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Supporting Information

Cellular Internalization of Water-Soluble Helical Aromatic Amide Foldamers

Jone Iriondo-Alberdi,[a] Katta Laxmi-Reddy,[a] Benaissa Bouguerne,[a] Cathy Staedel,[b] and Ivan Huc*[a]

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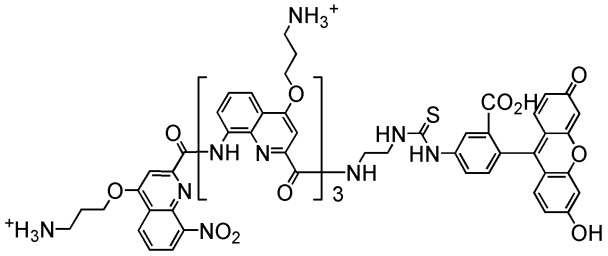
1. Additional data (1H-NMR, MALDI and HPLC)

a. Tetramer **Q4**



Q4

Reaction of tetramer-ester **4**[1] with ethylene diamine in the presence of DMAP and gentle heating afforded the amine functionalized tetramer **7** in good yield. This compound was then tagged with fluorescein 5-isothiocyanate in DMF. Subsequently treatment of the crude FITC-functionalised tetramer with a 1:1 mixture of CH_2Cl_2 and TFA yielded the desired water-soluble tetramer **Q4**, which was purified by reverse-phase HPLC and characterised by MALDI-TOF mass spectometry.

