73 (s, 1H), 10.69 (s, 1H), 10.25–10.41 (m, 10H), 9.93 (m, 4H), 8.30 (s, 2H), 7.67–6.60 (m, 72H), 6.52 (s, 1H), 6.35 (m, 13H), 4.82 (m, 9H), 4.63 (m, 6H), 4.38 (m, 5H), 3.97–3.49 (m, 122H), 3.39–3.09 (m, 50H), 2.34–2.09 (m, 17H), 1.27 (m, 24H). ESI-MS calculated for C₁₉₀H₂₀₀N₂₈O₄₅S₄: 3721.31; found 1862.67 [M + 2H]²⁺, 1242.27 [M + 3H]³⁺.

Compound 7. 11.6 mg (0.036 mmol) of **Q_{Phen}** was dissolved in 550 μL anhydrous CH₂Cl₂ and stirred at rt under N₂. 9.5 μL of 1-chloro-*N,N*,2-trimethyl-1-propenylamine was added and the mixture stirred for 1 h at rt, then evaporated to dryness on a vacuum manifold. 30 mg of **13**^[21] (0.030 mmol) was dissolved in 230 μL of anhydrous CHCl₃, to which was added 12.6 μL (0.072 mmol) *i*Pr₂EtN and the mixture stirred at 0 °C under N₂. The acid chloride was then added dropwise in 230 μL anhydrous CHCl₃ over approximately 5 min, and the mixture stirred at rt for 15 h. It was then diluted with CHCl₃ and washed with a saturated solution of NaHCO₃, 0.1 M HCl, H₂O and brine, and the organic phase dried over MgSO₄. The crude residue was then purified by silica gel chromatography (100% cyclohexane to cyclohexane/EtOAc 7:3) to yield the title compound as a pale yellow solid (28 mg, 72%). ¹H-NMR (300 MHz, CDCl₃): Approximately 55:45 ratio of diastereoisomers: δ = 11.97 (s, 1H), 11.94 (s, 1H), 11.93 (s, 1H), 11.87 (s, 1H), 11.79 (s, 1H), 11.77 (s, 1H), 11.61 (s, 1H), 11.16 (s, 1H), 8.72 (m, 2H), 8.55 (m, 2H), 8.27 (m, 2H), 8.16 (m, 1H), 8.08 (m, 7H), 7.92 (m, 1H), 7.81 (m, 1H), 7.75–7.57 (m, 5H), 7.53 (s, 1H), 7.48 (s, 1H), 7.43–7.28 (m, 5H), 7.03 (m, 4H), 6.82 (m, 4H), 6.70 (m, 2H), 6.57 (s, 1H), 6.45–6.26 (m, 7H), 6.14 (t, 1H, *J* = 7.2), 5.75 (m, 1H), 5.65 (m, 1H), 4.49–3.38 (m, 8H), 4.27 (m, 2H), 3.95–3.79 (m, 10H), 3.70 (m, 2H), 3.20 (s, 3H), 3.15 (s, 1H), 2.53 (m, 2H), 2.40–2.17 (m, 6H), 1.43–1.11 (m, 48H), 0.91 (d, 3H, *J* = 5.9), 0.34 (d, 3H, *J* = 6.4). ¹³C-NMR (75 MHz, CDCl₃): δ = 163.9, 163.8, 163.7, 163.1, 163.0, 162.3, 162.2, 161.9, 161.7, 161.6, 161.3, 161.0, 160.6, 157.9, 151.0, 150.1, 149.6, 148.9, 141.1, 139.1, 138.6, 138.4, 134.1, 134.0, 133.8, 133.7, 132.5, 129.1, 128.4, 127.8, 127.6, 127.1, 127.0, 126.9, 125.6, 122.7, 122.5, 122.2, 122.0, 121.9, 120.0, 119.6, 117.1, 117.0, 116.9, 116.5, 116.2, 115.8, 115.6, 114.8, 100.3, 99.6, 99.4, 98.7, 98.3, 97.8, 97.6, 97.2, 75.6, 75.4, 75.2, 75.0, 74.9, 70.0, 68.7, 56.2, 52.1, 28.4, 28.3, 28.2, 28.1, 26.9, 21.4, 19.5, 19.4, 19.3, 16.8. HRMS calculated for C₇₆H₇₅N₉O₁₂: 1305.5535; found 1306.5644 [M + H]⁺.

