Supporting Information

Development of Human Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists: Part 1. Potent and Selective Small Molecule CGRP Antagonists. 1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine: The First CGRP Antagonist for Clinical Trials in Acute Migraine

Klaus Rudolf, Wolfgang Eberlein, Wolfhard Engel, Helmut Pieper, Michael Entzeroth, Gerhard Hallermayer and Henri Doods

Contents of Supporting Information

N^2-(1,1-Dimethylethoxycarbonyl)-N^6-(phenylmethoxycarbonyl)-L-lysine-2-phenethyl-amide (precursor of 21a).

^{1}H NMR ($CDCl_3$): δ 1.43 (9H, s), 1.20-2.00 (6H, m), 2.82 (2H, t), 3.08-3.24 (2H, m), 3.38-3.64 (2H, m), 3.87-4.05 (1H, m), 4.81 (1H, br), 5.03 (1H, br), 5.07 (2H, s), 6.10 (1H, br), 7.12-7.38 (10H, m).

N^6-(Phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (21a).

^{1}H NMR ($CDCl_3$): δ 1.15-1.90 (6H, m), 2.77 (2H, t), 3.10 (2H, t), 3.30-3.80 (3H, m, br), 5.00 (1H, br), 5.04 (2H, s), 7.1-7.4 (10H, m), 7.57 (1H, t, br).

N^2-(1,1-Dimethylethoxycarbonyl)-N^6-(phenylmethoxycarbonyl)-D-lysine-2-phenethyl-amide (precursor of 21b).

^{1}H NMR ($CDCl_3$): δ 1.45 (9H, s), 1.20-2.03 (6H, m), 2.84 (2H, t), 3.10-3.26 (2H, m), 3.38-3.67 (2H, m), 3.91-4.8 (1H, m), 4.83 (1H, br), 5.04 (1H, br), 5.08 (2H, s), 6.13 (1H, br), 7.10-7.42 (10H, m).

N^6-(Phenylmethoxycarbonyl)-D-lysine-2-phenethylamide trifluoroacetate (21b).

^{1}H NMR ($CDCl_3$): δ 1.18-1.95 (6H, m), 2.80 (2H, t), 3.16 (2H, t), 3.40-4.03 (3H, m), 5.02 (1H, br), 5.07 (2H, s), 7.1-7.4 (10H, m), 7.61 (1H, t, br).

N^2-[N-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysin-2-phenethylamide (22a).

^{1}H NMR (DMSO-d_6): δ 1.42 (9H, s), 0.95-1.70 (6H, m), 2.58-2.85 (4H, m), 2.85-3.08 (2H, m), 3.23-3.45 (2H, m), 4.00-4.22 (2H, m), 4.98 (2H, s), 6.97 (1H, d), 7.1-7.4 (13H, m), 7.90 (1H, t), 8.15 (1H, d).

N^2-[4-Amino-3,5-dibromo-N-(1,1-dimethylethoxycarbonyl)-D-phenylalanyl]-N^6-phenylmeth-oxycarbonyl)-L-lysin-2-phenethylamide (22b).

^{1}H NMR ($CDCl_3$): δ 1.36 (9H, s), 0.85-1.85 (6H, m), 2.55-2.83 (4H, m), 2.83-3.03 (2H, m), 3.20-3.40 (2H, m), 3.97-4.20 (2H, m), 4.97 (2H, s), 5.15 (2H, s), 7.05 (1H, d), 7.1-7.4 (13H, m), 7.96 (1H, t), 8.18 (1H, d).

N^2-[N-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-D-lysin-2-phenethylamide (22c).

^{1}H NMR (DMSO-d_6): δ 1.45 (9H, s), 0.95-1.68 (6H, m), 2.68-2.82 (4H, m), 2.92-3.05 (2H, m), 3.25-3.38 (2H, m), 3.95-4.17 (2H, m), 4.95 (2H, s), 6.97 (1H, d), 7.1-7.4 (13H, m), 7.88 (1H, t), 8.12 (1H, d).

N^2-[N-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-D-lysin-2-phenethylamide (22d).

^{1}H NMR (DMSO-d_6): δ 1.34 (9H, s), 1.05-1.67 (6H, m), 2.50-3.05 (6H, m), 3.20-3.45 (2H, m), 4.00-4.27 (2H, m), 4.98 (2H, s), 6.46 (1H, br), 6.83 (1H, d), 7.1-7.37 (10H, m), 7.45 (2H, s), 7.80-8.05 (2H, m), 9.61 (1H, br).

N^2-[N-(1,1-Dimethylethoxycarbonyl)-3,5-dibromo-L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysin-2-phenethylamide (22e).

^{1}H NMR (DMSO-d_6): δ 1.31 (9H, s), 1.08-1.67 (6H, m), 2.50-3.05 (6H, m), 3.20-3.45 (2H, m), 4.00-4.27 (2H, m), 5.00 (2H, s), 6.46 (1H, br), 6.90 (1H, d), 7.1-7.37 (10H, m), 7.45 (2H, s), 7.80-8.05 (2H, m), 9.65 (1H, br).

N^2-[3,5-Dibromo-N-(4-phenyl-1-oxobutyl)-D-tyrosyl]- N^6-(phenylmethoxycarbonyl)-L-lysin-2-phenethylamide (precursor of 1).