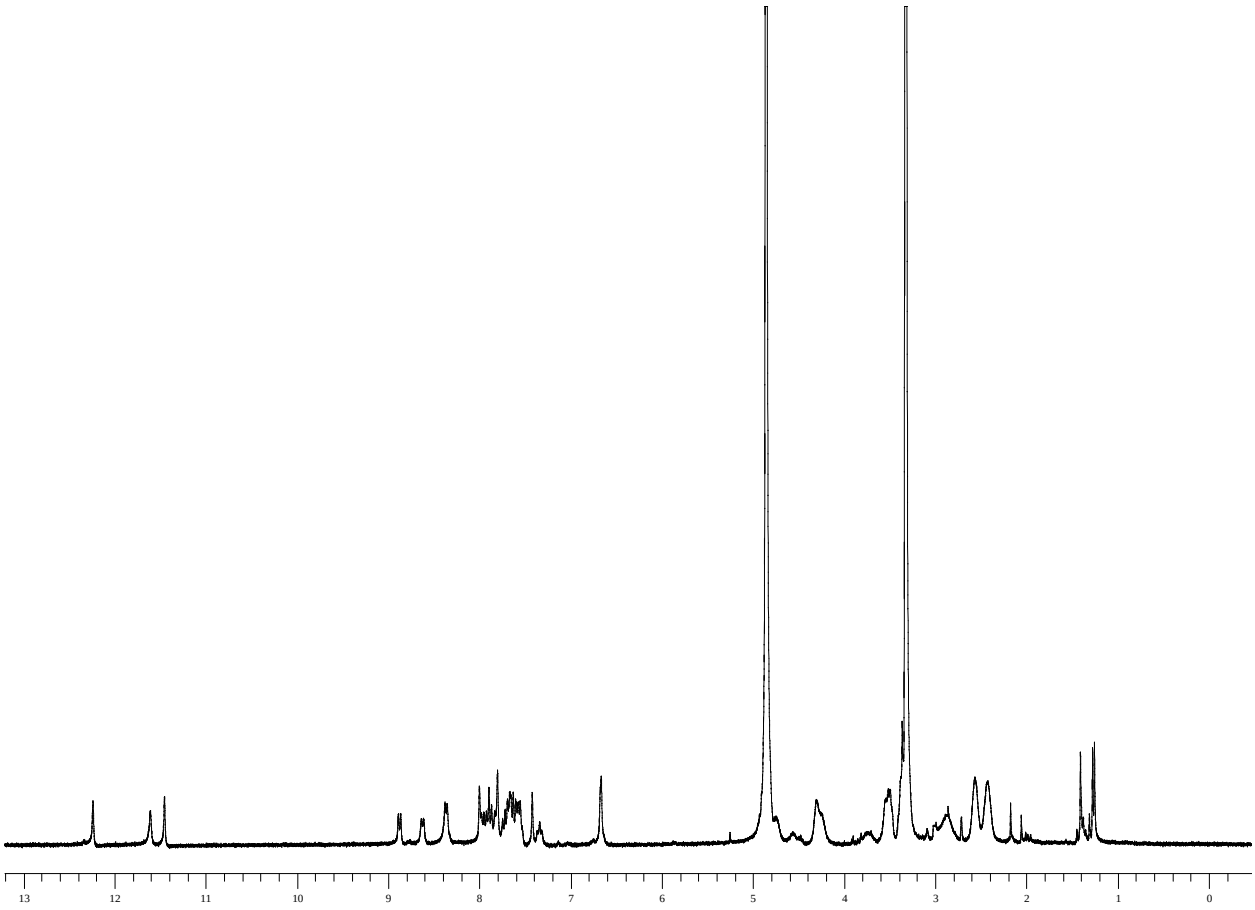


Figure SI-1. 1H NMR spectrum of **Q4**.

[1] E. R. Gillies, F. Deiss, C. Staedel, J.-M. Schmitter, I. Huc, *Angew. Chem.* **2007**, *119*, 4159-4162; *Angew. Chem. Int. Ed.* **2007**, *46*, 4081–4084.