General method for coupling of tertiary amine-based chiral monomer unit exemplified by compound 8. 17.5 mg of **R-Q_{Morph}** (0.055 mmol) was suspended in 1 mL THF and 5.4 μL of conc. HCl (0.055 mmol) was added. The mixture was stirred at rt for 20 min, then solvents evaporated under reduced pressure, co-evaporating twice with toluene. The resulting hydrochloride salt was dissolved in 850 μL anhydrous CH₂Cl₂ and stirred at rt under N₂. 15.0 μL of chloro-*N,N*,2-trimethyl-1-propenylamine was then added and the mixture stirred for 1 h at rt, then evaporated to dryness on a vacuum manifold. 46 mg of **13**^[21] (0.046 mmol) was dissolved in 350 μL anhydrous CHCl₃ to which was added 19.2 μL (0.110 mmol) *i*Pr₂EtN and the mixture stirred at 0 °C under N₂. The acid chloride was then added dropwise in 350 μL anhydrous CHCl₃ over approximately 5 min, and the mixture stirred at rt for 15 h. It was then diluted with CHCl₃ and washed with a saturated solution of NaHCO₃, 0.1 M HCl, H₂O and brine, and the organic phase dried over MgSO₄. The crude residue was then purified by silica gel chromatography (100% cyclohexane to cyclohexane/EtOAc 7:3) to yield the title compound as a pale yellow solid (43 mg, 72%). ¹H-NMR (300 MHz, CDCl₃): 12.10 (m, 1H), 11.98 (s, 1H), 11.79 (s, 1H), 11.74 (s, 1H), 11.32 (s, 1H), 8.72 (dd, 1H, *J* = 7.6, 1.0), 8.47 (dd, 1H, *J* = 7.6, 1.2), 8.34 (dd, 1H, *J* = 8.1, 0.9), 8.18–7.91 (m, 6H), 7.80–7.63 (m, 3H), 7.52–7.35

(m, 4H), 7.16 (m, 3H), 6.94 (s, 1H), 6.88 (s, 1H), 6.59 (s, 1H), 4.93 (m, 1H), 4.44 (m, 4H), 4.22 (m, 1H), 4.06-3.92 (m, 4H), 3.82 (m, 3H), 3.70 (m, 1H), 3.49 (m, 1H), 3.19 (m, 5H), 2.53 (m, 1H), 2.36 (m, 7H), 1.92 (m, 1H), 1.24 (m, 24H), 0.35 (d, 3H, $J = 6.8$). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 164.3, 164.0, 163.7, 163.3, 163.2, 162.4, 161.9, 161.7, 161.4, 161.0, 151.8, 150.6, 150.2, 149.1, 145.4, 145.0, 139.0, 138.4, 137.9, 137.7, 135.8, 134.0, 133.6, 133.4, 131.3, 131.3, 129.1, 128.2, 127.7, 127.4, 127.0, 126.9, 125.5, 124.1, 122.7, 122.3, 122.2, 121.8, 121.7, 117.4, 117.2, 117.0, 116.9, 116.5, 116.1, 100.4, 99.8, 99.3, 98.2, 97.9, 75.7, 75.6, 75.4, 75.1, 63.2, 58.8, 56.6, 52.1, 51.3, 50.1, 34.3, 30.3, 28.4, 28.3, 28.2, 28.1, 19.5, 19.4, 19.3, 19.2, 14.8$. HRMS calculated for $\text{C}_{74}\text{H}_{78}\text{N}_{10}\text{O}_{12}$: 1298.5801; found 1299.5896 $[\text{M} + \text{H}]^+$.

Compound 9. Synthesised on a 0.042 mmol scale using the general method described above to yield the title compound as a pale yellow solid (32 mg, 59%). ^1H -NMR (CDCl_3): 12.10 (m, 1H), 11.97 (s, 1H), 11.79 (s, 1H), 11.74 (s, 1H), 11.32 (s, 1H), 8.72 (m, 1H), 8.47 (m, 1H), 8.35 (m, 1H), 8.18-7.91 (m, 6H), 7.80-7.63 (m, 3H), 7.49-7.35 (m, 4H), 7.17 (m, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 6.88 (s, 1H), 6.58 (s, 1H), 4.94 (m, 1H), 4.44 (m, 4H), 4.23 (m, 1H), 4.03-3.92 (m, 4H), 3.83 (m, 3H), 3.70 (m, 1H), 3.49 (m, 1H), 3.20 (m, 5H), 2.55 (m, 1H), 2.35 (m, 7H), 1.92 (m, 1H), 1.26 (m, 24H), 0.35 (d, 3H, $J = 6.1$). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 164.3, 164.0, 163.7, 163.3, 163.2, 162.4, 161.9, 161.7, 161.4, 161.0, 151.8, 150.6, 150.2, 149.2, 145.4, 145.0, 139.0, 138.4, 137.9, 137.7, 134.0, 133.6, 133.4, 131.3, 131.3, 129.1, 128.2, 127.7, 127.4, 127.0, 125.5, 125.3, 124.1, 122.7, 122.3, 122.2, 121.8, 121.7, 117.4, 117.2, 117.0, 116.9, 116.5, 116.1, 100.4, 99.8, 99.3, 99.2, 98.2, 97.9, 75.7, 75.6, 75.4, 75.1, 63.2, 58.8, 56.6, 52.1, 51.4, 50.1, 30.3, 29.7, 28.4, 28.3, 28.2, 28.1, 19.5, 19.4, 19.3, 19.2, 14.9$. HRMS calculated for $\text{C}_{74}\text{H}_{78}\text{N}_{10}\text{O}_{12}$: 1298.5801; found 1299.5878 $[\text{M} + \text{H}]^+$.