^{1}H NMR (DMSO-d_6): δ 0.97-1.85 (8H, m), 2.08 (2H, t), 2.35-3.07 (8H, m), 3.20-3.37 (2H, m), 4.02-4.25 (1H, m), 4.38-4.63 (1H, m), 4.96 (2H, s), 6.35 (1H, br), 7.0-7.55 (17H, m), 7.88-8.35 (3H, m), 9.62 (1H, s).

N^2-[3,5-Dibromo-N-(4-phenyl-1-oxobutyl)-D-tyrosyl]-L-lysin-2-phenethylamide Hydrobromide (1).

^{13}C NMR (DMSO-d_6): δ 22.1, 26.6, 27.0, 31.2, 34.5, 34.9, 35.8, 38.6, 40.2, 52.3, 54.4, 111.5, 125.6, 126.0, 128.2, 128.5, 132.0, 132.8, 139.2, 141.7, 149.2, 171.0, 172.4.

N^2-[4-Amino-3,5-dibromo-N-(4-phenyl-1-oxobutyl)-D-phenylalanyl]-N^6-(phenylmethoxycarbonyl)-L-lysin-2-phenethylamide (precursor of 2).

^{1}H NMR (DMSO-d_6): δ 1.01-1.11 (2H, m), 1.33-1.53 (3H, m), 1.55-1.65 (1H, m), 1.65-1.80 (2H, m), 2.05-2.17 (2H, m), 2.43-2.54 (2H, m), 2.60-2.90 (6H, m), 3.20-3.37 (2H, m), 4.04-4.13 (1H, m), 4.37-4.45 (1H, m), 5.08 (2H, s), 5.15 (2H, s), 7.10-7.40 (18H, m), 7.95 (1H, t), 8.16 (1H, d), 8.22 (1H, d).

N^2-[4-Amino-3,5-dibromo-N-(4-phenyl-1-oxobutyl)-D-phenylalanyl]-L-lysin-2-phenethyl-amide Hydrobromide (2).

^{13}C NMR (DMSO-d_6): δ 22.1, 26.6, 27.0, 31.1, 34.5, 34.9, 35.7, 38.7, 40.2, 52.3, 54.6, 107.3, 125.6, 126.0, 128.2, 128.5, 132.5, 139.2, 141.0 141.7, 171.0, 171.1, 172.3.

N^2-[3,5-Dibromo-L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-D-lysin-2-phenethylamide trifluoroacetate (precursor of 3).

^{1}H NMR (DMSO-d_6): δ 0.95-1.58 (6H, m), 2.60-3.05 (6H, m), 3.15-3.45 (2H, m), 3.95-4.13 (1H, m), 4.13-4.33 (1H, m), 4.96 (2H, s), 6.85 (1H, br), 7.05-7.40 (11H, m), 7.44 (2H, s), 8.18 (1H, t), 8.63 (1H, d).

N^2-[3,5-Dibromo-N-(4-phenyl-1-oxobutyl)-L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-D-lysine-2-phenethylamide (precursor of 3).

^{1}H NMR (DMSO-d_6): δ 0.95-1.20 (2H, m), 1.20-1.96 (6H, m), 1.95-2.17 (2H, m), 2.35-2.55 (2H, m), 2.55-3.05 (6H, m), 3.15-3.45 (2H, m), 4.05-4.20 (1H, m), 4.40-4.58 (1H, m), 4.96 (2H, s), 6.85 (1H, br), 7.05-7.40 (15H, m), 7.45 (2H, s), 7.96 (1H, t), 8.12 (1H, d), 8.23 (1H, d), 9.63 (1H, br).

N^2-[3,5-Dibromo-N-(4-phenyl-1-oxobutyl)-L-tyrosyl]-D-lysin-2-phenethylamide (3).

^{13}C NMR (DMSO-d_6): δ 22.3, 27.0, 27.1, 31.4, 34.3, 34.5, 34.9, 35.8, 38.5, 40.2, 52.7, 55.4, 113.5, 123.5, 125.6, 125.9, 128.2, 128.5, 132.2, 139.2, 141.7, 156.0, 171.0, 171.1, 172.3.

N^2-[3,5-Dibromo-N-(4-phenyl-1-oxobutyl)-D-tyrosyl]-D-lysine-2-phenethylamide (4).

^{13}C NMR (DMSO-d_6): δ 22.3, 26.9, 27.5, 31.5, 34.6, 34.9, 35.5, 38.9, 40.0, 52.4, 54.6, 113.3, 123.4, 125.6, 125.9, 128.2, 128.5, 132.2, 139.3, 141.7, 156.1, 170.4, 170.8, 172.5.

N^2-[3,5-Dibromo-N-(4-phenyl-1-oxobutyl)-L-tyrosyl]-L-lysine-2-phenethylamide (5).

^{13}C NMR (DMSO-d_6): δ 22.1, 26.7, 27.0, 31.6, 34.4, 34.6, 34.9, 35.7, 38.7, 40.0, 52.3, 53.9, 111.7, 125.6, 126.0, 128.1, 128.2, 128.5, 130.8, 132.7, 139.3, 141.6, 150.3, 170.8, 171.0, 172.1.

(R)-4-Amino-3,5-dibromophenylalanine Methylester Hydrochloride (23).

