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Synthesis of functionalised polyethylene glycol derivatives of naproxen for biomedical applications

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ABSTRACT

The preparation of a series of mono-naproxen functionalised polyethylene glycol derivatives have been achieved. These compounds feature several different terminal functional groups, the identities of which have been chosen to facilitate conjugation of these hybrid molecules to nanomaterials.

1. Introduction

Naproxen **1** is a popular non-steroidal anti-inflammatory drug (NSAID), which is widely used to relieve the effects of pain, fever and inflammation. However, there is concern that the frequent use of **1** may cause side effects such as gastrointestinal irritation, bleeding and ulceration.[1] Currently it is believed that these problems occur due to mechanism-based side effects related to the inhibition of constitutive cyclooxygenase **1**, the prostanoid products of which, such as PGE_2, play an important role in the regulation of stomach acidity.[2] One common approach to address these problems is to reduce the direct effect of **1** on the gastrointestinal tract by temporarily blocking its carboxylic acid group. This can be achieved by the binding of certain biocompatible molecules via the carboxylic acid functionality on formation of an amide or ester linkage. As a general concept, polyethylene glycol (PEG) derivatives have been used for this purpose.[3] The reasons for this are twofold; firstly, they are 'biocompatible', typically possessing very low toxicity and furthermore, on hydrolysis in the blood plasma, the gradual release of the original drug may be achieved. Additionally, the utilisation of PEG containing molecules as spacers can often also improve the physical properties of the drug, such as solubility. The main objective of our work is to use the carboxylic acid group present in **1** to prepare new naproxen derivatives, of the type **2**, containing PEG linkers and functionalities. The general structure of these derivatives includes a drug species attached to a linker (via atom/group X) and capped with a functional group (Y). We are interested in ultimately conjugating such derivatives to various biological substrates, polymers and nanoparticles for potential targeted drug delivery applications, i.e., **3**.

Previously, we published the synthesis, photophysical and biological studies of the first naproxen–CdTe nanocrystal conjugates, of the type **3**. These conjugates were prepared by chemically grafting a small diamino ethylenedioxy-linker to naproxen followed by conjugation of this moiety to the carboxylic acid functionality of the thiol capping groups on the surface of the quantum dots (QDs) using a carbodiimide coupling reaction (X and Y=NH). These nanocomposites demonstrated the potential to act as drug delivery vehicles and cellular imaging agents.[4] Herein, we report details of the synthesis and characterisation of a series of naproxen derivatives with variable PEG spacers serving to link the drug to several functional groups such as amino-, mercapto-, hydroxyl-, carboxyl- and 1,2-dihydroxyaryl-, which could be utilised for the preparation of various new nanoparticle–drug conjugates.

2. Results and discussion

Two alternative methods were investigated in order to derivatise naproxen **1** according to Figure 1. Firstly, the conversion of commercially available **1** into the corresponding acyl chloride was

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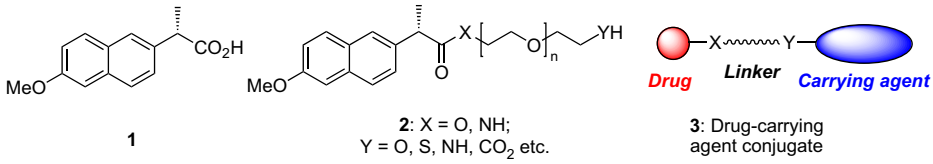


Figure 1. Strategy for the covalent modification of nanoparticulate materials with the NSAID, naproxen.

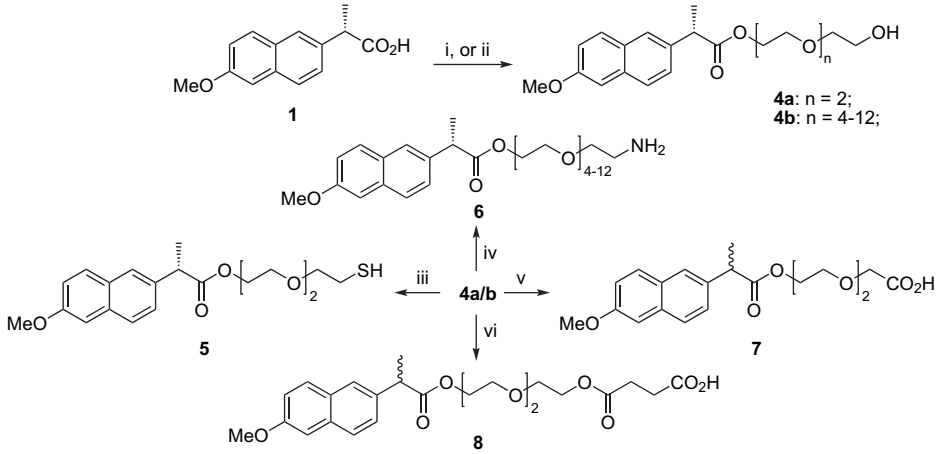
carried out on treatment with thionyl chloride, following a literature procedure.[5,6] This material was freshly prepared and directly used in subsequent esterification reactions with an excess of triethylene glycol gave ester **4a** (71%).[7] The preparation of this type of material using the alternative carbodiimide based coupling was also studied. Thus, treatment of a mixture of **1**, PEG 400 (n=4–12) and a catalytic amount of 1-hydroxybenzotriazole (HOBt) afforded **4b** (62%). In both instances, use of an excess of the water-soluble glycol derivatives minimised formation of the corresponding diesters (Scheme 1). Reactions under similar conditions to produce esters and amides without significant epimerisation of the asymmetric centre have been reported[8] and both adducts did rotate the plane of polarised light, but further studies to investigate the integrity of this stereogenic centre were not performed. Esters **4a** and **4b**, possessing primary hydroxyl groups, were then converted into compounds displaying functional groups that might be amenable for attachment to nanoparticulate materials.

Thus, **4a** was converted in three steps into thiol **5**; initially, the toluene sulfonate ester was prepared under standard conditions.[9] This compound smoothly underwent nucleophilic displacement with potassium thioacetate,[10,11] which was then reduced with sodium borohydride to generate the desired thiol **5**. The conversion of the thioester species into the thiol required optimisation; in our hands we found basic conditions also led to significant carboxylic ester cleavage and additionally it was found that the desired thiol **5** readily underwent oxidation to afford the corresponding disulfide. Formation of this latter side-product could be minimised by careful handling of the work-up and purification process. Once again the identity of the stereogenic centre is not determined but **5** displays an $[\alpha]_D$ of +16.55 (c 0.47, CH_2Cl_2). The corresponding PEG 400 derivative **4b** was converted to the amino derivative **6** in three steps (65%) via the azide, which, in the last step, was reduced under palladium catalysed hydrogenolysis.[12] Finally two different procedures for the formation of carboxylic acid capped species were investigated. In the first, **4a** was oxidised with pyridinium dichromate in dimethylformamide[13] to afford **7** in reasonable yield (58%) and in the second, following a reported method,[14] **4a** was derivatised with succinic anhydride in the presence of acid, which gave **8** in 35% yield. In both the formation of **7** and **8** the optical rotation values measured for the purified products proved to be zero. Therefore, using this criterion we assume that the integrity of the stereogenic centre has been lost during the formation of these carboxylic acid derivatives.

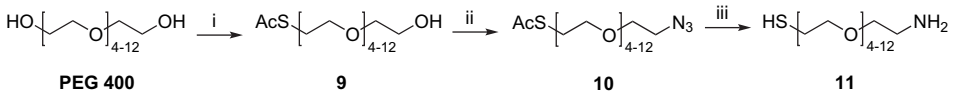
Following on from the studies described above and illustrated in Scheme 1 the differential bis-terminal derivatisation of PEG 400 was studied using analogous methods (Scheme 2). Thus, treatment of an excess of PEG 400 with toluene sulfonyl chloride and subsequent displacement with thioacetate gave **9** in good yield. Hydroxyl activation, again with toluene sulfonyl chloride, and displacement with azide gave **10**, which was converted into **11** on treatment with lithium aluminium hydride.[11]

As shown in Scheme 3, it was hoped that the reaction of naproxen acid chloride and **11** in the presence of triethylamine would prove to be chemoselective. However, in the event, mixtures of adducts **12** and **13** were observed, which proved to be inseparable by flash column chromatography. Additionally, mass spectrometry indicated the formation of difunctionalised naproxen products. Attempts to circumvent this issue by the use of a Staudinger reaction, to convert the azido group present in **10** into the corresponding amine in the presence of the labile thioester, were unsuccessful.

