Experimental Section

General. All reagents were obtained from Aldrich, and all solvents from VWR, unless otherwise indicated. Anhydrous solvents (e.g. THF, DMF, dichloromethane) were used as received.

Reaction progress was monitored with analytical thin-layer chromatography (TLC) plates on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved using phosphomolybdic acid (PMA), potassium permanganate, or ninhydrin spray reagents, or UV illumination.

^{1}H and ^{13}C NMR spectra were obtained at 300 MHz and 75 MHz, respectively, on a Varian or Bruker spectrometer and are reported in parts per million downfield relative to tetramethylsilane (TMS) or to proton resonances resulting from incomplete deuteration of the NMR solvent (δ scale). Mass spectra were obtained at the University of California at Berkeley, using chemical ionization. Final compounds **1-39** were determined to be >95% pure by HPLC.

BACE enzyme (MBP-C125) assay

β-Cleavage ELISA assays were carried out in 200 mM sodium acetate, pH 4.8, 0.06% Triton X-100, with 10 μg/ml-1 MBPAPPC125 (or MBP-C125). MBP-C125 is a fusion protein containing the maltose-binding protein at the amino terminal end connected to the carboxyl-terminal 125 amino acids of APP at the carboxyl terminal end. Reaction mixtures were incubated at 37 °C for 1-2 h , and the quenched reaction mixtures were then loaded onto 96-well plates coated with a polyclonal antibody raised to MBP. Generated β-cleaved product was detected using biotinylated Sw192 or biotinyated

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

Wt192 as specific reporter antibodies and quantitated against the appropriate MBP-C26 standard.

The reported data are an average of two or more runs. For all the compounds tested, the (standard error) / (mean value) ≤ 0.2, except for the following compounds: **2** (0.41), **3** (0.26), **7** (0.22), **23** (0.40), **32** (0.25), **35** (0.30).

20%

Aβ cell assay

The 293Swe cell assays were performed according to the protocol outlined in ref. 3 of the text.

Peptide synthesis

The peptide inhibitors were generated in a peptide synthesizer using Boc-protected amino acids for chain assembly. All chemicals, reagents, and Boc amino acids were purchased from Applied Biosystems (ABI; Foster City, CA) with the exception of dichloromethane (DCM) and N,N-dimethylformamide (DMF) which were from Burdick and Jackson and Boc-statine which was purchased from Neosystem. The starting resin, Boc-Phe-OCH2-Pam resin was also purchased from ABI. All amino acids were coupled following preactivation to the corresponding HOBT ester using 1.0 equivalent of 1-hydroxybenzotriazole (HOBT), and 1.0 equivalent of N,N-dicyclohexylcarbodiimide (DCC) in DMF. The Boc protecting group on the amino acid α-amine was removed with 50% trifluoroacetic acid in DCM after each coupling step and prior to hydrogen fluoride (HF) cleavage. Amino acid side chain protection was as follows: Glu(Bzl). All

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

other amino acids were used with no further side chain protection including Boc-Statine [(Bzl) benzyl, (CBZ) carbobenzyloxy, (Cl-CBZ) chlorocarbobenzyloxy, (OBzl) O-benzyl]. The side chain protected peptide resin was deprotected and cleaved from the resin by reacting with anhydrous HF at 0 °C for one hour. This generated the fully deprotected crude peptide as a C-terminal carboxylic acid.

HPLC purification of peptides

Following HF treatment, the peptide was extracted from the resin in acetic acid and lyophilized. The crude peptide was then purified using reverse phase HPLC on a Phenomenex Luna C18(2), 5 µm column 4.6 mm I.D. x 25 cm in length [P] or a Vydac C18, 10µm column 4.6 mm I.D. x 25 cm in length [V]. The solvent systems used with these columns were [A] = 0.1% trifluoroacetic acid / H_2O and [B] = 0.1% trifluoroacetic acid / acetonitrile as the mobile phase. The gradient conditions were as follows: (1) 20-50% [B] in 30 min. at 1mL/min; (2) 30% [B] hold 5 min., 30-60% [B] in 30 min. at 1mL/min; (3) 35% [B] hold 5 min.; 35-65%[B] in 30 min. at 1mL/min. Gradient conditions and columns are reported in sequential order, e.g. (1, V). The purified peptide was subjected to mass spectrometry, and analytical reverse phase HPLC to confirm its composition and purity.

Phenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**2**). MH+ = 740.8; retention time =26.4 min (3, V).