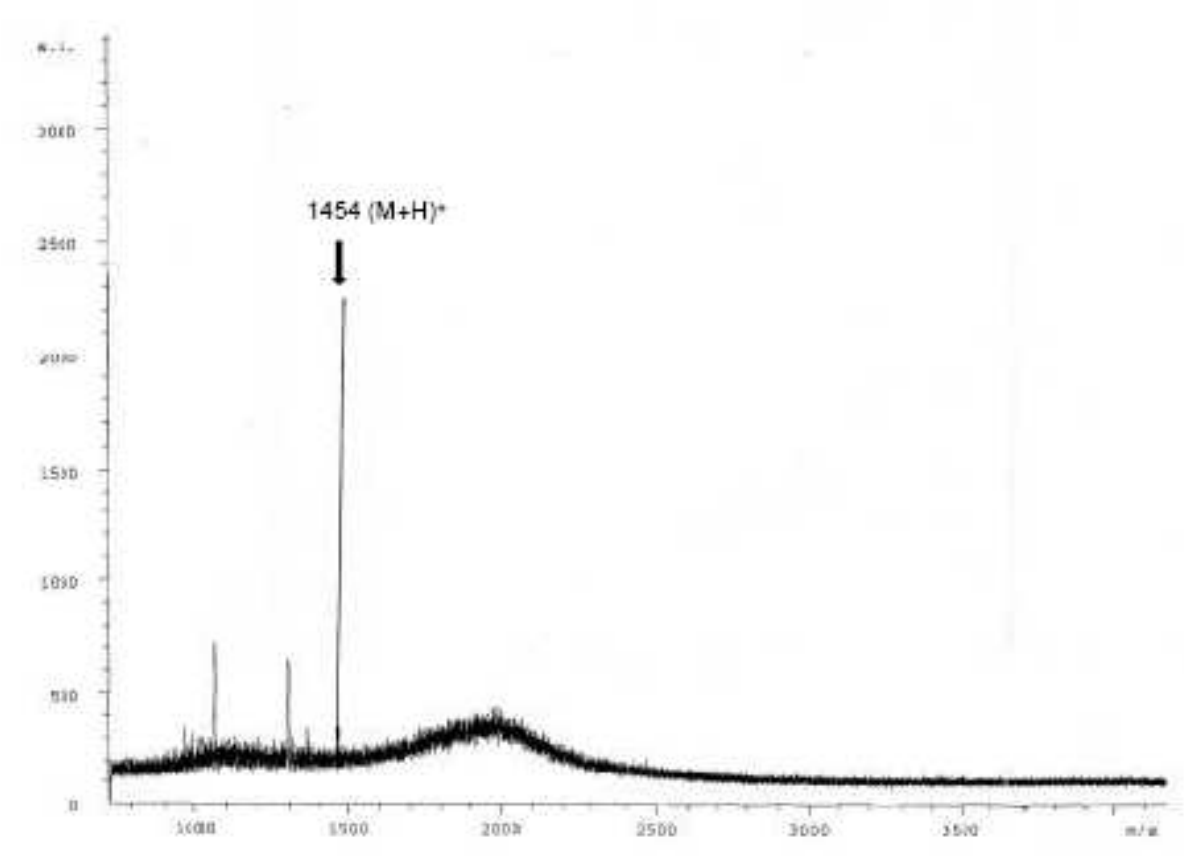


Figure SI-2. Maldi mass spectrum of **Q4**.

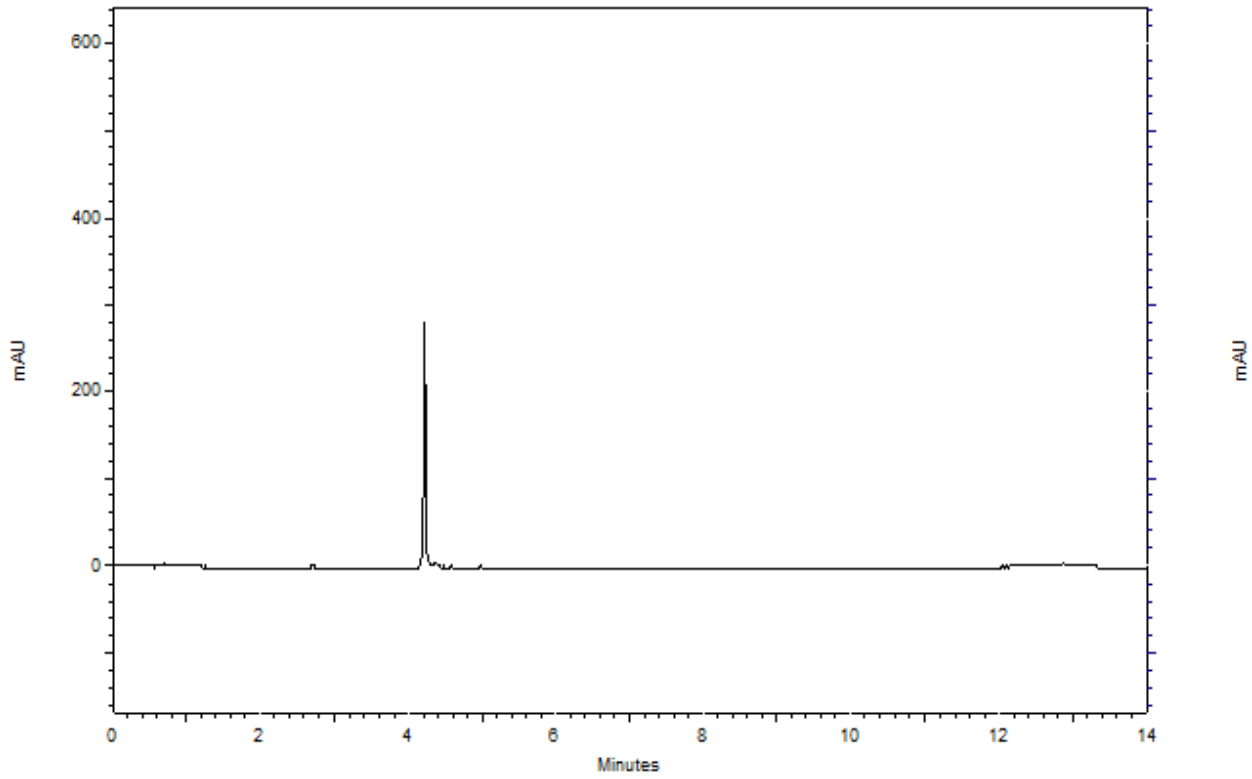
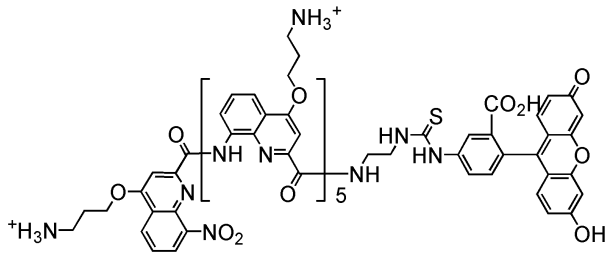