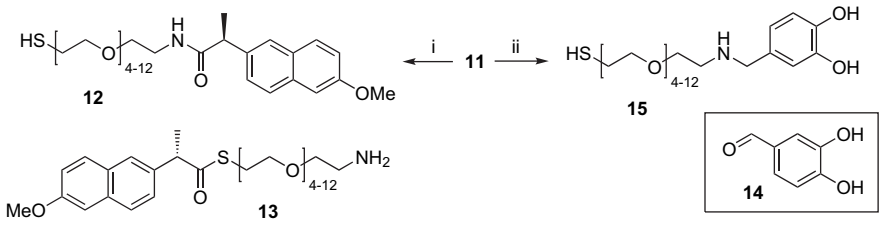
It has recently been demonstrated that the 1,2-dihydroxybenzene functional group efficiently enables the association between an organic derivative and iron oxide (Fe_3O_4) nanoparticles.[16] Amongst the many potential applications such novel organomagnetic materials offer interesting possibilities for the delivery of biologically active compounds dependant on their manipulation by an external magnetic field exist.[17] In relation to this possibility a standard two-step reductive alkylation[15] procedure between **11** and 3,4-dihydroxybenzaldehyde **14** was also performed. However, again, we were unable to obtain the hoped for secondary amine **15**. In order to further investigate if this motif could be effectively



Scheme 1. (i) (a) SOCl2, cat. DMF, CH_2Cl_2, 40 °C, quant.; (b) triethylene glycol (9 equiv), Et_3N, CH_2Cl_2, rt, 71%; (ii) PEG 400 (7 equiv), DCC, HOBt (0.1 equiv), CH_2Cl_2, rt, 62%; (iii) (a) TsCl, Et_3N, CH_2Cl_2, rt, 85%; (b) KSAc, DMSO, rt, 88%; (c) $NaBH_4$, EtOH, 0 °C to rt, 75%; (iv) (a) TsCl, Et_3N, CH_2Cl_2, rt, 70%; (b) NaN_3, DMF, rt, 94%; (c) H_2, Pd/C, EtOH, rt, 99%; (v) PDC, DMF, rt, 58%; (vi) succinic anhydride, H_2SO_4, THF, rt, 35%.



Scheme 2. (i) (a) TsCl, Et_3N, CH_2Cl_2, rt, 99%; (b) KSAc, DMF, rt, 81%; (ii) (a) TsCl, Et_3N, CH_2Cl_2, rt, 88%; (b) NaN_3, DMF, rt, 72%; (iii) $LiAlH_4$, THF, −10 °C to rt, 97%.



Scheme 3. (i) Naproxen acid chloride, Et_3N, CH_2Cl_2; (ii) (a) **14**, CH_2Cl_2/MeOH (8:3), 4 Å M.S.; (b) $NaBH_4$ (10 equiv), MeOH.

incorporated for the preparation of such novel materials, the preparation of a naproxen derivatised diethylene glycol linked 1,2-dihydroxybenzene was investigated. In this instance 2,2′-(ethylenedioxy)diethylamine **16** was converted into the corresponding mono-Boc protected primary amine **17**.[4,18] As described (Scheme 1) this compound was then coupled with naproxen acid chloride, or with naproxen **1** itself using DCC. Removal of the Boc group under standard conditions followed by a two-step reductive amination[19] gave the hoped for secondary amine **19**. We felt that the presence of the basic amino group within the linker unit would be beneficial since conversion into the corresponding ammonium salt would confer greater aqueous solubility, thereby facilitating the formation of the organo-derivatised Fe_3O_4 conjugate since the preparation of these materials is often dependant on the use of aqueous conditions. Based on optical rotation measurements it appears that during this synthetic sequence the labile stereogenic centre has also undergone epimerisation (Scheme 4).

3. Conclusion

In summary, a series of functionalised naproxen derivatives where the drug is attached to various functionalities via a PEG linker have been prepared and characterised. We expect that these naproxen derivatives and the general strategies reported will prove to be useful for the synthesis of various prodrugs and for the construction of bio- and nanoparticle conjugates. Our future work will include the conjugation of these naproxen derivatives to functionalised biopolymers, metal (e.g., Au and Ag), metal oxide (e.g., Fe_3O_4) and II–VI semiconducting nanoparticles (e.g., CdTe and CdSe).

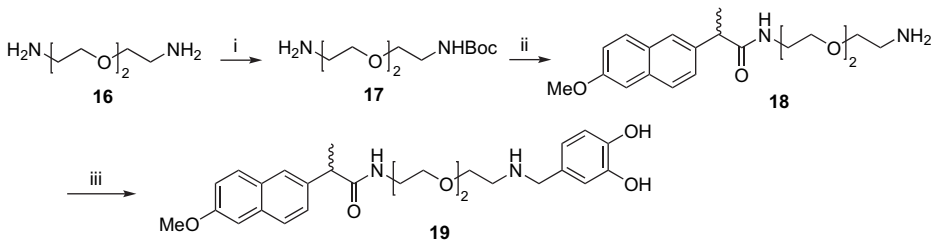
4. Experimental

4.1. General

Starting materials were purchased from commercial sources and were used without further purification. Air or/and moisture sensitive manipulations were carried out under argon or nitrogen as noted. Anhydrous tetrahydrofuran was distilled under nitrogen from the sodium/benzophenone ketyl radical. Dichloromethane was distilled from CaH_2. Flash column chromatography, under moderate pressure was performed using silica gel-ICN 32–63, 60 Å. ^1H and ^{13}C spectra were recorded on a Bruker Advance® AC-400 instrument at 400 and 100 MHz, respectively. Chemical shifts were measured relative to that of $CDCl_3$ (δ 7.26) for ^1H, (δ 77.24) for ^{13}C. The following abbreviations are used to describe the signal multiplicities: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Chemical shifts are expressed in parts per million [ppm] and listed as follows: shift in parts per million (integration, multiplicity, coupling and assignment). IR spectra (450–4000 cm^{-1}) were recorded using NaCl disks and a Perkin Elmer® instrument. Optical rotation measurements were recorded using an Optical Activity, Polaar 2001 polarimeter at 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra (MS) were recorded on a Micromass Time of Flight (oa-TOF) equipped with an electrospray ionisation (ES) interface operated in the positive mode or negative mode as indicated.

4.2. (*S*)-2-(6-Methoxynaphthalen-2-yl)propionyl chloride (naproxen acid chloride)[5a]

At room temperature, a solution of naproxen **1** (3.45 g, 14.99 mmol) in CH_2Cl_2 (50 mL) was added dropwise to thionyl chloride (2.16 g, 18.16 mmol) with a catalytic amount of DMF (seven drops). The mixture was heated to reflux for 3 h. Evaporation in vacuo gave the crude acid chloride (3.88 g, quant.) and spectroscopic analysis indicated that this material was sufficiently pure for further use. Mp 79–82 °C; ^1H NMR (400 MHz, $CDCl_3$) 1.70 (3H, d, J=7.0 Hz, CH_3), 3.90 (3H, s, CH_3), 4.23 (1H, q, J=7.0 Hz, CH), 7.11 (1H, d, J=2.5 Hz, ArH), 7.20 (1H, dd, J=2.5, 9.0 Hz, ArH), 7.33 (1H, d, J=8.5 Hz, ArH), 7.66 (1H, s, ArH), 7.69–7.75 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.7 (CH_3), 55.3 (CH_3), 57.4 (CH), 105.6 (CH), 119.4 (CH), 125.9 (CH), 127.0 (CH), 127.6 (CH), 128.9 (C), 129.3 (CH), 132.4 (C), 134.1 (C), 158.0 (C), 175.7 (CO); ν_{max} (neat/cm^{-1}) 3041, 2989, 2965, 2939, 2844, 1788, 1708, 1630, 1602, 1504, 1458, 1391, 1376,



Scheme 4. (i) Boc_2O, 1,4-dioxane, rt, 80%; (ii) (a) **1**, DCC, HOBt, CH_2Cl_2, rt, 76%; (b) TFA/CH_2Cl_2 (1:3), rt, 99%; (iii) (a) **14**, $MgSO_4$, CH_2Cl_2, rt; (b) $NaBH_4$, MeOH/1,4-dioxane (5:1), 69%.

