Experimental Section

All *in vitro* testing was carried out at the University of Oxford in the Department of Physiology, Anatomy & Genetics. Affinity and transport studies were carried out using *Xenopus laevis* oocytes as previously reported.[21] Caco-2 cell line was obtained from American Type Culture Collection, (Rockbille, MD, USA). Cells were grown routinely on 75 cm^2 plastic culture flasks (Falcon) in EMEM supplemented with 10% (v/v) foetal calf serum (FCS) and 1% (v/v) penicillin–streptomycin at 37 °C in an atmosphere of 5% CO_2 and 90% relative humidity. The medium was replaced every 2–3 days after incubation. Cells were passaged, 1:5, approximately every 5 days (at 70–80% confluence) using 0.25% (w/v) Trypsin – 0.53 mM EDTA.

Transcellular transport studies were performed on Caco-2 cell monolayers grown on Corning Transwell permeable supports (0.4 µm pore size, 0.33 cm^2 area polyester membrane; Appleton Woods Ltd, Birmingham, UK) until confluent (>18 days, trans-epithelial electrical resistance (TEER) >1000 Ω cm^{-2}). The compounds were added to the apical medium (250 µL Krebs pH 5.5 buffer) to give a final concentration of 2 mM. The cells were incubated at 37 °C for one hour, and the basolateral medium (600 µL Krebs pH 7.4 buffer) assayed by HPLC. The PepT1-mediated transport rate was taken to be the difference between the transport rates in the absence and presence of 20 mM Gly-L-Gln in the apical compartment during the incubation period, with at least three monolayers per compound. The rate of PheΨ[CS-NH]-Ala was used as a control to normalise between cultures of Caco-2 cells. A similar procedure was followed for the pH dependence assay using an apical Krebs medium buffered to either pH 5.5 or 7.4.

Separation was on a Chromolith RP18e 100-3 mm column (VWR, Leicestershire, UK) with 50% (v/v) methanol in 21 mM aqueous KH_2PO_4 mobile phase at 1 ml min^{-1}, and detection at 210 nm on a Jasco UV2077Plus UV/VIS detector (Jasco UK Ltd, Essex, UK). Each sample was injected in duplicate. HPLC data analysis was performed using EZChrom Elite software (Scientific Software Inc, Pleasanton CA, USA).

Anhydrous solvents and reagents were obtained as follows: DMF was dried three times over molecular sieves (3 Å). DCM was dried by distillation over CaH_2. All reactions were conducted in dry glassware under a nitrogen atmosphere. All chemicals were used directly from the supplier's (Sigma-Aldrich) vessel without further purification. Protected amino acids were supplied by Novabiochem.

^{1}H NMR spectra were recorded at 300, 400 or 500 MHz and ^{13}C NMR spectra at 75, 100 or 125 MHz on a Bruker AC300, AC400, Avance II or Varian Unity INOVA 300 spectrometer. Chemical shifts are denoted in ppm (δ) relative to the internal solvent standard. The splitting patterns for NMR spectra are designated as follows: s (singlet), br (broad), d (doublet), t (triplet), p (pentet), m (multiplet), or combinations thereof. Coupling constants (*J*) are designated in Hz and reported to 1 decimal place. Assignments were made with the aid of DEPT135, COSY and HMQC experiments.

ES-MS (and HRMS) spectra were recorded on a Micromass LCT orthogonal acceleration time-of-flight mass spectrometer (positive ion mode) with flow injection *via* a Waters 2790 separation module autosampler. IR spectra were obtained using a Nicolet-Nexus 670/680 FT-IR or ATI Mattson Genesis Series FT-IR spectrometer and are quoted in cm^{-1}. Optical rotations were measured at 589 nm in a 1 dm cell using an Optical Activity AA1000 polarimeter and are quoted in 10^{-2} deg cm^2 g^{-1}. Melting point determinations were made using a Stuart Scientific SMP1 apparatus and are uncorrected.

Detailed experimental for the synthesis of **16** follows and is representative of the conditions used for the synthesis of **17**.

4-(6-Methoxy-naphthalen-2-yl)-butan-2-one oxime, 2

Nabumetone **1** (1 g; 4.35 mmol) and hydroxylamine.HCl (325 mg; 4.7 mmol) was dissolved in 40 ml ethanol and stirred for 72 hours at room temperature. 4 M NaOH was added dropwise until a white precipitate began to form. The suspension was stirred for a further 8 hours at room temperature. It was then cooled to -10°C, the precipitate filtered and dried under vacuum to give **2** as a white crystalline solid (Yield = 0.952 g; 91%).