Figure SI-3. HPLC profile on a chromolith C18 column, 100% H_2O-0.1% TFA, 15 min for **Q4**.

b. Hexamer **Q6**



Q6

Reaction of tetramer-ester **5**[5] with ethylene diamine in the presence of DMAP and gentle heating afforded the amine functionalized tetramer **8** in moderate yield. This compound was then tagged with fluorescein 5-isothiocyanate in DMF. Subsequently treatment of the crude FITC-functionalised hexamer with a 1:1 mixture of CH_2Cl_2 and TFA yielded the desired water-soluble tetramer **Q6**, which was purified by reverse-phase HPLC and characterised by MALDI-TOF mass spectometry.

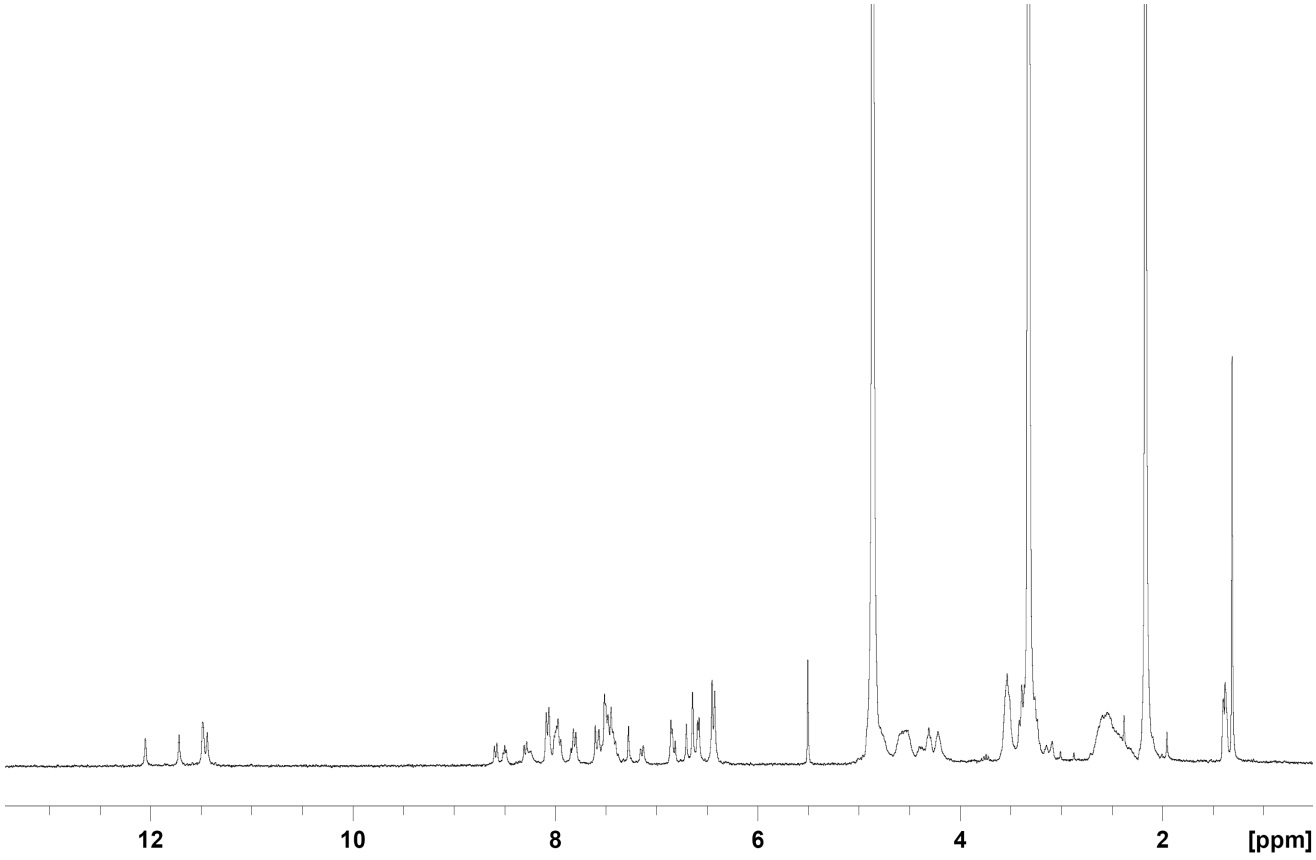


Figure SI-4. ^{1}H NMR spectrum of **Q6**.

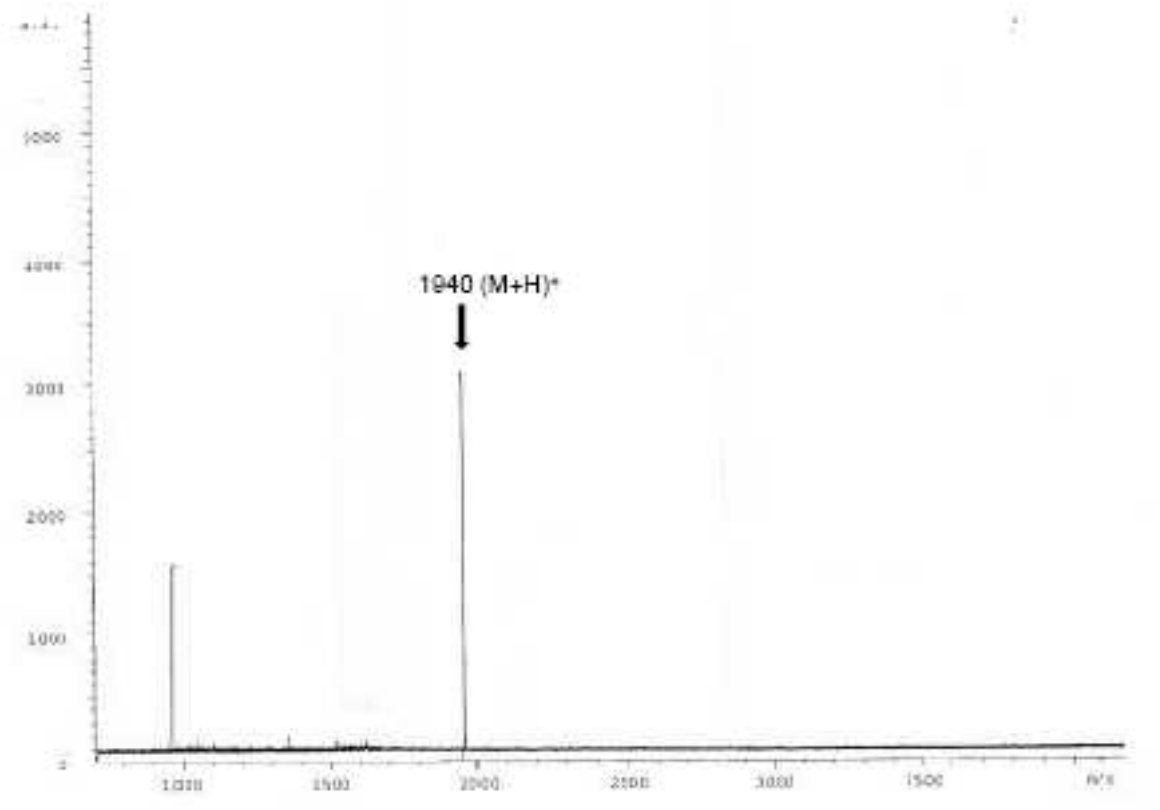


Figure SI-5. Maldi mass spectrum of **Q6**.