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

3, 5-Difluorophenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**3**). MH+ = 775.5; retention time =18.6 min (1, V).

(*R*)-Mandelyl [Sta]-Val-Ala-Glu-Phe-OH (**4**). MH+ = 778.4; retention time =14.1 min (1, P).

4-Biphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**5**). M+Na = 838.7; retention time =21.3 min (2, V).

1-Naphthylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**6**). MH+ = 790.6; retention time =26.4 min (2, V).

3, 4, 5-Trimethoxyphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**7**). M+Na = 852.8; retention time =15.1 min (1, P).

5-Carbomethoxypentanoyl [Sta]-Val-Ala-Glu-Phe-OH (**8**). MH+ = 764.4; retention time = 14.8 (1, P).

4-Phenoxybutanoyl [Sta]-Val-Ala-Glu-Phe-OH (**9**). MH+ = 784.0; retention time = 21.6 (1, P).

2-Napththoyl [Sta]-Val-Ala-Glu-Phe-OH (**10**). MH+ = 776.2; retention time = 23.1 (1, P).

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

(4-Isobutyl)benzoyl [Sta]-Val-Ala-Glu-Phe-OH (**11**). M+Na = 804.6; retention time = 27.7 (1, P).

(4-Butoxy)benzoyl [Sta]-Val-Ala-Glu-Phe-OH (**12**). M+Na = 820.4; retention time = 26.4 (1, P).

(*R*)-α-Methoxyphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**13**). MH+ = 770.9; retention time = 18.0 (1, P).

(*R*)-α-Hydroxy-α-methylphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**14**). MH+ = 770.2; retention time = 15.6 (1, P).

(2-Phenoxy)-α-hydroxyphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**15**). MH+ = 848.6; retention time = 23.4 (1, P).

(3-Phenoxy)-α-hydroxyphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**16**). MH+ = 848.4; retention time = 23.2, 24.1 (1, P).

(2-Benzyloxy)-α-hydroxyphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**17**). MH+ = 863.6; retention time = 24.2 (1, P).

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

(2-Bromo)-α-hydroxyphenylacetyl [Sta]-Val-Ala-Glu-Phe-OH (**18**). MH+ = 835.6; retention time = 16.5, 16.9 (1, P).

(2-Naphthoxy)-α-hydroxyphenylacetyl [Leu-Sta]-Val-Ala-Glu-Phe-OH (**19**). MH+ = 806.6; retention time = 18.7, 19.5 (1, P).

Boc-Val-Met-[Sta]-Val cyclohexylamide (**20**)

^{1}H NMR (DMSO-d_6): δ 8.88 (d, 1H), 7.77 (d, 1H), 7.55 (d, 1H), 6.88 (d, 1H), 4.88 (d, 1H), 4.55 (m, 1H), 3.98 (m, 3H), 3.55 (m, 1H) 3.33 (s, 2H), 2.49 (m, 2H), 2.14 (m, 2H), 2.01 (s, 3H), 1.90-1.80 (m, 2H), 1.66 (m, 3H), 1.45 (m, 1H), 1.44 (s, 9H), 1.30-1.00 (m, 4H), 0.98 (s, 18H); ^{13}C NMR (DMSO-d_6): δ 179.6, 171.7, 171.6, 171.5, 170.6, 114.6, 60.6, 59.2, 51.4, 48.0, 33.0, 32.8, 31.2, 30.6, 28.7, 25.8, 25.1, 23.8, 22.3, 19.7, 19.6, 18.6, 15.2; MH+(CI)= 686; retention time =12.03 min (2, P).

Boc-Val-Met-[Sta]-Val benzylamide (**21**)

^{1}H NMR (DMSO-d_6) δ 7.88(d, 1H); 7.77(d, 1H); 7.41(d, 1H); 7.34(m, 5H); 6.88(d, 1H); 4.88(d, 1H); 4.45(m, 1H); 4.36(d, 2H); 3.88(m, 2H); 3.45(s, 2H); 2.44(m, 2H); 2.22(m, 2H); 2.10(s, 3H); 1.9-1.80(m, 2H); 1.50(m, 3H); 1.44(s, 9H); 1.38(m, 1H); 0.98(m, 18H); ^{13}C NMR (DMSO-d_6) δ 172.2, 171.8, 171.7, 140.2, 128.9, 127.9, 127.4, 78.7, 58.5, 51.2, 42.6, 32.6, 30.8, 30.1, 28.7, 24.7, 23.8, 22.3, 19.8, 18.7, 18.4, 15.2; MH+(CI) = 694; retention time =11.94 min (2, P)..