1267, 1228, 1173, 1159, 1093, 1025, 966, 934, 913, 895; $[\alpha]_D$ +43.0 (*c* 0.25, $CHCl_3$).

4.3. (*S*)-2-(6-Methoxynaphthalen-2-yl)propionic acid 2-[2-(2-hydroxyethoxy)ethoxy]ethyl ester 4a

A solution of naproxen acid chloride (3.88 g, 14.99 mmol, 1 equiv) in CH_2Cl_2 (35 mL) was slowly added to a stirred mixture of triethylene glycol (11.73 g, 78.12 mmol, 9 equiv) and Et_3N (3.5 mL, 25.11 mmol, 3 equiv) in dichloromethane (20 mL) at room temperature. The reaction was stirred for 7 h, then was washed with 0.3 M HCl (3×50 mL). Aqueous layers were combined and extracted with CH_2Cl_2 (3×30 mL). All CH_2Cl_2 layers were combined, dried over $MgSO_4$ and filtered, then purified by flash column chromatography (Hex/EtOAc 2:1 then EtOAc/MeOH (9:1)) thus the ester **4a** (3.86 g, 71%) was obtained as a viscous oil. R_f=0.10 (Hex/EtOAc; 1:1) and 0.6 (CH_2Cl_2/MeOH; 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, *J*=7.0 Hz, CH_3), 1.80 (1H, br s, OH), 3.47 (4H, br s, CH_2), 3.50 (2H, t, *J*=5.0 Hz, CH_2), 3.59–3.62 (2H, m, CH_2), 3.65 (2H, t, *J*=5.0 Hz, CH_2), 3.87 (1H, q, *J*=7.0 Hz, CH), 3.89 (3H, s, CH_3), 4.16–4.28 (2H, m, CH_2), 7.08 (1H, d, *J*=2.5 Hz, ArH), 7.11 (1H, dd, 1H, *J*=2.5, 8.5 Hz, ArH), 7.39 (1H, dd, *J*=2.5, 8.5 Hz, ArH), 7.66 (1H, *J*=2.5 Hz, ArH), 7.67 (1H, d, *J*=8.5 Hz, ArH), 7.68 (1H, d, *J*=8.5 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.5 (CH_3), 45.3 (CH), 55.3 (CH_3), 61.7 (CH_2), 63.8 (CH_2), 69.0 (CH_2), 70.2 (CH_2), 70.5 (CH_2), 72.3 (CH_2), 105.5 (CH), 118.9 (CH), 126.0 (CH), 126.2 (CH), 127.1 (CH), 128.9 (C), 129.2 (CH), 133.6 (C), 135.5 (C), 157.6 (C), 174.6 (CO); ν_{max} (neat/cm^{-1}) 3450, 3059, 2936, 2875, 1731, 1606, 1455, 1378, 1265, 1179, 1123, 1069, 1031, 856, 814; *m*/*z* (ES$^+$) 385 (M+Na$^+$, 100%); found 385.1629; $C_{20}H_{26}O_6Na$ requires 385.1627 (+0.2 ppm); $[\alpha]_D$ +15.20 (*c* 6.8, CH_2Cl_2).

4.4. (*S*)-2-(6-Methoxynaphthalen-2-yl)propionic acid 2-{2-[2-(toluene-4-sulfonyloxy)ethoxy]ethoxy}ethyl ester

Toluene sulfonyl chloride (2.04 g, 10.66 mmol, 2 equiv), alcohol **4a** (1.82 g, 5.01 mmol, 1 equiv) and pyridine (0.87 mL, 10.78 mmol, 2.1 equiv) were dissolved in CH_2Cl_2 (5.5 mL) and stirred at room temperature for 72 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with 0.1 M aqueous HCl (25 mL). The resultant CH_2Cl_2 layer was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc; 2:1), which gave the title compound (2.20 g, 85%) as colourless, viscous oil. R_f=0.30 (Hex/EtOAc; 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.54 (3H, d, *J*=7.5 Hz, CH_3), 2.39 (3H, s, CH_3), 3.38 (4H, br s, CH_2), 3.51–3.58 (4H, m, CH_2), 3.85 (1H, q, *J*=7.5 Hz, CH), 3.89 (3H, s, CH_3), 4.06 (2H, t, *J*=5.0 Hz, CH_2), 4.15–4.21 (2H, m, CH_2), 7.07–7.12 (2H, m, ArH), 7.29 (2H, d, *J*=8.0 Hz, ArH), 7.38 (1H, dd, *J*=2.5, 8.5 Hz, ArH), 7.63 (1H, d, *J*=2.5 Hz, ArH), 7.65–7.68 (2H, m, ArH), 7.75 (2H, d, *J*=8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.5 (CH_3), 21.6 (CH_3), 45.3 (CH), 55.3 (CH_3), 63.9 (CH_2), 68.6 (CH_2), 70.0 (CH_2), 70.1 (CH_2), 70.4 (CH_2), 70.6 (CH_2), 105.5 (CH), 118.9 (CH), 125.9 (CH), 126.2 (CH), 127.1 (CH), 127.9 (CH), 128.8 (C), 129.2 (CH), 129.8 (CH), 132.9 (C), 133.6 (C), 135.5 (C), 144.8 (C), 157.6 (C), 174.6 (C); ν_{max} (neat/cm^{-1}) 3059, 2939, 1730, 1606, 1453, 1357, 1265, 1177, 1029, 925, 816, 776, 664; *m*/*z* (ES$^+$) 539 (M+Na$^+$, 100%); found 539.1717; $C_{27}H_{32}O_8NaS$ requires 539.1716 (+0.3 ppm); $[\alpha]_D$ +14.40 (*c* 21.9, CH_2Cl_2).

4.5. (*S*)-2-(6-Methoxynaphthalen-2-yl)propionic acid 2-[2-(2-acetylsulfanylethoxy)ethoxy]ethyl ester

A mixture of (*S*)-2-(6-methoxynaphthalen-2-yl)propionic acid 2-{2-[2-(toluene-4-sulfonyloxy)ethoxy]ethoxy}ethyl ester (2.695 g, 5.217 mmol, 1 equiv) and potassium thioacetate (0.893 g, 7.819 mmol, 1.5 equiv) was stirred in dimethyl sulfoxide (25 mL) for 20 h. Water (100 mL) was added and the mixture extracted with dichloromethane (3×75 mL). The combined organic layers were dried over $MgSO_4$, filtered, evaporated and purified by flash column chromatography (Hex/EtOAc; 3:1 to 2:1), which gave the title compound (1.931 g, 88%) as a colourless oil. R_f=0.15 (Hex/EtOAc; 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, *J*=7.5 Hz, CH_3), 2.30 (3H, s, CH_3), 3.01 (2H, t, *J*=6.5 Hz, CH_2), 3.41–3.46 (4H, m, CH_2), 3.49 (2H, t, *J*=6.5 Hz, CH_2), 3.58–3.62 (2H, m, CH_2), 3.86 (1H, q, *J*=7.5 Hz, CH), 3.89 (3H, s, CH_3), 4.17–4.25 (2H, m, CH_2), 7.09 (1H, d, *J*=2.5 Hz, ArH), 7.11 (1H, dd, *J*=2.5, 9.0 Hz, ArH), 7.39 (1H, dd, *J*=2.0, 8.5 Hz, ArH), 7.65 (1H, d, *J*=2.0 Hz, ArH), 7.66–7.69 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.5 (CH_3), 28.7 (CH_2), 30.5 (CH_3), 45.3 (CH), 55.3 (CH_3), 63.9 (CH_2), 69.0 (CH_2), 69.7 (CH_2), 70.1 (CH_2), 70.4 (CH_2), 105.5 (CH), 118.9 (CH), 125.8 (C), 126.0 (CH), 126.2 (CH), 127.1 (CH), 128.8 (C), 129.2 (CH), 135.6 (C), 157.6 (C), 174.6 (CO), 190.4 (CO); ν_{max} (neat/cm^{-1}) 3054, 2936, 2873, 1732, 1691, 1607, 1455, 1392, 1354, 1265, 1179, 1136, 1032, 955, 856, 814, 747; *m*/*z* (ES$^+$) 443 (M+Na$^+$, 100%); found 443.1506; $C_{22}H_{28}O_6NaS$ requires 443.1504 (+0.4 ppm); $[\alpha]_D$ +16.31 (*c* 10.6, CH_2Cl_2).