^{1}H NMR (DMSO-d_6): δ 3.12 (2H, d), 3.75 (3H, s), 4.23 (2H, t), 5.30 (2H, br), 7.40 (2H, s), 8.82 (3H, br).

4-Amino-3,5-dibromo-N-(3-phenyl-1-oxopropyl)-D-phenylalanine (24a).

^{1}H NMR (DMSO-d_6): δ 2.24-2.95 (6H, m), 4.20-4.58 (1H, m), 5.17 (2H, br), 7.0-7.4 (7H, m), 8.15 (1H, d), ca. 13 (1H, br).

N^2-[4-Amino-3,5-dibromo-N-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-N^6-(phenylmeth-oxycarbonyl)-L-lysine methylester (precursor of 25).

^{1}H NMR (DMSO-d_6): δ 1.15-1.30 (2H, m), 1.33-1.45 (2H, m), 1.50-1.75 (2H, m), 2.25-2.46 (2H, m), 2.49-2.64 (1H, m), 2.65-2.82 (3H, m), 2.90-3.05 (2H, m), 3.65 (3H, s), 4.18-4.28 (1H, m), 4.53-4.62 (1H, m), 4.97 (2H, s), 5.21 (2H, s), 6.93 (1H, br), 7.10-7.40 (12H, m), 8.13 (1H, d), 8.48 (1H, d).

N^2-[4-Amino-3,5-dibromo-N-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-N^6-(phenylmethoxy-carbonyl)-L-lysine (25).

^{1}H NMR (DMSO-d_6): δ 1.13-127 (2H, m), 1.30-1.45 (2H, m), 1.47-1.51 (1H, m), 1.52-1.75 (1H, m), 2.25-2.44 (2H, m), 2.49-2.60 (1H, m), 2.62-2.82 (3H, m), 2.90-3.02 (2H, m), 4.14-4.24 (1H, m), 4.51-4.62 (1H, m), 4.97 (2H, s), 5.18 (2H, s), 6.88 (1H, br), 7.08-7.18 (3H, m), 7.18-7.28 (3H, m), 7.28-7.40 (6H, m), 8.11 (1H, d), 8.35 (1H, d), ca. 12.7 (1H, s).

N^2-[4-Amino-3,5-dibromo-N-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-N^6-(phenylmeth-oxycarbonyl)-L-lysine-2-phenethylamide (precursor of 10).

^{1}H NMR (DMSO-d_6): δ 1.00-1.13 (2H, m), 1.27-1.48 (3H, m), 1.49-1.63 (1H, m), 2.27-2.47 (2H, m), 2.54-2.65 (1H, m), 2.65-2.83 (5H, m), 2.87-2.98 (2H, m), 3.18-3.35 (2H, m), 4.06-4.16 (1H, m), 4.40-4.50 (1H, m), 4.97 (2H, s), 5.17 (2H, s), 6.86 (1H, br), 7.08-7.40 (17H, m), 8.00 (1H, t), 8.19 (1H, d), 8.26 (1H, d).

N^2-[4-Amino-3,5-dibromo-N-(3-phenyl-1-oxopropyl)-D-phenylalanyl]-L-lysine-2-phenethyl-amide Hydrochloride (10).

^{13}C NMR (DMSO-d_6): δ 22.2, 26.7, 31.0, 31.2, 34.9, 35.9, 36.7, 38.6, 40.2, 52.3, 54.5, 107.4, 125.8, 126.0, 128.0, 128.1, 128.2, 128.6, 132.5, 139.3, 141.1, 170.9, 171.0, 171.7.

1-[N^6-(Phenylmethoxycarbonyl)]-L-lysyl]-4-(4-pyridinyl)-piperazine (21c).

^{1}H NMR (DMSO-d_6): δ 1.15-1.60 (6H, m), 2.77-2.95 (2H, m), 3.15-3.88 (9H, m), 5.05 (2H, s), 6.72-6.85 (1H, m), 6.82 (2H, d), 7.30-7.45 (5H, m), 8.19 (2H, d).

1-[N^2-(3,5-Dibromo-D-tyrosyl)-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine (26).

^{1}H NMR (DMSO-d_6): δ 0.95-1.70 (6H, m), 2.37-2.95 (4H, m), 3.20-3.80 (9H, m), 4.65-4.84 (1H, m), 5.04 (2H, s), 6.75 (1H, t), 6.82 (2H, d), 7.30-7.45 (7H, m), 8.17 (2H, d), 8.23 (1H, d).

1-[N^2-[3,5-Dibromo-N-[[[2-(2-methoxyphenyl)ethyl]-amino]carbonyl]-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine (precursor of 12).

^{1}H NMR (DMSO-d_6): δ 1.08-1.30 (2H, m), 1.30-1.50 (3H, m), 1.50-1.74 (1H, m), 2.4-2.68 (3H, m), 2.68-3.23 (5H, m), 3.23-3.85 (8H, m), 3.75 (3H, s), 4.27-4.50 (1H, m), 4.55-4.80 (1H, m), 4.96 (2H, s), 5.95-6.15 (2H, m), 6.74-6.96 (4H, m), 6.97-7.43 (10H, m), 8.15 (2H, d) 8.39 (1H, d).

1-[N^2-[3,5-Dibromo-N-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (12).