Boc-Val-Met-[Sta]-Val butylamide (**22**)

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

^{1}H NMR (DMSO-d_6) δ 7.89(d, 1H); 7.66(d, 1H); 7.44(d, 1H); 6.88(d, 1H); 4.88(d, 1H); 4.45(m, 1H); 3.78(m, 2H); 3.1-3.0(m, 2H); 2.50(m, 2H); 2.22(d, 1H); 2.04(s, 3H); 2.0-1.80(m, 2H); 1.55(m, 3H); 1.44(s, 9H); 1.32(t, 3H); 0.98(m, 18H); ^{13}C NMR (DMSO-d_6) δ 187.9, 183.5, 171.7, 164.0, 156.2, 117.4, 114.6, 117.4, 114.6, 100.4, 61.4, 58.4, 51.2, 32.7, 30.8, 30.1, 29.2, 29.1, 28.7, 24.7, 23.8, 22.3, 19.2, 18.5, 15.2, 14.4; MH+(CI) = 674; retention time =12.45 min (2, P).

Boc-Val-Met-[Sta]-Val-OH (**23**)

^{1}H NMR (CD_3OD) δ 8.33(d, 1H); 7.00(d, 1H); 4.55(m, 1H); 4.33(d, 2H); 4.1-3.8(m, 4H); 2.50(m, 2H); 2.42(d, 2H); 2.10(m, 2H); 2.08(s, 2H); 2.00(s, 3H); 1.55(m, 3H); 1.44(s, 9H); 1.33(m, 1H); 0.99(m, 18H); ^{13}C NMR (CD_3OD) δ 194.6, 174.3, 174.0, 100.5, 71.7, 71.6, 59.1, 54.1, 52.7, 41.7, 41.3, 31.7, 31.5, 31.1, 28.7, 26.0, 25.8, 23.8, 22.6, 22.2, 20.7, 19.8, 19.5, 18.6, 18.3; MH+(CI) = 605; retention time =8.43 min (2, P).

Boc-Val-Met-[Sta]-Val (3-carbomethoxy)propylamide (**24**)

^{1}H NMR (DMSO-d_6) δ 4.88(d, 1H); 4.44(m, 1H); 4.11(m, 2H); 3.88(m, 3H); 3.66(s, 3H); 3.44(d, 2H); 3.10(m, 2H); 2.43(m, 1H); 2.25(t, 2H); 2.14(d, 2H); 2.04(s, 3H); 1.88(m, 2H); 1.60(t, 2H); 1.44(s, 9H); 1.40(m, 1H); 0.98(m, 18H); ^{13}C NMR (DMSO-d_6) δ 173.8, 172.1, 171.7, 78.8, 60.4, 58.5, 52.4, 51.8, 51.1, 32.6, 31.3, 30.7, 30.6, 30.1, 28.7, 25.0, 24.8, 23.8, 22.3, 19.7, 19.7, 18.7, 18.5, 15.5; MH+(CI) = 704; retention time =6.32 min (2, P).

Boc-Val-Met-[Sta]-Val (3-carboxy)propylamide (**25**)

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

^{1}H NMR (CD_3OD) δ 4.56(m, 1H), 4.20(m, 1H); 4.01-3.98(m, 2H); 3.32(m, 2H); 2.50(m, 2H); 2.24(m, 2H); 2.10(m, 3H); 2.00(m, 4H); 1.88(t, 2H); 1.55(m, 1H); 1.44(s, 9H); 1.44(s, 9H); 1.34(m, 1H); 0.99(m, 18H); ^{13}C NMR (CD_3OD) δ 173.7, 74.2, 71.4, 54.5, 43.8, 41.4, 39.8, 32.2, 31.4, 31.2, 28.7, 25.7, 23.6, 22.3, 20.6, 19.7, 18.6, 18.2, 15.2; MH+(CI)= 690.1; retention time =5.40 min (2, P).