4.6. (*S*)-2-(6-Methoxynaphthalen-2-yl)propionic acid 2-[2-(2-mercaptoethoxy)ethoxy]ethyl ester 5

Under N_2, a solution of the above thioester (0.702 g, 1.669 mmol, 1 equiv) was dissolved in ethanol (54 mL), then deoxygenated water (63 mL) was added. Sodium borohydride (0.126 g 3.339 mmol, 2 equiv) was added to the stirred solution. After 13 h another batch of sodium borohydride (0.026 g, 0.687 mmol, 0.4 equiv) in EtOH (8 mL) was added. After 35 min diethyl ether (100 mL) and 0.1 M aqueous HCl (100 mL) were added and stirred vigorously (ca. 30 min). After separation, the resultant organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resultant residue was purified by flash column chromatography (Hex/EtOAc; 9:1 to 1:1), which gave **5** (0.472 g, 75%) as a colourless, viscous oil. R_f=0.30 (Hex/EtOAc; 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.52 (1H, t, *J*=8.0 Hz, SH), 1.55 (3H, d, *J*=7.5 Hz, CH_3), 2.61 (2H, dt, *J*=6.5, 8.0 Hz, CH_2), 3.41–3.47 (4H, m, CH_2), 3.49 (2H, t, *J*=6.5 Hz, CH_2), 3.58–3.63 (2H, m, CH_2), 3.86 (1H, q, *J*=7.5 Hz, CH), 3.89 (3H, s, CH_3), 4.16–4.26 (2H, m, CH_2), 7.08 (1H, d, *J*=2.5 Hz, ArH), 7.11 (1H, dd, *J*=2.5, 9.0 Hz, ArH), 7.39 (1H, dd, *J*=2.0, 8.5 Hz, ArH), 7.65 (1H, d, *J*=2.0 Hz, ArH), 7.66–7.69 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.5 (CH_3), 24.2 (CH_2), 45.3 (CH), 55.3 (CH_3), 63.9 (CH_2), 69.0 (CH_2), 70.1 (CH_2), 70.4 (CH_2), 72.8 (CH_2), 105.5 (CH), 118.9 (CH), 126.0 (CH), 126.2 (CH), 127.1 (CH), 128.8 (C), 129.2 (CH), 133.6 (C), 135.6 (C), 157.6 (C), 174.6 (CO); ν_{max} (neat/cm^{-1}) 3058, 2934, 2872, 2569, 1731, 1607,1506, 1461, 1392, 1325, 1266, 1232, 1178, 1122, 1032, 927, 891, 855, 813, 746, 668; *m*/*z* (ES$^+$) 401 (M+Na$^+$, 100%); found 401.1417; $C_{20}H_{26}O_5SNa$ requires 401.1399 (+4.6 ppm); $[\alpha]_D$ +16.55 (*c* 0.47, CH_2Cl_2). Further elution gave by-products (*S*)-2-(6-methoxynaphthalen-2-yl)propan-1-ol (7 mg, 2%) [R_f=0.15 (CH_2Cl_2/Hex/MeOH; 100:1:1)] and (*S*)-2-(6-methoxynaphthalen-2-yl)-propionic acid 2-[2-(2-mercaptoethoxy)-ethoxy]ethyl ester disulfide (43 mg, 7%) [R_f=0.10 (CH_2Cl_2/Hex/MeOH; 100:1:1)].

4.7. α-Hydroxy-(PEG 400)-ω-2-(6-methoxynaphthalen-2-yl)propionate 4b

Naproxen **1** (0.995 g, 4.32 mmol, 1.0 equiv), PEG 400 (11.00 mL, ca. 31.00 mmol, 7.0 equiv) and HOBt (66 mg, 0.49 mmol, 0.1 equiv) were dissolved in dichloromethane (45 mL) and stirred vigorously at −15 °C. DCC (0.988 g, 4.79 mmol, 1.1 equiv) in dichloromethane (4 mL) was added to the reaction mixture and stirring was continued for 15 h. Water (60 mL) was added and the resultant aqueous layer was further extracted with dichloromethane (5×30 mL). The combined dichloromethane extracts were then dried over $MgSO_4$, filtered, evaporated and purified by flash column

chromatography (Hex/EtOAc; 6:1 to 1:2, then EtOAc/MeOH; 9:1). Selected samples gave **4b** (1.625 g, 62%) as a colourless viscous oil. R_f=0.10 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, J=7.0 Hz, CH_3), 2.72 (1H, br s, OH), 3.47 (4H, br s, CH_2), 3.52–3.66 (22–50H, m, CH_2), 3.68 (2H, t, J=4.5 Hz, CH_2), 3.86 (1H, q, J=7.0 Hz, CH), 3.89 (3H, s, CH_3), 4.20 (2H, m, CH_2), 7.08 (1H, d, J=2.5 Hz, ArH), 7.10 (1H, dd, J=2.5, 9.0 Hz, ArH), 7.39 (1H, dd, J=2.0, 8.5 Hz, ArH), 7.65 (1H, d, J=2.0 Hz, ArH), 7.67 (1H, d, J=8.5 Hz, ArH), 7.68 (1H, d, J=9.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.7 (CH_3), 45.4 (CH), 55.4 (CH_3), 61.8 (CH_2), 64.1 (CH_2), 69.1 (CH_2), 70.2 (CH_2), 70.4 (CH_2), 70.5 (CH_2). 70.6 (CH_2), 70.65 (CH_2), 70.7 (CH_2), 72.8 (CH_2), 72.9 (CH_2), 105.6 (CH), 119.1 (CH), 126.1 (CH), 126.4 (CH), 127.0 (CH), 129.0 (C), 129.4 (CH), 133.8 (C), 135.7 (C), 157.7 (C), 174.8 (CO); ν_{max} (neat/cm^{-1}) 3447, 2867, 1731, 1633, 1606, 1454, 1349, 1294, 1248, 1093, 944, 885, 851; m/z (ES$^+$) 561 (M+Na$^+$, n=6, 7%), 605 (M+Na$^+$, n=7, 29%), 649 (M+Na$^+$, n=8, 39%), 693 (M+Na$^+$, n=9, 23%), 737 (M+Na$^+$, n=10, 2%); found 627.3358; $C_{32}H_{51}O_{12}$ (n=8) requires 627.3381 (−3.6 ppm); $[\alpha]_D$ +106.0 (c 0.02, $CHCl_3$).