^{1}H NMR (DMSO-d_6): δ 0.6-0.9 (2H, m), 1.0-1.4 (4H, m), 2.25-2.80 (4H, m), 3.05-3.80 (12H, m), 3.78 (3H, s), 4.30-4.45 (1H, m), 4.45-4.57 (1H, m), 5.97 (1H, t), 6.09 (1H, d), 6.73-6.97 (4H, m), 7.02-7.25 (4H, m), 8.04 (1H, d), 8.15 (2H, d).

1-[N^2-[3,5-Dibromo-N-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (13).

^{13}C NMR (DMSO-d_6): δ 22.0, 26.7, 31.0, 36.0, 37.2, 38.5, 40.7, 40.8, 43.4, 44.9, 45.6, 47.9, 54.2, 54.8, 107.4, 111.4, 114.1, 120.7, 129.2, 132.4, 132.8, 139.9, 141.1, 148.9, 156.5, 157.3, 159.2, 169.8, 171.4.

3,5-Dibromo-N-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosine (27).

^{1}H NMR (DMSO-d_6): δ 2.63 (2H, t), 2.68-3.00 (2H, m), 3.05-3.22 (2H, m), 3.35 (1H, br), 3.76 (3H, s), 4.20-4.37 (1H, m), 6.02-6.17 (2H, m), 6.77-6.96 (2H, m), 7.02-7.25 (2H, m), 7.32 (2H, s).

N^2-[3,5-Dibromo-N-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosyl]-N^6-(phenylmethoxycarbonyl)-L-lysine-2-phenethylamide (precursor of 11).

^{1}H NMR (DMSO-d_6): δ 0.85-1.75 (6H, m), 2.38-2.48 (1H, m), 2.55-2.64 (1H, m), 2.64-2.77 (6H, m), 3.13-3.28 (4H, m), 3.73 (3H, s), 3.76-3.86 (1H, m), 4.11-4.20 (1H, m), 5.05 (2H, s),

6.06 (1H, t), 6.26 (1H, d), 6.75 (1H, t), 6.83 (1H, dd), 6.93 (1H, d), 7.04-7.30 (14H, m), 7.91 (1H, d), 7.92 (1H, t).

N^2-[3,5-Dibromo-N-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]-D-tyrosyl]-L-lysine-2-phenethylamide (11).

^{13}C NMR (DMSO-d_6): δ 22.3, 27.2, 30.6, 34.9, 36.7, 38.6, 39.4, 40.2, 52.6, 55.2, 55.8, 110.6, 113.8, 120.2, 124.7, 125.9, 127.2, 127.4, 128.2, 128.4, 129.8, 132.0, 139.3, 157.1, 157.7, 171.1, 171.8.

1-[N^6-(1,1-Dimethylethoxycarbonyl)-N^2-(phenylmethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (precursor of 28).

^{1}H NMR (DMSO-d_6): δ 1.20-1.63 (6H, m), 1.35 (9H, s), 2.80-2.95 (2H, m), 3.20-3.74 (8H, m), 4.35-4.54 (1H, m), 5.02 (2H, s), 6.72-6.87 (1H, m), 6.81 (2H, d), 7.22-7.40 (5H, m), 7.55 (1H, d), 8.17 (2H, d).

1-[N^6-(1,1-Dimethylethoxycarbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (28).

^{1}H NMR (DMSO-d_6): δ 1.20-1.63 (6H, m), 1.35 (9H, s), 2.80-2.95 (2H, m), 3.20-3.85 (9H, m), 6.72-6.85 (1H, m), 6.82 (2H, d), 8.17 (2H, d).

1-[N^2-(3,5-Dibromo-D-tyrosyl)-N^6-(1,1-dimethylethoxy-carbonyl)-L-lysyl]-4-(4-pyridinyl)-piperazine (29).

^{1}H NMR (DMSO-d_6): δ 1.00-1.69 (6H, m), 1.35 (9H, s), 2.40-2.95 (4H, m), 3.20-3.75 (9H, m), 3.90 (3H, br), 4.63.4.82 (1H, m), 6.70-6.85 (1H, m), 6.82 (2H, d), 7.33 (2H, s), 8.17 (2H, d), 8.10-8.26 (1H, m).

1-[N^2-[3,5-Dibromo-N-[[4-(2-methoxyphenyl)-1-piperazinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (14).

^{13}C NMR (DMSO-d_6): δ 21.7, 27.4, 31.3, 36.8, 38.7, 40.9, 43.7, 43.9, 45.0, 45.4, 44.9, 48.1, 50.0, 55.3, 55.9, 108.3, 111.9, 114.0, 118.1, 120.8, 121.8, 122.6, 133.2, 141.0, 149.8, 152.0, 154.1, 156.6, 157.9, 169.1, 170.8.

1-[N^2-[3,5-Dibromo-N-[[4-(2-methoxyphenyl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine bis(trifluoroacetate) (15).

^{13}C NMR (DMSO-d_6): δ 21.9, 26.8, 31.2, 31.5, 34.8, 35.8, 38.6, 40.8, 43.3, 44.2, 44.5, 44.9, 45.6, 47.8, 55.3, 56.0, 107.4, 110.7, 111.3, 120.5, 126.2, 127.0, 133.0, 133.2, 133.3, 139.8, 148.9, 156.3, 156.6, 156.9, 169.8, 171.9.