Melting point: 128-129 °C. R_f (4:1 hex:EtOAc) 0.34 & 0.24. u_{max}(DCM, cm^{-1}): 3954, 2986, 1510, 1421, 1272, 896, 742, 705. δ_H (400 MHz, $CDCl_3$): 7.72-7.70 (2H, m), 7.62-7.59 (1H, m), 7.38-7.32 (1H, m), 7.29 (1H, s), 7.17-7.16 (1H, m), 3.94 (3H, s), 3.02-2.97 (2H, m), 2.79-2.75 (0.67H, m), 2.63-2.59 (1.33H, m), 1.97 (2H, s), 1.85 (1H, s). δ_C (100 MHz, $CDCl_3$): 158.8, 157.7, 136.6, 133.5, 129.5, 129.4, 127.9, 127.3, 126.7, 125.7, 119.2, 106.0, 55.7, 38.2, 33.1, 30.1, 20.8, 14.2. MS: $C_{15}H_{17}NO_2$ *m/z* (ES^+) 344.1 [$M+H^+$]. HRMS: Calculated $C_{15}H_{18}NO_2$: 244.1332, found: 244.1335.

4-(6-Methoxy-naphthalen-2-yl)-butan-2-one O-{2-[2-(2-benzyloxy-ethoxy)-ethoxy]-ethyl}-oxime, 10.

A solution of **2** (388 mg; 1.6 mmol), **8** (490 mg; 1.9 mmol), potassium *tert*-butoxide (192 mg; 1.7 mmol) and potassium iodide (295 mg; 1.8 mmol) in 10 cm^3 DMF was stirred at room temperature for 30 hours. The DMF was removed *in vacuo* and the residue taken up in 10 ml EtOAc. The cloudy mixture was washed successively with water (10 cm^3); $NaHCO_3$ (sat.) (10 cm^3l) and 0.6 M citric acid (10 cm^3) to give a golden brown organic layer which was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (4:1 hex:EtOAc → 1:1 hex:EtOAc) to give **10** (mix of *cis* and *trans* isomers, 2:1 *E:Z* by NMR) as brown oil (Yield = 702 mg; 95%).

R_f (4:1 hex:EtOAc): 0.26 & 0.18 u_{max} (Thin film, cm^{-1}): 2866, 1609, 1585, 1484, 1454, 1391, 1366, 1264, 1229, 1118, 1031, 946, 850. δ_H (300 MHz, $CDCl_3$): 7.70 (1H, s), 7.68 (1H, s), 7.57 (1H, s), 7.36-7.29 (6H, m), 7.15-7.12 (2H, m), 4.59 (1.33H, s), 4.54 (0.67H, s), 4.19-4.18 (2H, m), 3.92 (3H, s), 3.68-3.63 (10H, m), 2.99-2.94 (2H, m), 2.74-2.68 (0.67H, m), 2.58-2.53 (1.33H, m), 1.90 (2H, s), 1.81 (1H, s). δ_C (75 MHz, $CDCl_3$): 158.4, 157.6, 138.6, 136.7, 133.5, 129.4, 128.7-128.0, 127.9, 127.2, 126.7, 126.6, 119.1, 106.0, 73.0, 72.9, 71.0, 70.1, 69.8, 55.7, 38.1, 33.1, 32.0, 31.8, 20.8, 14.9. MS: $C_{28}H_{35}NO_5$ *m/z* (ES^+) 466.0 [$M+H^+$].

4-(6-Methoxy-naphthalen-2-yl)-butan-2-one O-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl}-oxime, 12.

10 (93 mg; 0.22 mmol) was dissolved in 8 cm^3 of ethanol and 110 mg 5% palladium hydroxide on carbon was added. The mixture was stirred for two hours at room temperature under hydrogen at atmospheric pressure. The mixture was filtered through a Celite® bed and the solvent removed under vacuum to give **12** (mix of *cis* and *trans* isomers, 2:1 *E:Z* by NMR) as a cream solid (Yield = 73 mg; 99%).