Boc-Val-Met-[Sta]-Val (2-carboxy)ethylamide (**26**)

^{1}H NMR (CD_3OD) δ 4.45(m, 1H); 4.1-4.0(m, 2H); 4.0-3.98(m, 3H); 3.54(m, 2H); 2.56(m, 3H); 2.40(m, 2H); 2.1-2.0(m, 4H); 1.66(m, 2H); 1.44(m, 11H); 1.22(t, 2H); 0.98(m, 18H); ^{13}C NMR (CD_3OD) δ 174.2, 173.7, 100.5, 74.2, 71.4, 43.8, 41.6, 36.4, 34.5, 32.6, 31.4, 31.2, 30.9, 28.7, 25.9, 23.6, 22.3, 19.8, 15.3; MH+(CI) = 676; retention time =4.95 min (2, P).

Boc-Val-Met-[Sta]-Val (4-carboxy)benzylamide (**27**)

^{1}H NMR (CD_3OD) δ 8.88 (m, 1H); 7.88 (d, 2H); 7.44 (d, 2H); 4.55 (m, 2H); 4.22 (m, 1H); 4.0-3.9 (m, 2H); 2.5-2.3 (m, 3H); 2.14 (m, 1H); 2.0-1.9 (m, 4H); 1.55 (m, 1H); 1.44 (s, 9H); 1.33 (m, 1H); 0.99 (m, 18H); ^{13}C NMR (CD_3OD) δ 172.0, 171.2, 171.0, 166.8, 142.6, 128.0, 127.8, 125.4, 77.9, 68.5, 59.1, 57.8, 51.6, 49.2, 40.9, 38.7, 38.4, 29.3, 28.6, 28.4, 28.3, 25.8, 23.0, 20.7, 19.3, 16.9, 16.8, 15.7, 15.2 12.3; MH+(CI) = 738.3; retention time =8.60 min (1, P).

Boc-Val-Met-[Sta]-Val (3-carboxy)benzylamide (**28**)

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

^{1}H NMR ($CD_3OD/CDCl_3$) δ 8.0(s, 1H); 7.89(d, 1H); 7.89(s, 1H); 7.66(s, 1H); 7.55(d, 1H); 7.50(d, 1H); 7.44(t, 1H); 6.88(d, 1H); 6.77(d, 1H); 4.6-4.4(m, 3H); 4.33(m, 1H); 4.0-3.8(m, 3H); 2.5-2.3(m, 4H); 2.22(m, 1H); 2.1-1.9(m, 5H); 1.5-1.4((m, 11H); 1.40(m, 1H); 0.99(m, 18H); ^{13}C NMR ($CD_3OD/CDCl_3$) δ 169.1, 168.1, 168.0, 139.9, 134.4, 127.0, 124.2, 123.7, 75.3, 56.1, 54.6, 48.7, 45.9, 35.7, 35.5, 29.4, 25.9, 25.7, 25.3, 25.2, 25.1, 24.1, 23.0, 19.9, 17.9, 16.5, 14.0, 12.9, 12.4, 12.3, 9.6; retention time =11.58 min (2, P).

Boc-Val-Met-[Sta]-Val benzo[1,3]dioxol-5-ylmethylamide (**29**)

^{1}H NMR (DMSO-d_6): δ8.55 (d, 1H), 7.88 (d, 1H), 7.66 (d, 1H), 7.55 (d, 1H), 6.88 (m, 2H), 6.80 (d, 1H), 5.98 (s, 2H), 4.88 (d, 1H), 4.45 (m, 1H), 4.22 (m, 3H), 3.78 (m, 2H), 3.34 (m, 2H), 2.44 (m, 2 H), 2.22 (d, 2H), 2.00-1.80 (m, 5 H), 1.66 (m, 1H), 1.50 (m, 1H), 1.44 (s, 9H), 1.33 (m, 1 H), 0.99 (m, 18H); ^{13}C NMR (DMSO-d_6): δ 171.7, 171.6, 147.9, 146.6, 134.1, 121.0, 109.6, 108.5, 104.4, 100.4, 78.7, 58.2, 52.2, 42.3, 42.2, 30.7, 30.0, 28.7, 24.7, 23.9, 22.2, 20.2, 19.7, 18.7, 18.4, 15.1; MH+(CI) = 738; retention time =9.67 min (1, P).

Boc-Val-Met-[Sta]-Val (4-pyridyl)methylamide (**30**)

MH+(CI) = 695.2; retention time =9.45 min (2, P).