4.8. α-Tosylate-(PEG 400)-ω-2-(6-methoxynaphthalen-2-yl)propionate

Alcohol **4b** (0.625 g, 1.021 mmol, 1.0 equiv), toluene sulfonyl chloride (0.371 g, 1.943 mmol, 1.9 equiv), Et_3N (0.27 mL, 1.948 mmol, 1.9 equiv) and CH_2Cl_2 (5 mL) were stirred at room temperature for 21 h. CH_2Cl_2 (10 mL) and 0.2 M aqueous HCl (15 mL) were added. The resultant aqueous layer was further extracted with dichloromethane (3×5 mL) and the combined organic extracts were dried over $MgSO_4$. On filtration, silica (ca. 2 g) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH; 99:1 to 3:1) gave the title compound (0.550 g, 70%) as a thick colourless oil. R_f=0.30 (CH_2Cl_2/MeOH; 12:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, J=7.5 Hz, CH_3), 2.42 (3H, s, CH_3), 3.48 (4H, s, CH_2), 3.52–3.62 (12–40H, m, CH_2), 3.63–3.67 (2H, m, CH_2), 3.86 (1H, q, J=7.5 Hz, CH), 3.89 (3H, s, CH_3), 4.11 (2H, t, J=5.0 Hz, CH_2), 4.15–4.25 (2H, m, CH_2), 7.09 (1H, d, J=2.5 Hz, ArH), 7.11 (1H, dd, J=2.5, 9.0 Hz, ArH), 7.31 (2H, d, J=8.0 Hz, ArH), 7.39 (1H, dd, J=2.5, 8.5 Hz, ArH), 7.65 (1H, d, J=2.5 Hz, ArH), 7.65–7.69 (2H, m, ArH), 7.77 (2H, d, J=8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.8 (CH_3), 21.9 (CH_3), 45.5 (CH), 55.5 (CH_3), 64.2 (CH_2), 68.9 (CH_2), 69.2 (CH_2), 69.5 (CH_2), 70.65 (CH_2), 70.7 (CH_2), 70.75 (CH_2), 70.8 (CH_2), 70.9 (CH_2), 105.8 (CH), 119.2 (CH), 126.2 (CH), 126.5 (CH), 127.3 (CH), 128.2 (CH), 129.1 (C), 129.5 (CH), 130.0 (CH), 133.2 (C), 133.9 (C), 135.8 (C), 145.0 (C), 157.8 (C), 174.9 (CO); ν_{max} (neat/cm^{-1}) 2870, 1730, 1606, 1454, 1352, 1264, 1175, 1094, 1028, 922, 854, 814; m/z (ES$^+$) 666 (M+NH$_4^+$, n=5, 5%), 710 (M+NH$_4^+$, n=6, 11%), 754 (M+NH$_4^+$, n=7, 17%), 798 (M+NH$_4^+$, n=8, 19%), 842 (M+NH$_4^+$, n=9, 19%) 886 (M+NH$_4^+$, n=10, 16%), 930 (M+NH$_4^+$, n=11, 11%), 974 (M+NH$_4^+$, n=12, 2%); found 798.3697; $C_{39}H_{60}O_{14}NS$ (n=8) requires 798.3735 (−4.7 ppm); $[\alpha]_D$ +94.0 (c 0.02, $CHCl_3$).

4.9. α-Azido-(PEG 400)-ω-2-(6-methoxynaphthalen-2-yl)propionate

The PEG 400 tosylate (0.524 g, 0.683 mmol, 1.0 equiv), sodium azide (0.056 g, 0.861 mmol, 1.3 equiv) and DMF (10 mL) were stirred for 50 h. Ethanol (10 mL) was added and the solvent was removed under reduced pressure (repeated three times). The title compound (0.410 g, 94%) was thus obtained as a yellow oil. R_f=0.25 (EtOAc/MeOH; 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, J=7.0 Hz, CH_3), 3.46 (2H, br s, CH_2), 3.58 (4H, br s, CH_2), 3.62–3.81 (16–44H, m, CH_2), 3.86 (1H, q, J=7.0 Hz, CH), 3.89 (3H, s, CH_3), 4.14–4.26 (2H, m, 2H, CH_2), 7.08 (1H, d, J=2.5 Hz, ArH), 7.11 (1H, dd, J=2.5, 8.5 Hz, ArH), 7.38 (1H, dd, J=2.0, 8.5 Hz, ArH), 7.65 (1H, d, J=2.0 Hz, ArH), 7.66–7.69 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.8 (CH_3), 45.5 (CH), 50.9 (CH_2), 55.5 (CH_3), 64.2 (CH_2), 69.2 (CH_2), 70.2 (CH_2), 70.7 (CH_2), 70.8 (CH_2), 70.85 (CH_2), 70.9 (CH_2), 105.7 (CH), 119.2 (CH), 126.2 (CH), 126.5 (CH), 127.3 (CH), 129.1 (C), 129.5 (CH), 133.9 (C), 135.8 (C), 157.8 (C), 174.9 (CO); ν_{max} (neat/cm^{-1}) 2871, 2245, 2103, 1731, 1673, 1606, 1454, 1391, 1349, 1260, 1177, 1091, 1031, 908, 853, 811; m/z (ES$^+$) 630 (M+Na$^+$, n=7, 16%), 674 (M+Na$^+$, n=8, 50%), 718 (M+Na$^+$, n=9, 27%), 762 (M+Na$^+$, n=10, 6%), 806 (M+Na$^+$, n=11, 1%); found 674.3275; $C_{32}H_{49}O_{11}N_3Na$ (n=8) requires 674.3265 (+1.5 ppm); $[\alpha]_D$ +120.0 (c 0.02, $CHCl_3$).

4.10. α-Amino-(PEG 400)-ω-2-(6-methoxynaphthalen-2-yl)propionate 6

The azide (0.187 g, 0.294 mmol, 1.0 equiv) was dissolved in EtOH (20 mL) and 10% w/w Pd/C (0.070 g, 0.066 mmol, 0.2 equiv) was added before the mixture was stirred for 7 h under a hydrogen atmosphere (ca. 1.6 atm). The reaction mixture was filtered through Celite, washed with ethanol (3×10 mL), and the solvent was removed under reduced pressure. The material thus obtained as a colourless oil proved to be **6** (0.148 g, 82%). R_f=0.25 (EtOAc/MeOH; 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, 3H, J=7.0 Hz, CH_3), 2.74–2.88 (2H, m, CH_2), 3.48 (4H, s, CH_2), 3.52–3.57 (4H, m, CH_2), 3.58–3.64 (16–44H, m, CH_2), 3.86 (1H, q, J=7.0 Hz, CH), 3.89 (3H, s, CH_3), 4.14–4.26 (2H, m, CH_2), 7.08 (1H, d, J=2.5 Hz, ArH), 7.11 (1H, dd, J=2.5, 9.0 Hz, ArH), 7.38 (1H, dd, J=2.0, 8.5 Hz, ArH), 7.64 (1H, br s, ArH), 7.68 (1H, d, J=8.5 Hz, ArH), 7.67 (1H, d, J=9.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.8 (CH_3), 41.8 (CH_2), 45.5 (CH), 55.5 (CH_3), 64.2 (CH_2), 69.2 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.6 (CH_2), 70.7 (CH_2), 70.75 (CH_2), 70.9 (CH_2), 105.7 (CH), 119.2 (CH), 126.2 (CH), 126.5 (CH), 127.3 (CH), 129.1 (C), 129.5 (CH), 133.9 (C), 135.8 (C), 157.8 (C), 174.8 (CO); ν_{max} (neat/cm^{-1}) 3434, 2870, 1729, 1671, 1633, 1606, 1454, 1391, 1349, 1263, 1177, 1090, 1028, 947, 853, 813; m/z (ES$^+$) 494 (M+H$^+$, n=5, 2%), 538 (M+H$^+$, n=6, 7%), 582 (M+H$^+$, n=7, 18%), 626 (M+H$^+$, n=8, 22%), 670 (M+H$^+$, n=9, 18%), 714 (M+H$^+$, n=10, 13%), 758 (M+H$^+$, n=11, 9%), 802 (M+H$^+$, n=12, 6%); found 582.3260; $C_{30}H_{48}O_{10}N$ (n=7) requires 582.3278 (−3.1 ppm); $[\alpha]_D$ +95.0 (c 0.02, $CHCl_3$).

