Supporting Information

New, Potent and Selective Peptidic Oxytocin Receptor Agonists

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Synthetic examples

Analytical HPLC was performed on a Waters 600 Liquid Chromatograph using a Vydac C18, 5μm, 4.6 x 250 mm column at a flow rate of 2 mL/min. Preparative HPLC was performed on a Waters 2000 Liquid Chromatograph using a PrePak 47 x 300 mm cartridge at a flow rate of 100 mL/min. Final purity of analogues was assessed on a 1100 Agilent Liquid Chromatograph using the following analytical method: column – Vydac C18, 5 μm, 2.1 x 250 mm; column temperature – 40°C; flow rate – 0.3 mL/min; solvent A – 0.01% aqueous TFA; solvent B – 70% CH_3CN, 0.01% TFA; gradient – 0-20% B in 1 min., then 20-40% B in 20 min., then held at 100% B for 5 min.; when necessary the first two segments of the gradient were adjusted for compound lipophilicity; UV detection at 214 nm. The purity of all analogues exceeded 95%.

For capacity factor calculations the retention times were determined on a 1200rr Agilent Liquid Chromatograph using an Agilent Zorbax SB-C18, 1.8 μm, 4.6 x 50 mm column at 30°C and a flow rate of 1.5 mL/min. Solvent A – 0.05% aqueous TFA: solvent B – 90% CH_3CN, 0.045% TFA;gradient: 20% B for1 min., then 20-45% B in 10 min.; UV detection at 214 nm. Mass spectra were recorded on a Finnigan MAT spectrometer.

Compound **57**; carba-1-[4-FBzlGly^7]dOT:

The following amino acid derivatives were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Cys((CH_2)$_3$-COO-tBu))-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH and Boc-Tyr(tBu)-OH (Peptides International). Fmoc-Cys((CH_2)$_3$-COO-tBu))-OH was synthesized by a literature method as indicated in the experimental section.

The fully protected peptide resin was synthesized manually, starting from 1.45 g (0.87 mmol) of Rink Amide AM resin (200-400 mesh, Novabiochem). DIC/HOBt mediated single couplings in DMF with a 3-fold excess of amino acid Gly and Leu derivatives were performed. To introduce the *N*-(4-fluorobenzyl)glycine residue, the resin was acylated with a 4-fold excess of bromoacetic acid/DIC/HOBt in DMF followed by bromine displacement with a 10-fold excess of 4-fluorobenzyl amine in DMF. A DIC mediated coupling in DCM with a 4-fold excess of Fmoc-Cys((CH_2)$_3$-COO-*t*Bu))-OH was then performed. Subsequent DIC/HOBt mediated single couplings in DMF with a 3-fold excess of amino acid derivatives (Asn, Gln, Ile and Tyr) were performed. The Fmoc groups were removed with 20% piperidine in DMF. Upon completion of the solid phase synthesis, the resin was treated with a TFA/TIS/H_2O 96/2.5/1.5 (v/v/v) solution (50 mL) for 1.5 h and filtered off. The filtrate was concentrated *in vacuo* and the crude linear peptide was precipitated with diethyl ether. The precipitate was dissolved in DMF (300 mL) and the linear peptide solution was added in 3 portions (3 x 100 mL) to a vigorously stirred solution of DIPEA (1 mL) in DMF (100 mL). HBTU (150 mg) in DMF (5 mL) was added to the reaction mixture after addition of each 100 mL portion of peptide solution; the pH of the reaction solution was maintained at pH 9 by addition of neat DIPEA, as required. The HPLC analysis after addition of each portion of the linear peptide showed fast (within 5 min.) conversion to the cyclic product . The reaction mixture was concentrated *in vacuo* and the residue was dissolved in AcOH/CH_3CN/H_2O.

The crude peptide solution was loaded onto an HPLC column and purified using a triethylammonium phosphate buffer with pH 5.2. The compound was eluted with a gradient of acetonitrile. The fractions with a purity exceeding 97% were pooled, diluted with water (2 volumes), and loaded onto a column pre-equilibrated with 2% AcOH (aq). The product was eluted with a fast (3%/min) gradient of CH_3CN. The fractions containing the desired product were pooled and lyophilized. 434 mg (~40% yield, based on the loading of the starting resin) of white amorphous powder was obtained. HPLC: Rt = 19.4 min, gradient: 5% B for 0.5 min., 5→30% B in 0.5 min, 30→50% B over 20 min and 100% B for 5 min., t = 40°C, solvent A: 0.01% TFA (aq), solvent B: 70% CH_3CN, 0.01% TFA (aq); Purity: 99.3%; MS ($M+H^+$): expected 1042.4, observed 1042.5.

Compound **57** was also prepared by an alternative method where the *N*-(4-fluorobenzyl)glycine residue in position 7 was introduced with Fmoc-4-FBzlGly-OH prepared as indicated in the experimental section.