Boc-Val-Met-[Sta]-Val (3-carboxymethoxy)benzylamide (**31**)

^{1}H NMR (CD_3OD): δ7.25 (t, 1H), 6.98 (m, 2H), 6.77 (s, 2H), 4.77 (s, 2H), 4.44 (m, 1H), 4.32 (m, 1H), 3.8 (m, 3H), 3.33 (s, 2H), 2.4 (m, 5 H), 2.1 (m, 1H), 1.66 (m, 1H), 1.44 (s,

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

9H), 0.99 (m, 18H); ^{13}C NMR (CD_3OD): δ 169.0, 168.2, 168.0, 167.9, 166.7, 153.7, 135.8, 124.7, 124.6, 120.2, 115.7, 108.7, 108.5, 74.8, 65.4, 59.8, 55.9, 53.8, 54.5, 54.3, 48.4, 48.1, 46.1, 35.7, 35.5, 35.3, 26.5, 26.1, 25.6, 25.5, 25.3, 25.1, 24.8, 22.7, 19.7, 17.7, 16.2, 13.7, 13.6, 12.6, 12.2, 9.2; MH+(Cl) = 768; retention time =9.45 min (2, P).

Boc-Val-Met-[Sta]-Val-*cis*, *cis*-3,5-dicarboxycyclohexylamide (**32**)

^{1}H NMR (DMSO-d_6) δ 8.21 (m, 1H), 7.89 (m, 1H), 7.47 (m, 1H), 6.71 (m, 1H), 4.49 (m, 1H), 4.13 (m, 1H), 4.00 (m, 1H), 3.85 (m, 2H), 3.30 (t, 4H), 2.47 (m, 2H), 2.38 (m, 2H), 2.08 (s, 3H), 1.56 (m, 1H), 1.55 (m, 1H), 1.53 (m, 1H), 1.45 (s, 9H), 1.38 (m, 1H), 0.97 (m, 6H), 0.95 (m, 6H), 0.93 (m, 3H), 0.91 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 42.9, 41.9, 35.9, 32.1, 31.6, 29.2, 26.4, 24.1, 20.1, 19.1; MH+ = 774.4 ; retention time =17.2, 18.3 min (2, P).

Boc-Val-Met-[Sta]-Val-*cis*, *cis*-3,5-dicarbomethoxycyclohexylamide (**33**)

^{1}H NMR (DMSO-d_6) δ7.95 (m, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.43 (m, 1H), 6.80 (m, 1H), 4.84 (s, 1H), 4.37 (s, 1H), 4.03 (m, 1H), 3.77 (m, 2H), 3.68 (m, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 3.34 (m, 1H), 3.32 (m, 2H), 3.30 (m, 2H), 2.53 (m, 2H), 2.48 (m, 2H), 2.47 (m, 1H), 2.39 (m, 1H), 2.16 (m, 2H), 1.98 (s, 3H), 1.92 (m, 1H), 1.89 (m, 2H), 1.83 (m, 1H), 1.41 (m, 1H), 1.35 (s, 9H), 1.26 (m, 1H), 1.22 (m, 1H), 0.82 (m, 6H), 0.81 (m, 6H), 0.79 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 174.4, 170.4, 78.1, 51.6, 46.0, 33.9, 30.0, 29.4, 28.1, 23.3, 21.7, 19.1, 18.1, 14.6; MH+ = 802.4; retention time =24.92, 25.34 min (2, P)..

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

4-[(3*S*, 4*S*)-(2-{4-[2-(2-Bromophenyl)-2-hydroxyacetylamino]-3-hydroxy-6-methyl-heptanoylamino}-3-(*S*)-methylbutyrylamino)methyl]-benzoic acid (**34**)

^{1}H NMR (DMSO-d_6) δ8.56 (m, 1H), 7.87 (m, 2H), 7.60 (m, 2H), 7.53 (m, 1H), 7.32 (m, 3H), 7.24 (m, 1H), 5.37 (s, 1H), 4.33 (m, 2H), 4.18 (m, 1H), 3.92 (m, 2H), 2.28 (m, 2H), 2.06 (m, 1H), 1.49 (m, 2H), 1.30 (m, 1H), 0.87 (m, 12H); MS 620 (M + H), M + Na = 643; retention time = 39.89, 40.66 min (2-60% [B] in 58 min), Phenomenex column.