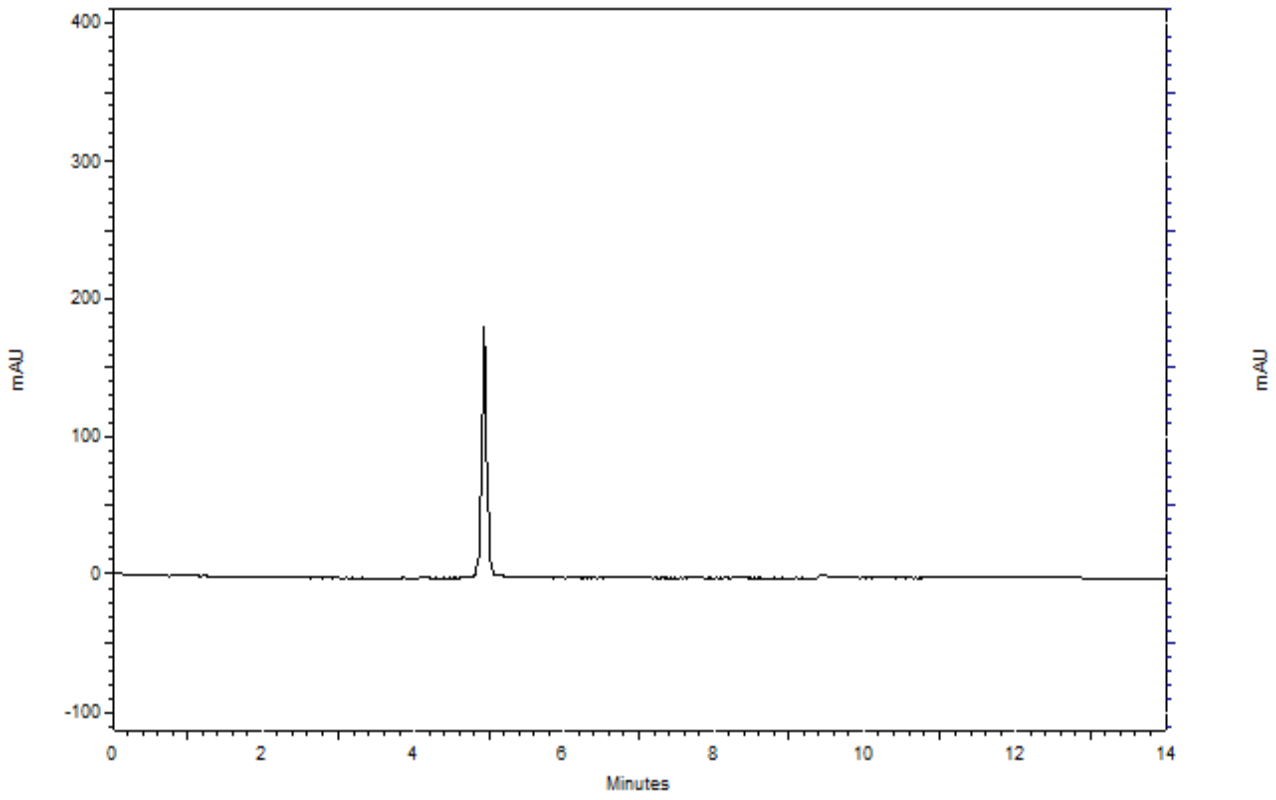


Figure SI-6. HPLC profile on a chromolith C18 column, 100% H_2O-0.1% TFA, 15 min for **Q6.**

2. Flow cytometry.

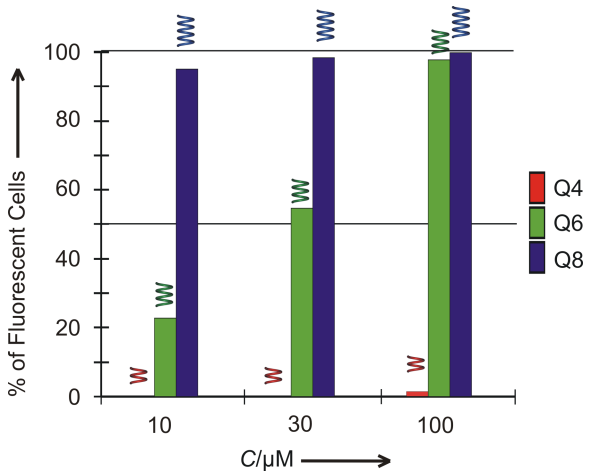


Figure SI-7. Percentage of fluorescent Huh-7 cells after incubation with various concentrations of Q4, **Q6** and **Q8**, at 37 ºC. C indicates concentration.