1-[N^2-[3,5-Dibromo-N-[[4-[2(3H)-oxobenzoxazol-3-yl]-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lys-yl]-4-(4-pyridinyl)piperazine bis(trifluoroacetate) (16).

^{1}H NMR (DMSO-d_6): δ 1.1-2.3 (10H, m), 2.65-2.90 (6H, m), 3.30-3.95 (8H, m), 4.0-4.2 (2H, m), 4.2-4.4 (2H, m), 4.67-4.87 (1H, m), 6.71 (1H, d), 6.95-7.4 (6H, ar H), 7.54 (2H, s), 7.60-7.84 (3H, br), 8.25 (2H, d), 8.47 (1H, d), 9.74 (1H, s), 13.57 (1H, br).

1-[N^2-[N-[[4-[N-(Aminocarbonyl)phenylamino]-1-piperidinyl]carbonyl]-3,5-dibromo-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine bis(trifluoroacetate (17).

^{1}H NMR (DMSO-d_6): δ 0.75-1.02 (2H, m), 1.10-1.35 (2H, m), 1.35-1.78 (6H, m), 2.55-2.85 (6H, m), 3.30-4.15 (11H, m), 4.23-4.5 (1H, m), 4.62-4.78 (1H, m), 5.2-5.4 (2H, br), 6.55 (1H, d), 7.05 (2H, d), 7.15 (2H, d), 7.25 -7.50 (5H, m), 7.65-7.85 (3H, br), 8.28 (2H, d), 8.36 (1H, d), 9.27 (1H, s), 13.65 (1H, br).

1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-2(2H)-oxobenzimidazol-1-yl)-1-piperidinyl]carbon-yl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (18).

^{13}C NMR (DMSO-d_6): δ 21.7, 27.5, 28.5, 28.6, 31.3, 36.8, 38.7, 40.9, 43.3, 43.9, 44.9, 45.4, 48.2, 50.0, 56.0, 108.3, 114.2, 120.3, 120.5, 121.1, 128.3, 129.2, 132.1, 149.7, 153.6, 154.1, 156.5, 158.5, 169.1, 170.8.

1-[N^2-[3,5-Dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)piperazine (19).

^{13}C NMR (DMSO-d_6): δ 21.8, 27.3, 28.0, 31.3, 36.6, 38.7, 40.9, 42.3, 43.0, 43.2, 44.0, 45.0, 45.5, 48.0, 50.9, 55.9, 108.3, 112.9, 113.6, 118.2, 120.8, 123.8, 125.6, 127.7, 132.3, 137.5, 149.8, 153.6, 154.1, 156.4 (2C, s, br), 169.2, 171.0.

1-[N^2-[3,5-Dibromo-N-[[4-(1,3-dihydro-4-phenyl-2(2H)-oxoimidazol-1-yl)-1-piperidinyl]car-bonyl]-D-tyrosyl]-L-lysyl]-4-(4-pyridinyl)-piperazine (20).

^{13}C NMR (DMSO-d_6): δ 21.8, 27.3, 31.0, 31.1, 31.3, 36.7, 38.7, 40.9, 42.9, 43.0, 44.0, 45.0, 45.4, 48.1, 49.5, 56.0, 105.7, 108.3, 113.9, 120.8, 122.7, 126.2, 128.6, 129.6, 132.2, 149.8, 152.9, 154.2, 156.3, 157.5, 169.2, 170.9.

4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanine (30).

^{1}H NMR (DMSO-d_6): δ 1.63-1.85 (2H, m), 2.12 (2H, t), 2.51 (2h, t), 2.68 (1H, dd), 2.94 (1H, dd), 4.27-4.44 (1H, m), 5.15 (2H, s), 7.05-7.34 (7H, m), 8.06 (1H, d), 12.40 (1H, br).

N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxycar-bonyl)-L-lysine (31).

^{1}H NMR (DMSO-d_6): δ 1.1-1.8 (8H, m), 1.95-2.13 (2H, m), 2.30-2.54 (2H, m), 2.54-2.65 (1H, m), 2.65-2.86 (1H, m), 2.86-3.04 (2H, m), 4.07-4.25 (1H, m), 4.45-4.64 (1H, m), 4.95 (2H, s), 5.07 (2H, s), 7.03-7.42 (13H, m), 7.95 (1H, d), 8.26 (1H, d), 12.56 (1H, s).

N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxycar-bonyl)-L-lysine-phenylamide (32a).

^{1}H NMR (DMSO-d_6): 1.10-1.35 (2H, m), 1.40-1.85 (6H, m), 2.12 (2H, t), 2.45 (2H, t), 2.60-2.95 (4H, m), 4.24-4.48 (1H, m), 4.48-4.56 (1H, m), 4.98 (2H, s), 5.15 (2H, s), 7.00-7.40 (16H, m), 7.69 (2H, s), 8.20 (1H, d), 8.43 (1H, d), 9.80 (1H, s).

1-[N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxy-carbonyl)-L-lysyl]-4-phenylpiperazine (32b).