4-({(3*S*, 4*S*)-2-[3-Hydroxy-4-(2-hydroxy-2-naphthalen-1-yl-acetylamino)-6-methyl-heptanoylamino]-3-(*S*)-methylbutyrylamino}methyl)-benzoic acid (**35**)

^{1}H NMR (DMSO-d_6) δ8.22 (m, 1H), 7.89 (m, 4H), 7.47 (m, 5H), 7.18 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.90 (m, 1H), 6.52 (m, 1H), 4.24 (m, 3H), 3.91 (m, 2H), 2.40 (m, 2H), 2.23 (m, 1H), 1.56 (m, 1H), 1.29 (m, 2H), 0.72 (m, 12H); ^{13}C NMR (DMSO-d_6) δ 173, 172, 171.8, 171.2, 166, 143.2, 143.1, 134.9, 134.8, 133, 130.9, 130.7, 129.6, 129.3, 128.8, 128.7, 127, 126, 125.8, 125, 123, 72, 70, 58, 50, 42, 40.5, 40.1, 30.4, 30.1, 24.6, 24.3, 22.9, 22.8, 21.6, 21.5, 19.1, 19.0, 17.9, 17.6; M H+ = 592; retention time =18.35, 19.17 min (2, P).

5-{(3*S*, 4*S*)-2-[3-Hydroxy-4-(2-hydroxy-2-naphthalen-1-yl-acetylamino)-6-methyl-heptanoylamino]-3-(*S*)-methylbutyrylamino}cyclohexane- *cis*, *cis*-1,3-dicarboxylic acid (**36**)

^{1}H NMR (CD_3OD) δ 8.35 (m, 1H), 7.85 (m, 3H), 7.66 (d, J = 6.6 Hz, 1H), 7.56 (m, 1H), 7.50 (m, 1H), 7.48 (m, 3H), 5.79 (d, J = 8.8 Hz, 1H), 4.14 (d, J = 6.0 Hz, 1H), 4.06 (m, 1H), 4.04 (m, 1H), 3.98 (m, 2H), 3.30 (dt, J = 1.7, 1.7, 1.7, 1.7 Hz, 2H), 2.43 (m, 2H),

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com

2.32 (m, 1H), 2.15 (m, 1H), 1.94 (m, 1H), 1.65 (m, 1H), 1.41 (m, 1H), 1.24 (m, 1H), 0.93 (m, 6H), 0.88 (m, 6H); ^{13}C NMR (CD_3OD) δ 130.6, 130.3, 127.9, 127.7, 127.6, 127.5, 127.4, 126.9, 126.2, 42.9, 32.3, 26.5, 23.0, 20.1; MH+ = 628.2; retention time =13.30, 13.46 min (2, P).

5-{(3*S*, 4*S*)-2-[3-Hydroxy-4-(2-hydroxy-2-naphthalen-1-yl-acetylamino)-6-methyl-heptanoylamino]-3-(*S*)-methylbutyrylamino}cyclohexane-*cis*, *cis*-1,3-dicarboxylic acid dimethyl ester (**37**) MH+ = 656.1; retention time = 25.52, 26.34 min (2, P).

5-{2-(3*S*, 4*S*)-[4-(2-Biphenyl-2-yl-2-hydroxyacetylamino)-5-(3,5-difluorophenyl)-3-hydroxypentanoylamino]-3-(*S*)-methylbutyrylamino}-cyclohexane-1,3-dicarboxylic acid dimethyl ester (**38** and **39**) as a mixture of isomers.
^{1}H NMR ($CDCl_3$) δ7.60-7.00 (m, 10H), 7.00-6.45 (m, 4H), 5.16 (s, 1H), 4.25-3.85 (m, 3H), 3.85-3.65 (m, 1H), 3.65-3.50 (m, 6H), 3.00-2.85 (m, 2H), 2.55-1.90 (m, 10H), 1.50-1.00 (m, 4H), 0.95-0.83 (m, 6H); ^{13}C NMR ($CDCl_3$) δ174.7, 174.6, 173.7, 172.1, 170.6, 164.7, 164.5, 161.4, 161.2, 142.2, 141.8, 140.3, 140.2, 137.1, 130.5, 130.4, 129.8, 129.3, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.5, 126.7, 126.5, 112.3, 112.1, 111.9, 102.4, 102.1, 101.7, 70.4, 70.3, 69.3, 68.9, 58.8, 53.8, 53.4, 51.8, 46.8, 40.8, 40.4, 37.4, 37.3, 33.9, 33.7, 30.9, 30.3, 19.0, 18.3, 18.2, 18.1; retention time =16.86 (inactive isomer **39**) (2, P), MH+ = 753; retention time = 17.27 min (active isomer **38**) (2,P), MH+ = 753.

* To whom correspondence should be addressed.
Tel: 650-877-7623; Fax: 650-877-7486; E-mail: varghese.john@elan.com