R_f (4:1 DCM:Et_2O): 0.53 & 0.42. u_{max} ($CHCl_3$, cm^{-1}): 3440, 2924, 1607, 1604, 1585, 1484, 1455, 1391, 1367, 1349, 1265, 1229, 1120, 1069, 1032, 939, 887, 850. δ_H (400 MHz, $CDCl_3$): 7.78 (1H, s), 7.76 (1H, s), 7.66 (1H, s), 7.42-7.39 (1H, m), 7.36 (1H, s), 7.20 (1H, s), 4.21-4.19 (2H, m), 3.86 (3H, s), 3.75 (2H, t, *J* = 4.0 Hz), 3.68-3.63 (8H, m), 3.05-2.99 (2H, m), 2.80-2.78 (0.67 H, m), 2.67-2.65 (1.33H, m), 1.98 (2H, s), 1.91 (1H, s). δ_C (100 MHz, $CDCl_3$): 158.1, 158.0, 136.8, 129.4, 127.9, 127.2, 126.7, 126.6, 119.1, 106.0, 72.9, 71.0, 70.8, 70.7, 70.2, 69.8, 62.0, 55.7, 38.1, 33.1, 32.0, 31.8, 20.8, 14.9. MS: $C_{21}H_{29}NO_5$ *m/z* (ES^+) 398.0 [$M+Na^+$]. HRMS: Calculated $C_{21}H_{30}NO_5$: 376.2118, found: 376.2131.

2-(2-tert-Butoxycarbonylamino-thiopropionylamino)-succinic acid 1-tert-butyl ester 4-[2-(2-{2-[3-(6-methoxy-naphthalen-2-yl)-1-methyl-propylideneaminooxy]-ethoxy}-ethoxy)-ethyl] ester, 14.

A solution of **23** (38 mg; 0.1 mmol), HBTU (40 mg; 0.1 mmol) and DIPEA (0.02 cm^3; 0.1 mmol) in 1 cm^3 DCM was stirred at room temperature for 30 minutes. A solution of **12** (28 mg; 0.075 mmol) in 1 cm^3 DCM was then added to the activated acid. After 5 days the solvent was removed *in vacuo* and the residue purified by flash column chromatography (9:1 DCM:Et_2O → 4:1 DCM:Et_2O) to give **14** (mix of *cis* and *trans* isomers, 2:1 *E:Z* by NMR) as a colourless oil (Yield = 30 mg; 54%).

R_f (4:1 DCM:Et_2O): 0.36 & 0.48. δ_H (300 MHz, $CDCl_3$): 8.53 (1H, d, *J* = 7.2 Hz), 7.53 (1H, s), 7.51 (1H, s), 7.41 (1H, s), 7.17-7.11 (1H, m), 6.98-6.96 (2H, m), 5.15-5.05 (1H, m), 4.09-4.00 (4H, m), 3.76 (3H, s), 3.62-3.45 (8H, m). 3.02 (1H, dd, *J* = 17.3 & 4.5), 2.90 (1H, dd, *J* = 17.3 & 3.8), 2.83-2.78 (2H, m), 2.59-2.51 (0.67H, m), 2.43-2.38 (1.33H, m), 1.74-1.71 (2H, m), 1.65-1.63 (1H, m), 1.31-1.28 (21H, m). δ_C (100 MHz, $CDCl_3$): 205.5, 170.9, 168.8, 158.0, 155.2, 136.7, 133.5, 129.4, 129.3, 128.0, 127.2, 126.7, 119.1, 106.0, 83.5, 80.5, 73.0, 71.0, 70.8, 70.1, 69.2, 64.4, 55.7*, 54.4, 38.0, 35.2, 33.1, 32.0, 31.8, 28.7, 28.2, 22.3, 20.8, 14.9. *Signal correlated to both OCH_3 and Ala-CH. MS: $C_{37}H_{55}N_3O_{10}S$ *m/z* (ES^+) 756.3 [$M+Na^+$]. HRMS: Calculated $C_{37}H_{55}N_3O_{10}SNa$: 756.3500, found: 756.3492.

2-(2-Amino-thiopropionylamino)-succinic acid 4-[2-(2-{2-[3-(6-methoxy-naphthalen-2-yl)-1-methyl-propylideneaminooxy]-ethoxy}-ethoxy)-ethyl] ester, 16.