^{1}H NMR (DMSO-d_6): δ 1.15-1.23 (2H, m), 1.32-1.51 (3H, m), 1.56-1.74 (3H, m), 2.05 (2H, t), 2.36-2.47 (2H, m), 2.57 (1H, dd), 2.79 (1H, dd), 2. 96 (2H, dd), 2.99-3.08 (2H, m), 3.08-3.17 (2H, m), 3.49-3.60 (2H, m), 3.64-3.72 (2H, m), 4.48-4.54 (1H, m), 4.70-4.75 (1H, m), 4.96 (2H, s), 5.11 (2H, s), 6.80 (1H, t), 6.92 (2H, d), 7.10 (2H, d), 7.12-7.39 (13H, m), 8.00 (1H, d), 8.37 (1H, d).

1-[N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxy-carbonyl)-L-lysyl]-4-(1,1-dimethylethoxycarbonyl)piperazine (32c).

^{1}H NMR (DMSO-d_6): δ 1.05-1.32 (2H, m), 1.47 (9H, s), 1.35-1.55 (4H, m), 1.83- 2.03 (2H, m), 2.17 (2H, t), 2.54-2.65 (2H, m), 2.82-2.93 (2H, m), 3.04-3.22 (2H, m), 3.30-3.65 (8H, m), 4.45 (2H, s), 4.53-4.70 (1H, m), 4.72-4.90 (1H, m), 4.98 (1H, br), 5.07 (2H, s), 5.97 (1H, d), 6.77 (1H, d), 7.07-7.37 (12H, m).

1-[N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxy-carbonyl)-L-lysyl]piperazine trifluoroacetate (32d).

^{1}H NMR (DMSO-d_6): δ 1.03-1.25 (2H, m), 1.25-1.72 (4H, m), 1.72-1.94 (2H, m), 2.00-2.24 (2H, m), 2.40- 2.60 (2H, m), 2.65-2.93 (2H, m), 2.93-3.25 (6H, br), 3.4-4.1 (7H, br), 4.55-4.87 (2H, m), 5.05 (1H, s), 4.98-5.18 (1H, br), 6.55 (1H, br), 7.0-7.4 (12H, m), 7.62 (1H, d), 8.02 (1H, br), 9.80 (1H, br).

1-[N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-N^6-(phenylmethoxy-carbonyl)-L-lysyl]-4-(4-pyridinyl)piperazine (32e).

^{1}H NMR (DMSO-d_6): δ 1.08-1.73 (8H, m), 2.05 (2H, t), 2.35-2.54 (2H, m), 2.54-2.64 (1H, m), 2.73-2.85 (1H, m), 2.87-3.01 (2H, m), 3.14-3.42 (4H, m), 3.45-3.86 (4H, m), 4.47-4.58 (1H, m), 4.58-4.80 (1H, m), 4.96 (2H, s), 5.12 (2H, s), 7.03-7.40 (15H, m), 8.00 (1H, d), 8.23 (2H, d), 8.41 (1H, d).

N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysine-phenylamide Hydrobromide (6).

^{13}C NMR (DMSO-d_6): δ 22.3, 26.6, 27.0, 31.2, 34.5, 35.8, 38.7, 53.0, 54.6, 107.4, 119.3, 123.4, 125.6, 128.1, 128.2, 128.6, 132.5, 138.7, 141.1, 141.7, 170.3, 171.3, 172.5.

1-[N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysyl]-4-phenyl-piperazine Hydrobromide (7).

^{1}H NMR (DMSO-d_6): δ 1.12-1.36 (2H, m), 1.36-1.85 (6H, m), 2.07 (2H, t), 2.35-2.55 (2H, m), 2.55-2.90 (4H, m), 2.90-3.35 (5H, m), 3.45-3.90 (3H, m), 4.40-4.63 (1H, m), 4.63-4.82 (1H, m), 6.82-7.04 (3H, m), 7.04-7.40 (9H, m), 7.68 (3H, br), 7.95-8.10 (1H, m), 8.34-8.45 (1H, m).

1-[N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysyl]-piperazine Dihydrobromide (8).

^{1}H NMR (DMSO-d_6): δ 1.10-1.34 (2H, m), 1.34-1.85 (6H, m), 2.11 (2H, t), 2.35-2.55 (2H, m), 2.55-2.88 (4H, m), 2.90-3.28 (4H, m), 3.45-3.92 (4H, m), 4.35-4.55 (1H, m), 4.60-4.75 (1H, m), 7.05-7.35 (5H, m), 7.39 (2H, s), 7.74 (3H, br), 8.04 (1H, d), 8.43 (1H, d), 8.8-9.2 (2H, br).

1-[N^2-[4-Amino-3,5-dibromo-N-(1-oxo-4-phenylbutyl)-D-phenylalanyl]-L-lysyl]-4-(4-pyridin-yl)-piperazine (9).

^{13}C NMR (DMSO-d_6): δ 22.0, 27.0, 27.3, 31.2, 34.4, 34.6, 36.2, 38.8, 41.0, 44.0, 45.0, 45.5, 47.8, 53.9, 107.3, 108.3, 125.6, 128.2, 132.5, 141.0, 149.7, 154.1, 169.4, 170.6, 171.8.

4-[N-(Aminocarbonyl)phenylamino]-1-phenylmethylpiperidine (precursor of 33).
^{1}H NMR (DMSO-d_6): δ 1.14-1.24 (2H, m), 1.63-1.68 (2H, m), 1.93-1.99 (2H, m), 2.73-2.78 (2H, m), 3.37 (2H, s), 4.16-4.24 (1H, m), 5.19 (2H, s), 7.11-7.15 (2H, m), 7.18-7.22 (3H, m), 7.24-7.29 (2H, m), 7.37-7.41 (1H, m), 7.42-7.47 (2H, m).