3. Fluorescence and phase contrast microscopy images.

Figure SI-8 shows the images obtained after incubating HeLa and Jurkat cells with the FITC-labeled **Q6** and **Q8** derivatives and FITC alone as a negative control, at 37 ºC and 4 ºC.

As for the case of Huh-7 cells, the ability of foldamers **Q6** and **Q8** to enter HeLa and Jurkat cells at 37 ºC is verified by images A) and B), and F) and G), respectively. In the case of HeLa cells, bright punctuated fluorescent granules appear randomly distributed in the cytoplasm, suggesting that the FTIC-foldamer conjugates are taken up by the cells *via* an endocytic pathway. Confocal microscopy images previously obtained for **Q8** in HeLa cells[1] under the same incubation conditions (Figure SI-9) showed no vesicle accumulation, implying that the helices are eventually released to the cytoplasm and accounting for the homogeneous fluorescence observed. At endocytosis inhibiting conditions (4 ºC)(Images D and E) the cytoplasmic fluorescence is largely reduced and a very diffuse fluorescence around the cell membrane might suggest that the helices remain associated to the external surface.
In the case of T-lymphocyte Jurkat cells the phase contrast images F) and G) show a very localized fluorescence pattern for both **Q8** and **Q6**, which provide a strong indication of membrane translocation. Furthermore, the homogeneous fluorescent pattern around the cell at 4 ºC (Images I and J for **Q8** and **Q6** respectively) agrees with membrane association of the helices rather than internalization, which bodes well with an energy dependant uptake mechanism.