1 cm^3 TFA was added to a solution of **14** (30 mg; 0.041 mmol) in 1 cm^3 DCM. Stirred at room temperature for 5 hours at which time the solution was aquamarine green in colour. The solvent was removed *in vacuo* and the residue taken up in water and lyophilized to give **16** as a white hygroscopic solid (mix of *cis* and *trans* isomers, 2:1 *E:Z* by NMR and HPLC) (Yield = 24 mg; 86% as TFA salt).

HPLC R_T: 5.8 and 6.2 min. R_f (1:1:1:1 EtOAc:BuOH:H_2O:CH_3CO_2H): 0.44. $[\alpha]_D^{24}$ (MeOH; c = 0.21): +31.07. δ_H (400 MHz, CD_3OD): 7.72 (1H, s), 7.70 (1H, s), 7.60-7.59 (1H, m), 7.37-7.33 (1H, m), 7.22 (1H, s), 7.12 (1H, d *J* = 9.0 Hz), 5.43-5.41 (1H, m), 4.33-4.21 (3H, m), 4.15-4.09 (2H, dt, *J* = 4.5 & 11.0 Hz), 3.92 (3H, s), 3.75-3.43 (8H, m), 3.18-3.03 (2H, m), 2.80 (2H, t, *J* = 7.5 Hz), 2.76-2.72 (0.67H, m), 2.60 (1.33H, t, *J* = 7.5 Hz), 1.91 (2H, s), 1.81 (1H, s), 1.58 (2H, d, *J* = 6.2 Hz), 1.51 (1H, d, *J* = 6.2 Hz). δ_C (100 MHz, D_2O): 200.8, 173.0†, 172.1, 163.4, 163.2†, 157.1, 136.8, 133.2, 129.1, 127.9, 127.1, 126.9, 125.6, 118.1, 106.0, 72.4, 70.1, 68.5, 64.6, 55.1*, 54.1, 36.9, 35.0, 32.0, 22.3, 19.9, 14.2. *Signal correlated to both OCH_3 and Ala-CH. MS: $C_{28}H_{39}N_3O_8S$ *m/z* (ES^+) 578.6 [$M+H^+$]. HRMS: Calculated $C_{28}H_{40}N_3O_8S$: 578.2531, found: 578.2535. † minor rotamer.

2-(2-Amino-thiopropionylamino)-succinic acid 4-{2-[3-(6-methoxy-naphthalen-2-yl)-1-methyl-propylideneaminooxy]-ethyl} ester, 17.

As a 2:1 mix of *E:Z* isomers by NMR and HPLC.

HPLC R_T: 7.8 and 8.2 min. R_f (1:1:1:1 EtOAc:BuOH:H_2O:CH_3CO_2H): 0.56. $[\alpha]_D^{34}$ (MeOH; c = 0.51) 25.89. δ_H (500 MHz, CD_3OD): 7.63-7.68 (2H, m), 7.54 (1H, s), 7.31 (1H, ddd, *J* = 1.6, 8.2 & 13.3 Hz), 7.15 (1H, d, *J* = 2.2 Hz), 7.05 (1H, m), 5.33-5.38 (1H, m), 4.16-4.30 (3H, m), 4.10-4.13 (2H, m), 3.86 (3H, s), 2.96-3.08 (2H, m), 2.92 (2H, t, *J* = 7.8 Hz), 2.67 (0.4H, t, *J* = 7.7 Hz), 2.52 (1.4H, t, *J* = 7.7 Hz), 1.85 (2H, s), 1.74 (1H, s), 1.49-1.54 (3H, m). δ_C (125 MHz, CD_3OD): 202.2, 172.1, 171.7, 158.9, 137.7, 134.9, 130.8, 130.7, 130.3, 129.8, 128.7, 127.8, 120.0, 119.7, 106.9, 106.6, 72.0, 64.0, 63.6, 56.3, 55.7, 54.5, 37.5, 35.8, 33.8, 21.3, 20.3, 15.1. MS: $C_{24}H_{31}N_3O_6S$ *m/z* (ES^+) 490.1 [$M+H^+$]. HRMS: Calculated $C_{24}H_{32}N_3O_6S$: 490.2006, found 490.2008. Elemental Analysis calculated for $C_{24}H_{31}N_3O_6S.CF_3CO_2H.½H_2O$ (C, H, N): 50.97, 5.43, 6.86%. found: 50.49, 5.43, 6.87%.