Compound 10. Synthesised on a 0.043 mmol scale using the general method described above to yield the title compound as a pale yellow solid (34 mg, 57%). ^1H -NMR (CDCl_3): 12.37 (brs, 1H), 11.95 (s, 1H), 11.79 (s, 1H), 11.73 (s, 1H), 11.25 (brs, 1H), 8.73 (m, 1H), 8.49 (m, 1H), 8.40 (m, 1H), 8.16-7.96 (m, 5H), 7.76-7.60 (m, 4H), 7.52 (m, 1H), 7.42 (m, 2H), 7.34 (m, 1H), 7.15 (m, 1H), 6.87 (s, 1H), 6.86 (s, 1H), 6.56 (s, 1H), 5.15 (brs, 1H), 4.42 (m, 4H), 4.22 (m, 1H), 3.98-3.78 (m, 7H), 3.56 (m, 1H), 3.20 (m, 7H), 2.98 (m, 2H), 2.54 (m, 1H), 2.32 (m, 5H), 1.86 (m, 3H), 1.24 (m, 24H), 0.39 (m, 3H). ^{13}C -NMR (75 MHz, CDCl_3): $\delta = 169.7, 164.3, 163.9, 163.8, 163.2, 163.1, 162.3, 162.0, 161.5, 160.9, 152.7, 150.0, 149.1, 145.3, 144.7, 139.0, 138.3, 137.5, 134.0, 133.7, 133.5, 129.8, 129.1, 128.2, 127.8, 127.3, 126.9, 126.1, 125.5, 125.3, 124.8, 122.7, 122.6, 122.1, 121.7, 121.5, 117.5, 117.1, 116.7, 116.6, 116.4, 116.0, 115.7, 100.3, 99.9, 99.7, 98.1, 97.6, 75.6, 75.3, 75.0, 58.7, 57.6, 56.6, 55.2, 52.1, 30.3, 28.3, 28.2, 28.1, 21.5, 20.7, 19.5, 19.4, 19.3, 19.2, 14.3$. HRMS calculated for $\text{C}_{78}\text{H}_{85}\text{N}_{11}\text{O}_{13}$: 1383.6328; found 1384.6437 $[\text{M} + \text{H}]^+$.

Compound 11. Synthesized on a 0.019 mmol (50 mg Wang resin loading 0.38 mmol g^{-1}) scale, using the general methods previously reported.^[18] The crude material was purified by RP-HPLC (C18, System E) to afford the title compound as a pale yellow solid (6 mg, 17%). RP-HPLC (System A): $R_t = 7.58 \text{ min}$. ^1H -NMR ($\text{D}_2\text{O}/\text{H}_2\text{O}$): 11.17 (s, 1H), 11.12 (s, 1H), 11.03 (s, 1H), 10.80 (s, 1H), 8.24 (m, 1H), 7.93 (m, 3H), 7.81-7.71 (m, 6H), 7.52 (m, 4H), 7.43-7.20 (m, 5H), 7.13 (s, 1H), 7.05 (s, 1H), 6.95 (m, 1H), 6.46 (s, 1H), 5.85 (m, 1H), 3.39 (m, 6H), 2.92 (m, 2H), 2.74-2.16 (m, 14H), 0.01 (d, 3H, $J = 6.7$). HRMS calculated for $\text{C}_{69}\text{H}_{72}\text{N}_{14}\text{O}_{12}$: 1288.5454; found 1289.5561 $[\text{M} + \text{H}]^+$.

Supporting Information (see footnote on the first page of this article): CD data, NMR and HPLC-based studies of helix stability, ^1H and ^{13}C -NMR spectra and details of X-ray diffraction experiments.

Acknowledgments

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Controlling the helix handedness of water soluble quinoline-based oligoamide foldamers has been investigated by the installation of chiral end groups at either the N- or C-terminus. This has respectively afforded either quantitative induction of handedness, or the ability to separate kinetically locked *P* and *M* helices as diastereoisomers.

Chirality of Helical Foldamers

Simon J. Dawson, Ádám Mészáros, Lilla Pethő, Cinzia Colombo, Márton Csékei, András Kotschy* and Ivan Huc*..... Page No. – Page No.

Controlling Helix Handedness in Water Soluble Quinoline Oligoamide Foldamers

Keywords: Quinoline oligoamide foldamers / Chirality / Helix handedness