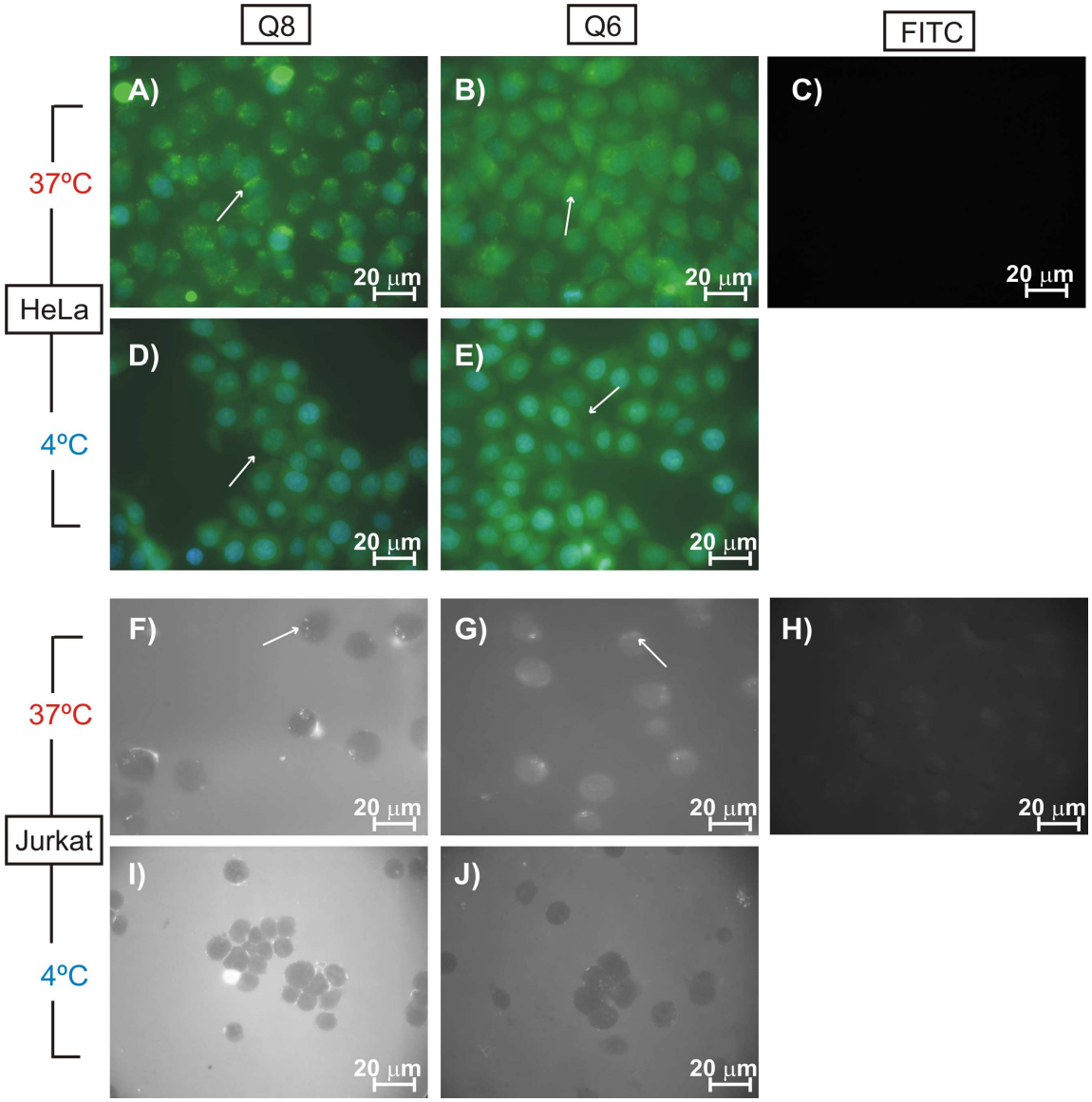


Figure SI-8. A) – E) Fluorescence microscopy images of HeLa cells incubated for 1 h with **Q6**, **Q8** and FITC at 100 µM concentration. Images A), B) and C) were taken following incubation at 37 ºC and images D) and E) were taken following incubation at 4 ºC. F) – J) Phase contrast microscopy images of Jurkat cells incubated for 1 h with **Q6**, **Q8** and FITC at 100 µM concentration. Images F), G) and H) were taken following incubation at 37 ºC and images I) and J) were taken following incubation at 4 ºC.

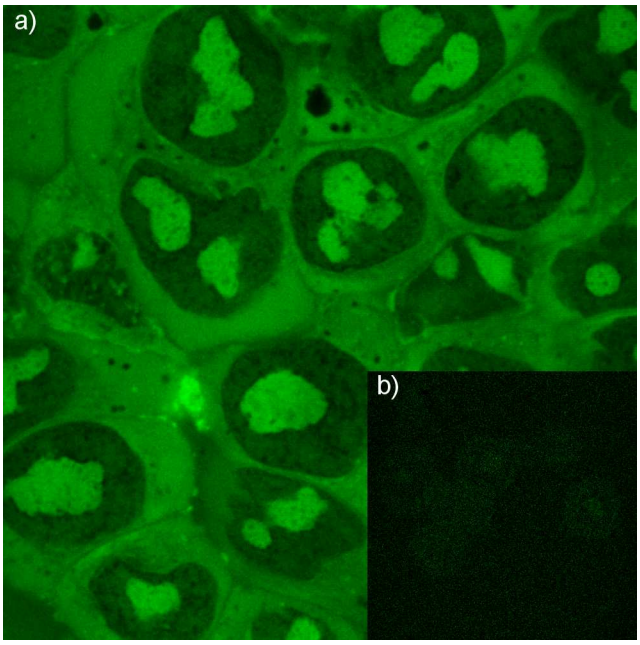


Figure SI-9. a) Fluorescence confocal microscopy image of HeLa cells after incubation in a 10μM solution of **Q8** for 1 h. b) Inset illustrates the absence of background fluorescence in cells not exposed to **Q8**.