4-[N-(Aminocarbonyl)phenylamino]piperidine (33).
^{1}H NMR (DMSO-d_6): δ 0.98-1.07 (2H, m), 1.60-1.65 (2H, m), 2.01 (1H, br), 2.42-2.49 (2H, m), 2.83-2.89 (2H, m), 4.21-4.29 (1H, m), 5.16 (2H, s), 7.11-7.14 (2H, m), 7.35-7.39 (1H, m), 7.41-7.46 (2H, m).

4-(1,3-Dihydro-2(2H)-oxo-4-phenylimidazol-1-yl)-1-(1,1-dimethylethoxycarbonyl)-piperidine (precursor of 34).
^{1}H NMR (DMSO-d_6): δ 1.44 (9H, s), 1.53-1.85 (4H, m), 2.73-2.95 (2H, m), 3.92-4.16 (3H, m), 7.10-7.22 (2H, m), 7.33 (2H, dd), 7.51 (2H, d), 10.65 (1H, s).

4-(1,3-Dihydro-2(2H)-oxo-4-phenyl-imidazol-1-yl)-piperidine Trifluoroacetate (34).
^{1}H NMR (DMSO-d_6): δ 1.75-2.13 (4H, m), 2.90-3.25 (2H, m), 3.25-3.50 (2H, m), 4.03-4.26 (1H, m), 7.02 (1H, s), 7.18 (1H, t), 7.32 (2H, dd), 7.54 (2H, d), 8.30-8.63 (1H, m), 8.63-8.95 (1H, m), 10.80 (1H, s).

Table 4. ELEMENTAL ANALYSES

		Calculated (%)				Found (%)			
Cpd	Formula	C	H	N	Br	C	H	N	Br
***21a**	$C_{27}H_{37}N_3O_5$	67.06	7.71	8.69		66.81	7.61	8.81	
21a	$C_{22}H_{29}N_3O_3$	68.90	7.62	10.96		68.77	7.54	10.75	
***21b**	$C_{27}H_{37}N_3O_5$	67.06	7.71	8.69		66.88	7.65	8.85	
21b	$C_{24}H_{30}F_3N_3O_5$	57.94	6.08	8.45		57.80	5.98	8.15	
22a	$C_{36}H_{44}Br_2N_4O_7$	53.74	5.51	6.96	19.86	53.71	5.48	6.95	19.50
22b	$C_{36}H_{45}Br_2N_5O_6$	53.81	5.64	8.72	19.89	53.55	5.57	8.61	19.57
22c	$C_{36}H_{44}Br_2N_4O_7$	53.74	5.51	6.96	19.86	53.69	5.39	7.05	19.65
22d	$C_{36}H_{44}Br_2N_4O_7$	53.74	5.51	6.96	19.86	53.52	5.49	6.85	19.48
22e	$C_{36}H_{44}Br_2N_4O_7$	53.74	5.51	6.96	19.86	53.65	5.38	6.82	19.66
***1**	$C_{41}H_{46}Br_2N_4O_6$	57.89	5.45	6.59	18.79	57.70	5.41	6.83	18.85
1	$C_{33}H_{41}Br_3N_4O_4$	49.70	5.18	7.03	30.06	49.49	5.24	6.85	29.95
***2**	$C_{41}H_{47}Br_2N_5O_5$	57.96	5.58	8.24	18.81	58.19	5.48	8.13	18.98
2	$C_{33}H_{42}Br_3N_5O_3$	49.77	5.32	8.79	30.10	49.55	5.35	8.75	29.84
***3**	$C_{33}H_{37}Br_2F_3N_4O_7$	48.43	4.56	6.85	19.53	48.25	4.46	6.98	19.15
***3'**	$C_{41}H_{46}Br_2N_4O_6$	57.89	5.45	6.59	18.79	57.94	5.38	6.70	18.45
3	$C_{33}H_{40}Br_2N_4O_4$	55.32	5.63	7.82	22.30	54.98	5.39	8.20	22.05
4	$C_{33}H_{40}Br_2N_4O_4$	55.32	5.63	7.82	22.30	55.15	5.54	7.95	21.97
5	$C_{33}H_{40}Br_2N_4O_4$	55.32	5.63	7.82	22.30	55.30	5.28	8.20	22.04
23	$C_{10}H_{13}Br_2ClN_2O_2$	30.92	3.37	7.21	41.14	30.76	3.34	7.40	40.80
24a	$C_{18}H_{18}Br_2N_2O_3$	45.98	3.86	5.96	33.99	45.65	3.74	6.00	34.10
***25**	$C_{33}H_{38}Br_2N_4O_6$	53.10	5.13	7.51	21.41	52.92	5.07	7.35	21.05
***10**	$C_{40}H_{45}Br_2N_5O_5$	57.49	5.43	8.38	19.12	57.28	5.36	8.52	18.80
10	$C_{32}H_{40}Br_2ClN_5O_3$	52.08	5.46	9.49	21.66	52.00	5.37	9.55	21.26
21c	$C_{23}H_{31}N_5O_3$	64.92	7.34	16.46		64.63	7.32	16.28	
26	$C_{32}H_{38}Br_2N_6O_5$	51.49	5.13	11.26	21.41	51.54	5.05	11.34	21.20
***12**	$C_{42}H_{49}Br_2N_7O_7$	54.61	5.35	10.61	17.30	54.24	5.30	10.75	17.08