4.11. 2-(6-Methoxynaphthalen-2-yl)propionic acid 2-[2-(carboxymethoxy)ethoxy]ethyl ester 7

PDC (1.80 g, 4.785 mmol, 9.3 equiv) was added to a solution of alcohol **4a** (0.187 g, 0.515 mmol, 1.0 equiv) in dimethylformamide (4 mL). After 20 h, water (30 mL) was added and the mixture extracted with Et_2O (5×15 mL). The diethyl ether layers were combined and washed with brine (20 mL), before drying over $MgSO_4$. After filtration and solvent removal, the title compound **7** (0.112 g, 58%) was isolated yellow solid. R_f=0.35 (EtOAc/MeOH; 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.57 (3H, d, J=7.0 Hz, CH_3), 3.44–3.51 (4H, m, CH_2), 3.59–3.67 (2H, m, CH_2), 3.85–3.91 (1H, m, CH), 3.90 (3H, s, CH_3), 4.00 (2H, br s, CH_2), 4.20–4.26 (2H, m, CH_2), 7.09 (1H, d, J=2.5 Hz, ArH), 7.12 (1H, dd, J=2.5, 9.0 Hz, ArH), 7.40 (1H, dd, J=2.0, 8.5 Hz, ArH), 7.66 (1H, d, J=2.0 Hz, ArH), 7.68 (1H, d, J=8.5 Hz, ArH), 7.69 (1H, d, J=9.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.6 (CH_3), 29.9 (CH_2), 45.5 (CH), 55.5 (CH_3), 64.3 (CH_2), 69.4 (CH_2), 70.1 (CH_2), 70.7 (CH_2), 105.7 (CH), 119.2 (CH), 126.2 (CH), 126.4 (CH), 127.3 (CH), 129.0 (C), 129.4 (CH), 133.8 (C), 135.7 (C), 157.8 (C), 174.8 (CO), 176.5 (CO); ν_{max} (neat/cm^{-1}) 3441, 2937, 1730, 1604, 1506, 1484, 1454, 1420, 1392, 1373, 1324, 1233, 1176, 1121, 1087, 1029, 925, 890, 852, 811; m/z (ES$^+$) 399 (M+Na$^+$, 15%); found 399.1425; $C_{20}H_{24}O_7Na$ requires 399.1420 (+1.3 ppm).

4.12. Succinic mono-ester of 2-(6-methoxynaphthalen-2-yl)-propionic acid 2-[2-(2-hydroxyethoxy)ethoxy]ethyl ester 8

Under argon a mixture of **4a** (0.945 g, 2.607 mmol, 1.0 equiv) and succinic anhydride (0.261 g, 2.609 mmol, 1.0 equiv) in THF

(5 mL) was treated with concd H_2SO_4 (0.05 mL, ca. 0.938 mmol, 0.4 equiv) in THF (4 mL) and stirred under argon. The reaction progress was monitored by TLC (Hex/EtOAc; 1:1). After 2 h, concd H_2SO_4 (0.2 mL, 3.725 mmol, 1.4 equiv) was added and stirring was continued for a further 4 h. Chloroform (35 mL) and saturated brine solution (35 mL) were added. The resultant aqueous layer was extracted with $CHCl_3$ (3×15 mL) and the combined organic layers were dried over $MgSO_4$. Filtration, solvent removal under reduced pressure and purification by flash column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH; 99:1 to 9:1) gave **8** (0.424 g, 35%) as a colourless viscous oil. R_f=0.15 (Hex/EtOAc; 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) 1.59 (3H, d, J=7.0 Hz, CH_3), 2.61–2.73 (4H, m, CH_2), 3.45–3.55 (4H, m, CH_2), 3.59 (2H, t, J=4.5 Hz, CH_2), 3.66 (2H, t, J=5.0 Hz, CH_2), 3.87 (1H, q, J=7.0 Hz, CH), 3.89 (3H, s, CH_3), 4.22 (2H, t, J=4.5 Hz, CH_2), 4.24–4.29 (2H, m, CH_2), 7.13 (1H, d, J=2.5 Hz, ArH), 7.16 (1H, dd, J=2.5, 9.0 Hz, ArH), 7.43 (1H, dd, J=1.5, 8.5 Hz, ArH), 7.69 (1H, d, J=1.5 Hz, ArH), 7.71 (1H, d, J=8.5 Hz, ArH), 7.72 (1H, d, J=9.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.0 (CH_3), 29.0 (CH_2), 44.9 (CH), 53.0 (CH_2), 54.9 (CH_3), 63.4 (CH_2), 63.45 (CH_2), 68.5 (CH_2), 68.6 (CH_2), 69.8 (CH_2), 70.1 (CH_2), 105.1 (CH), 118.5 (CH), 125.4 (C), 125.5 (CH), 125.8 (CH), 126.7 (CH), 128.4 (C), 128.8 (CH), 133.2 (C), 135.1 (C), 157.2 (C), 172.2 (CO), 174.2 (CO), 174.9 (CO); ν_{max} (neat/cm^{-1}) 3105, 2937, 1729, 1632, 1605, 1506, 1485, 1453, 1391, 1374, 1262, 1231, 1217, 1159, 1029, 926, 890, 853, 811; m/z (ES^-) 461 ($M-H^-$, 100%); found 461.1833; $C_{24}H_{29}O_9$ requires 461.1812 (−4.6 ppm).

4.13. α-Hydroxy-(PEG 400)-ω-tosylate

PEG 400 (50 mL, ca. 140.0 mmol, 7.0 equiv), Et_3N (2.9 mL, 21.0 mmol, 1.1 equiv) and CH_2Cl_2 (20 mL) were stirred vigorously. A solution of toluene sulfonyl chloride (3.75 g, 20.0 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) was added slowly using a syringe pump (ca. 0.5 mL/h). Following addition, the reaction mixture was stirred for 24 h before a 1.0 M solution of HCl (25 mL), H_2O (25 mL) and a saturated solution of brine (30 mL) were added. The resultant aqueous layer was further extracted with dichloromethane (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed. The crude product was then purified by flash column chromatography (Hex/EtOAc; 3:1 to 4:5). This afforded the title compound (10.90 g, 99%) as a colourless oil. R_f=0.10 (EtOAc/MeOH; 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, CH_3), 2.88 (1H, br s, OH), 3.51–3.74 (22–50H, m, CH_2), 4.14 (2H, t, J=5.0 Hz, CH_2), 7.34 (2H, d, J=8.0 Hz, ArH), 7.79 (2H, d, J=8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (CH_3), 61.6 (CH_2), 68.5 (CH_2), 69.1 (CH_2), 70.2 (CH_2), 70.4 (CH_2), 70.6 (CH_2), 72.4I(CH_2), 72.5 (CH_2), 127.9 (CH), 129.7 (CH), 132.8 (C), 144.7 (C); ν_{max} (neat/cm^{-1}) 3415, 2874, 1720, 1647, 1454, 1350, 1292, 1245, 1176, 1092, 1010, 922, 885, 818; m/z (ES^+) 437 ($M+H^+$, n=5, 32%), 481 ($M+H^+$, n=6, 27%), 525 ($M+H^+$, n=7, 15%), 569 ($M+H^+$, n=8, 3%); found 525.2371; $C_{23}H_{41}O_{11}S$ (n=7) requires 525.2370 (+0.3 ppm).

4.14. α-Hydroxy-(PEG 400)-ω-thioacetate 9

To the above compound, α-hydroxy-ω-tosylate-PEG 400 (2.205 g, 3.981 mmol, 1.0 equiv), KSAc (0.684 g, 5.989 mmol, 1.5 equiv) and DMF (14 mL) were added and the mixture stirred under argon for 18 h. A saturated solution of NH_4Cl (10 mL), CH_2Cl_2 (12 mL) and brine (2 mL) were added and the resultant mixture was stirred vigorously for 15 min. The resultant aqueous layer was further extracted with dichloromethane (2×20 mL) and the organic layers were combined, dried, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH; 99:1 to 3:1) gave **9** (1.473 g, 81%) as a colourless oil. R_f=0.25 (CH_2Cl_2/MeOH; 12:1); ^{1}H NMR (400 MHz, $CDCl_3$) 2.32 (3H, s, CH_3), 3.07 (2H, t, J=6.5 Hz, CH_2), 3.55–3.74 (22–50H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) 28.7 (CH_2), 31.3 (CH_3), 61.5 (CH_2), 69.6 (CH_2), 70.2 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 195.4 (CO); ν_{max} (neat/cm^{-1}) 3451, 2868, 1687, 1454, 1350, 1294, 1249, 1092, 948, 884, 843; m/z (ES^+) 319 ($M+Na^+$, n=4, 10%), 363 ($M+Na^+$, n=5, 40%), 407 ($M+Na^+$, n=6, 80%), 451 ($M+Na^+$, n=7, 95%), 495 ($M+Na^+$, n=8, 100%), 541 ($M+Na^+$, n=9, 85%), 583 ($M+Na^+$, n=10, 65%), 627 ($M+Na^+$, n=11, 30%), 671 ($M+Na^+$, n=12, 15%); found 495.2245; $C_{20}H_{40}O_{10}SNa$ (n=8) requires 495.2240 (+1.0 ppm).