* = Precursor of

*3' = N^2-[3,5-Dibromo-N-(4-phenyl-1-oxobutyl)-L-tyrosyl]-N^6-(phenylmethoxycarbonyl)-D-lysine-2-phenethylamide

Table 4 (Part 2). ELEMENTAL ANALYSES

		Calculated (%)				Found (%)			
Cpd	Formula	C	H	N	Br	C	H	N	Br
12	$C_{34}H_{43}Br_2N_7O_5$	51.72	5.49	12.42	20.24	51.40	5.37	12.13	20.05
***13**	$C_{42}H_{49}Br_2N_7O_7$	54.61	5.35	10.61	17.30	54.25	5.31	10.73	17.10
13	$C_{34}H_{43}Br_2N_7O_5$	51.72	5.49	12.42	20.24	52.02	5.50	12.05	20.12
27	$C_{19}H_{20}Br_2N_2O_5$	44.21	3.91	5.43	30.96	44.08	3.86	5.60	31.05
***11**	$C_{41}H_{47}Br_2N_5O_7$	55.85	5.37	7.94	18.13	55.81	5.32	7.95	17.88
11	$C_{33}H_{41}Br_2N_5O_5$	53.02	5.53	9.37	21.38	53.34	5.65	9.10	21.05
***28**	$C_{28}H_{39}N_5O_5$	63.98	7.48	13.32		63.97	7.43	13.49	
28	$C_{20}H_{33}N_5O_3$	61.36	8.50	17.89		61.15	8.19	17.75	
29	$C_{29}H_{40}Br_2N_6O_5$	48.89	5.66	11.80	22.43	48.78	5.59	11.58	22.12
14	$C_{36}H_{46}Br_2N_8O_5$	52.06	5.58	13.49	19.24	51.75	5.47	13.15	18.95
15	$C_{41}H_{49}Br_2F_6N_7O_9$	46.56	4.67	9.27	15.11	46.19	4.51	8.99	14.89
16	$C_{41}H_{46}Br_2N_8O_{10}$	45.40	4.27	10.33	14.73	45.02	4.14	10.11	14.50
17	$C_{41}H_{49}Br_2F_6N_9O_9$	45.36	4.55	11.61	14.72	44.98	4.51	11.25	14.38
18	$C_{37}H_{45}Br_2N_9O_5$	51.94	5.30	14.73	18.68	52.02	5.18	14.77	18.43
19	$C_{38}H_{47}Br_2N_9O_5$	52.48	5.45	14.50	18.38	52.12	5.34	14.25	18.18
20	$C_{39}H_{47}Br_2N_9O_5$	53.13	5.37	14.30	18.13	52.88	5.16	14.15	17.97
30	$C_{19}H_{20}Br_2N_2O_3$	47.13	4.16	5.79	33.01	46.89	4.14	5.85	32.79
31	$C_{33}H_{38}Br_2N_4O_6$	53.10	5.13	7.51	21.41	53.04	5.05	7.65	21.02
32a	$C_{39}H_{43}Br_2N_5O_5$	57.01	5.28	8.52	19.45	56.89	5.22	8.40	19.16
32b	$C_{43}H_{50}Br_2N_6O_5$	57.98	5.66	9.44	17.94	57.96	5.69	9.28	17.77
32c	$C_{42}H_{54}Br_2N_6O_7$	55.15	5.95	9.19	17.47	54.94	5.89	9.02	17.10
32d	$C_{39}H_{47}Br_2F_3N_6O_7$	50.44	5.10	9.05	17.21	50.34	5.04	8.95	17.02
32e	$C_{42}H_{49}Br_2N_7O_5$	56.57	5.54	11.00	17.92	56.49	5.51	10.78	17.89
6	$C_{33}H_{38}Br_3N_5O_3$	48.46	4.98	9.11	31.20	48.08	5.12	8.78	30.85
7	$C_{35}H_{45}Br_3N_6O_3$	50.20	5.42	10.03	28.62	49.98	5.30	9.85	28.38
8	$C_{29}H_{42}Br_4N_6O_3$	41.35	5.03	9.98	37.95	41.50	5.25	9.90	37.55
9	$C_{34}H_{43}Br_2N_7O_3$	53.91	5.72	12.94	21.10	54.02	5.60	12.82	20.90

* = Precursor of

Table 4 (Part 3). ELEMENTAL ANALYSES

		Calculated (%)				Found (%)			
Cpd	Formula	C	H	N	Br	C	H	N	Br
***33**	$C_{19}H_{23}N_3O$	73.76	7.49	13.58		73.65	7.44	13.39	
33	$C_{12}H_{17}N_3O$	65.73	7.81	19.16		65.66	7.79	19.00	
***34**	$C_{19}H_{25}N_3O_3$	66.45	7.34	12.24		66.28	7.30	11.98	
34	$C_{16}H_{18}F_3N_3O_3$	53.78	5.08	11.76		53.75	5.07	11.51	

* = Precursor of