4.15. α-Tosylate-(PEG 400)-ω-thioacetate

α-Hydroxy-(PEG 400)-ω-thioacetate **9** (2.560 g, 5.59 mmol, 1.0 equiv) and Et_3N (1.80 mL, 12.99 mmol, 2.3 equiv) in CH_2Cl_2 (20 mL) were stirred at room temperature before a solution of toluene sulfonyl chloride (1.526 g, 8.00 mmol, 1.4 equiv) in CH_2Cl_2 (12 mL) was added. The mixture was stirred for 15 h. CH_2Cl_2 (15 mL), 0.6 M aqueous HBr solution (25 mL), then brine (12 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL) and the resultant organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH; 99:1 to 9:1) gave the title compound (3.024 g, 88%) as a colourless, viscous oil. R_f=0.25 (CH_2Cl_2/MeOH; 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) 2.33 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.08 (2H, t, J=6.5 Hz, CH_2), 3.57–3.70 (20–48H, m, CH_2), 4.15 (2H, t, J=4.5 Hz, CH_2), 7.34 (2H, d, J=8.0 Hz, ArH), 7.79 (2H, d, J=8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (CH_3), 28.7 (CH_2), 30.5 (CH_3), 68.3 (CH_2), 68.5 (CH_2), 69.2 (CH_2), 69.6 (CH_2), 70.2 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.6 (CH), 127.9 (CH), 129.7 (CH), 132.8 (C), 144.7 (C), 195.4 (CO); ν_{max} (neat/cm^{-1}) 2868, 1724, 1690, 1598, 1452, 1352, 1292, 1247, 1175, 1094, 1034, 1010, 917, 816; m/z (ES^+) 512 ($M+NH_4^+$, n=5, 3%), 556 ($M+NH_4^+$, n=6, 9%), 600 ($M+NH_4^+$, n=7, 16%), 644 ($M+NH_4^+$, n=8, 18%), 688 ($M+NH_4^+$, n=9, 19%), 732 ($M+NH_4^+$, n=10, 16%), 776 ($M+NH_4^+$, n=11, 11%), 820 ($M+NH_4^+$, n=12, 5%); found 644.2753; $C_{27}H_{50}O_{12}NS_2$ (n=8) requires 644.2774 (−3.3 ppm).

4.16. α-Azido-(PEG 400)-ω-thioacetate 10

The above tosylate (2.975 g, 4.861 mmol, 1.0 equiv) was dissolved in DMF (7 mL) and NaN_3 (0.348 g, 5.350 mmol, 1.1 equiv) in DMF (4 mL) was added. Stirring was continued for 18 h at room temperature before the solvent was removed under reduced pressure. CH_2Cl_2 (20 mL) and silica (ca. 2 g) were added and solvent was removed and the residue was purified by flash column chromatography (Hex/EtOAc; 9:1 to 1:9, then EtOAc, then EtOAc/MeOH; 9:1), which gave **10** (1.692 g, 72%) as a colourless oil. R_f=0.30 (EtOAc/MeOH; 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) 2.34 (3H, s, CH_3), 3.05 (2H, t, J=6.5 Hz, CH_2), 3.35 (2H, t, J=4.5 Hz, CH_2), 3.53–3.72 (20–48H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) 28.5 (CH_2), 30.3 (CH_3), 38.0 (CH_2), 50.4 (CH_2), 68.8 (CH_2), 69.3 (CH_2), 69.5 (CH_2), 69.8 (CH_2), 70.0 (CH_2), 70.1 (CH_2), 70.2 (CH_2), 70.3 (CH_2), 70.4 (CH_2), 76.5 (CH_2), 76.8 (CH_2), 77.0 (CH_2), 77.1 (CH_2), 195.3 (CO); ν_{max} (neat/cm^{-1}) 2920, 2860, 2101, 1736, 1689, 1456, 1349, 1288, 1248, 1094, 947, 848; m/z (ES^+) 476 ($M+Na^+$, n=7, 1%), 520 ($M+Na^+$, n=8, 16%), 564 ($M+Na^+$, n=9, 48%), 608 ($M+Na^+$, n=10, 32%), 652 ($M+Na^+$, n=11, 3%); found 520.2297; $C_{20}H_{39}N_3O_9SNa$ (n=8) requires 530.2305 (−1.5 ppm).

4.17. α-Amino-(PEG 400)-ω-mercaptan 11

Under argon at −10 °C, $LiAlH_4$ (0.653 g, 17.21 mmol, 4.5 equiv) was stirred in dry flask. A solution of **10** (1.839 g, 3.807 mmol, 1.0 equiv) in THF (10 mL) was slowly added and the mixture was stirred for 2 h. The presence of a thiol group was confirmed with DTMB (Ellman's reagent) and the amino group was confirmed with ninhydrin. Degassed H_2O (5 mL) was cautiously added. This mixture was then centrifuged for 10 min (3000 rpm), filtered and the

solid residue was washed with EtOH (30 mL). The process of centrifugation and separation was repeated. The solutions were combined and the solvent was removed under reduced pressure to afford **11** (0.981 g, 62%) as a colourless oil. The solid residue was then washed again with THF (5 mL), MeOH (10 mL) and CH_2Cl_2 (10 mL). These washings were combined, filtered and evaporated. The crude residue was dissolved CH_2Cl_2 (12 mL) and extracted with H_2O (2×12 mL). The aqueous layers were combined and further extracted with CH_2Cl_2 (3×6 mL). The organic layers were combined, washed with brine (12 mL), dried over $MgSO_4$, filtered and the solvent was removed, which gave **11** (0.556 g, 35%) [combined total yield (1.538 g, 97%)]. R_f=0.25 (CH_2Cl_2/MeOH; 12:1); ^{1}H NMR (400 MHz, $CHCl_3$) 1.07–1.28 (1H, m, SH), 1.97 (2H, s, NH_2), 2.57–2.92 (6H, m, CH_2), 3.41–3.82 (18–46H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) 24.5 (CH_2SH), 41.8 (CH_2NH_2), 70.5 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 72.7 (CH_2), 73.1 (CH_2); ν_{max} (neat/cm^{-1}) 3362, 2863, 1603, 1455, 1349, 1295, 1248, 1094, 945; *m*/*z* (ES$^+$) 386 (M+H$^+$, *n*=7, 1%), 430 (M+H$^+$, *n*=8, 36%), 474 (M+H$^+$, *n*=9, 36%), 518 (M+H$^+$, *n*=10, 18%), 562 (M+H$^+$, *n*=11, 8%), 606 (M+H$^+$, *n*=12, 1%); found 430.2486; $C_{18}H_{40}NO_8S$ (*n*=8) requires 430.2475 (+2.6 ppm).

4.18. {2-[2-(2-Aminoethoxy)ethoxy]ethyl}carbamic acid *tert*-butyl ester 17[18]

Boc_2O (5.992 g, 27.46 mmol, 1.0 equiv) in 1,4-dioxane (40 mL) was added slowly (over a 7 h period) to a vigorously stirred solution of diamine **16** (25.0 mL, 171.20 mmol, 6.2 equiv) in 1,4-dioxane (175 mL). The reaction mixture was stirred at room temperature for 17 h before solvent removal under reduced pressure. Water (60 mL) was added and the mixture was extracted with chloroform (10×25 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (basic Al_2O_3/Hex→Hex/EtOAc; 9:1→1:1→EtOAc→EtOAc/MeOH; 9:1), which afforded the title compound **17** (5.482 g, 80%) as a colourless oil. R_f=0.05 (CH_2Cl_2/MeOH; 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.16–1.46 (2H, m, CH_2), 1.40 (9H, s, CH_3), 2.69–3.04 (2H, br s, NH_2), 3.24–3.31 (2H, m, CH_2), 3.46–3.54 (4H, m, CH_2), 3.58 (4H, s, CH_2), 5.14 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) 28.6 (CH_3), 40.5 (CH_2), 41.9 (CH_2), 70.4 (C), 70.45 (CH_2), 73.7 (CH_2), 79.4 (CH_2), 156.2 (CO); ν_{max} (neat/cm^{-1}) 3363, 2974, 2869, 1693, 1521, 1454, 1391, 1365, 1275, 1249, 1169, 1100, 967, 863; *m*/*z* (ES$^+$) 249 (M+H$^+$, 100%); found 249.1805; $C_{11}H_{25}N_2O_4$ requires 249.1814 (−3.7 ppm).

4.19. [2-(2-{2-[2-(6-Methoxynaphthalen-2-yl)-propionylamino]ethoxy}ethoxy)ethyl]carbamic acid *tert*-butyl ester

Under argon, naproxen **1** (0.354 g, 1.536 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8 mL) and cooled to −10 °C. DCC (0.398 g, 1.927 mmol, 1.3 equiv) was added and the mixture stirred for 6 min before a solution of the amine **17** (0.381 g, 1.535 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added in a dropwise fashion. Stirring was continued at approx. −10 °C for 45 min, then at room temperature for 70 min. The reaction mixture was centrifuged, filtered, then extracted with a 1.5 M NaOH solution (10 mL). The resultant aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined CH_2Cl_2 layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by flash column chromatography (Hex to Hex/EtOAc; 9:1 to 1:1, then EtOAc) gave the title compound (0.536 g, 76%) as a colourless solid. Further purification (removing traces of dicyclohexylurea) by recrystallisation (Hex/EtOAc; 5:1) gave the adduct as colourless, needle shaped crystals. Mp 93–96 °C (Hex/EtOAc; 5:1); R_f=0.10 (Hex/EtOAc 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 (9H, s, CH_3), 1.56 (3H, d, *J*=7.0 Hz, CH_3), 3.15–3.21 (2H, m, CH_2), 3.31–3.47 (10H, m, CH_2), 3.67 (1H, q, *J*=7.0 Hz, CH), 3.89 (3H, s, CH_3), 4.87 (1H, s, NH), 5.85 (1H, s, NH), 7.08–7.14 (2H, m, ArH), 7.34–7.14 (1H, m, ArH), 7.63–7.70 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.7 (CH_3), 28.6 (CH_3), 39.5 (CH_2), 40.4 (CH_2), 47.2 (CH), 55.5 (CH_3), 70.0 (CH_2), 70.2 (CH_2), 70.25 (CH_2), 70.4 (CH_2), 79.5 (C), 105.8 (CH), 119.3 (CH), 126.2 (CH), 126.5 (CH), 127.6 (CH), 129.2 (C), 129.4 (CH), 133.9 (C), 136.8 (C), 156.1 (C), 157.9 (CO), 174.5 (CO); ν_{max} (neat/cm^{-1}) 3351, 3322, 3059, 2977, 2938, 2879, 1682, 1644, 1606, 1537, 1464, 1389, 1364, 1252, 1210, 1171, 1128, 1029, 972, 924, 850, 809; *m*/*z* (ES$^+$) 461 (M+H$^+$, 100%); found 461.2643; $C_{25}H_{37}N_2O_6$ requires 461.2652 (−1.9 ppm); $[\alpha]_D$ 0 (*c* 0.64, $CHCl_3$).

4.20. *N*-{2-[2-(2-Aminoethoxy)ethoxy]ethyl}-2-(6-methoxynaphthalen-2-yl)propionamide 18

A solution of the above amide (0.987 g, 2.144 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) was cooled (approx. −5 °C) before TFA (7 mL) was added. After 2.5 h, the mixture was diluted with CH_2Cl_2 (30 mL), transferred to a separating funnel and shaken with a solution of 35% NH_3 (30 mL). The resultant aqueous layer was then extracted with CH_2Cl_2 (3×10 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and filtered. Following solvent removal, the amine **18** (0.768 g, 99%) was obtained as a yellow solid. Mp 66–68 °C; R_f=0.05 (CH_2Cl_2/MeOH; 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.53 (3H, d, *J*=7.0 Hz, CH_3), 2.56 (2H, br s, NH_2), 2.72 (2H, t, *J*=5.0 Hz, CH_2), 3.29–3.48 (10H, m, CH_2), 3.68 (1H, q, *J*=7.0 Hz, CH), 3.78 (3H, s, CH_3), 6.36 (1H, br s, NH), 7.06–7.12 (2H, m, ArH), 7.35–7.39 (1H, m, ArH), 7.64–7.68 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.8 (CH_3), 39.5 (CH_2), 41.3 (CH_2), 47.0 (CH), 55.5 (CH_3), 70.1 (CH_2), 70.15 (CH_2), 70.3 (CH_2), 72.1 (CH_2), 105.7 (CH), 119.2 (CH), 126.2 (CH), 126.5 (CH), 127.5 (CH), 129.1 (C), 129.4 (CH), 133.8 (C), 137.0 (C), 157.8 (C), 174.8 (CO); ν_{max} (neat/cm^{-1}) 3300, 3058, 2872, 1642, 1605, 1543, 1486, 1455, 1390, 1357, 1262, 1211, 1117, 1025, 925, 890, 856; 813; *m*/*z* (ES$^+$) 361 (M+H$^+$, 100%); found 361.2124; $C_{20}H_{29}N_2O_4$ requires 361.2127 (−0.9 ppm); $[\alpha]_D$ 0 (*c* 0.025, $CHCl_3$).

4.21. *N*-(2-{2-[2-(3,4-Dihydroxybenzylamino)ethoxy]-ethoxy}ethyl)-2-(6-methoxynaphthalen-2-yl)-propionamide 19

Amine **18** (0.361 g, 1.00 mmol, 1.0 equiv), $MgSO_4$ (ca. 0.5 g) and 3,4-dihydroxybenzaldehyde **14** (0.139 g, 1.00 mmol, 1.0 equiv) were stirred for 48 h in CH_2Cl_2 (20 mL). The mixture was filtered and the solvent removed under reduced pressure affording the imine (0.482 g, quant.) as a yellow amorphous solid [mp 58–73 °C (decomp.)]. MeOH (25 mL) was added to the imine (0.433 g, 0.901 mmol, 1.0 equiv) and due to poor solubility 1,4-dioxane (7 mL) was also added and the mixture agitated to effect dissolution. Solid $NaBH_4$ (0.155 g, 4.084 mmol, 4.5 equiv) was then added and the reaction mixture was stirred for 2 h. The bulk of the solvent was removed and EtOAc (15 mL) and saturated NH_4Cl (25 mL) were added. The resultant aqueous layer was then re-extracted with EtOAc (4×15 mL) and finally with $CHCl_3$ (5×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Thus, the title compound **19** (0.300 g, 69%) was obtained as a brown, glassy, amorphous solid. R_f=0.10 (CH_2Cl_2/MeOH; 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.47 (3H, d, *J*=7.0 Hz, CH_3), 2.62–2.70 (2H, m, CH_2), 3.19–3.45 (12H, m, CH_2), 3.66 (1H, q, *J*=7.0 Hz, CH), 3.84 (3H, m, CH_3), 6.44–6.56 (4H, m, ArH, NH), 7.03 (1H, br s, ArH), 7.07 (1H, dd, *J*=2.0, 8.5 Hz, ArH), 7.34 (1H, d, *J*=8.5 Hz, ArH), 7.55–7.66 (3H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 18.3 (CH_3), 29.7 (CH_2), 39.1 (CH_2), 39.3 (CH_2), 45.9 (CH), 55.0 (CH_3), 69.9 (CH_2), 70.0 (CH_2), 70.2 (CH_2), 70.3 (CH_2), 105.3 (CH), 108.3 (CH), 109.8 (CH), 118.5 (CH), 120.9 (CH), 125.6 (CH), 126.2 (CH), 126.6 (CH), 128.5 (C), 128.9 (CH), 133.3 (C), 136.7 (C), 136.8 (C), 151.0 (C), 152.1 (C), 157.2 (C), 174.8 (CO); ν_{max}

(neat/cm^{-1}) 1651, 1606, 1541, 1491, 1451, 1370, 1264, 1231, 1212, 1122, 1056, 853; *m/z* (ES^+) 483 ($M+H^+$, 100%); found 483.2478; $C_{27}H_{35}N_2O_6$ requires 483.2495 (−3.5 ppm); $[\alpha]_D$ 0 (*c* 0.145, $CHCl_3$).

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