Compound **30**; [4-PicGly^7]dOT:

The following amino acid derivatives were used: Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Cys(Trt)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(tBu)-OH and Mpa(Trt)-OH (Peptides International). The fully protected peptide resin was synthesized manually, starting from 1.33 g (0.65 mmol) of Rink AM resin (200-400 mesh, Novabiochem). DIC/HOBt mediated single couplings in DMF with a 3-fold excess of amino acid Gly and Leu derivatives were performed. To introduce the *N*-(4-picolyl)glycine residue, the resin was acylated with a 4-fold excess of bromoacetic acid/DIC/HOBt in DMF followed by bromine displacement with a 10-fold excess of 4-picolyl amine in DMF. A DIC mediated coupling in DCM with a 4-fold excess of Fmoc-Cys(Trt)-OH was then performed. Subsequent DIC/HOBt mediated single couplings in DMF with a 3-fold excess of amino acid derivatives (Asn, Gln, Ile, Tyr and Mpa) were performed. The Fmoc groups were removed with 20% piperidine in DMF. Upon completion of the solid phase synthesis, the resin was treated with TFA/TIS/H_2O 96/2/2 (v/v/v) solution (50 mL) for 1.5 h and filtered off. The filtrate was concentrated *in vacuo* and the crude linear peptide was precipitated with diethyl ether. The precipitate was dissolved in neat TFA (50 mL), poured onto a magnetically stirred 5% aqueous acetonitrile (600 mL) solution and the peptide was oxidized by adding 0.1 M I_2 in methanol until yellow color persisted. Excess of iodine was reduced with solid ascorbic acid (Sigma-Aldrich) and the pH of the solution was adjusted to about 4 by adding concentrated ammonia (aq). The mixture was loaded onto an HPLC column and purified using a triethylammonium phosphate buffer with pH 5.2. The compound was eluted with a gradient of acetonitrile. The fractions with a purity exceeding 97% were pooled, diluted with water (2 volumes), and loaded onto a column pre-equilibrated with 2% AcOH (aq). The desired compound was eluted with a fast (3%/min) gradient of acetonitrile. The fractions containing the desired product were pooled and lyophilized. 348.7 mg (~44% yield, based on the loading of the starting resin) of white amorphous powder was obtained. HPLC: Rt = 21.7 min, gradient: 5% B for 0.5 min., 5→10% B in 0.5 min, 10→30% B over 20 min and 100% B for 5 min., t = 40°C, solvent A 0.01% TFA (aq), solvent B 70% CH_3CN, 0.01% TFA (aq); Purity: 99.9%; MS ($M+H^+$): expected 1043.4, observed 1043.4.

Compound **40**; carba-6-[Phe^2,MeOEtGly^7]dOT:

The amino acid derivatives used were Boc-Gly-OH and Boc-Leu-OH (Bachem), Fmoc-Hcy((CH$_2$)$_2$-COO-tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH and Boc-Phe-OH (Peptides International). Fmoc-Hcy((CH$_2$)$_2$-COO-tBu)-OH was synthesized as indicated in the experimental section.

The fully protected peptide resin was synthesized manually starting from 1.33 g of MBHA resin (0.94 mmol, Novabiochem). The resin was neutralized with 10% TEA in DCM. DIC mediated single couplings in DCM with a 1.7-fold excess of amino acids Boc-Gly-OH and Boc-Leu-OH were performed. To introduce the *N*-(2-methoxyethyl)glycine residue, the resin was acylated with a 3.6-fold excess of bromoacetic acid/DIC/HOBt in DMF followed by bromine displacement with a 7-fold excess of 2-methoxyethyl amine and a 4-fold excess of DIPEA in DMF. DIC mediated single coupling in DCM with a 4-fold excess of Fmoc-Hcy((CH$_2$)$_2$-COO-tBu)-OH and DIC/HOBt mediated single couplings in DMF with a 3-fold excess of amino acid derivatives (Asn and Gln) were then performed. The two final single couplings with Fmoc-Ile-OH and Boc-Phe-OH were performed with DIC/DCM to provide the desired protected resin-bound linear peptide. The Fmoc groups were removed with 20% piperidine in DMF. The resin was treated with TFA/H$_2$O/TIS 95/3/2 (v/v/v) for 2 h to remove the trityl, Boc, and *t*-butyl protecting groups. BOP (4 eq) and DIPEA (10 eq) were added to a stirred suspension of the resin in DMF (10 mL); after 2 h the resin was washed with DMF. The resin was resuspended in DMF and PyBOP (2 eq) and DIPEA (5 eq) were subsequently added. The cyclization was carried out overnight and the resin tested negative in the nihidrine test. The cyclic peptide was cleaved from the resin by using 70 mL of anhydrous HF containing 5 mL of anisole at 0 ^{o}C for 90 min. The HF was removed *in vacuo* and the crude linear peptide was washed with diethyl ether (300 mL). The peptide was dissolved in AcOH/CH$_3$CN/H$_2$O 1/2/7 (v/v/v) (400 mL). The resulting mixture was loaded directly onto an HPLC column and purified using triethylammonium phosphate buffer at pH 2.3. The compound was eluted with an acetonitrile gradient. The fractions with a purity exceeding 97% were pooled, diluted with water (2 volumes), and loaded onto a column pre-equilibrated with 2% acetic acid (aq). The product was eluted with a 1% AcOH/CH$_3$CN gradient. The fractions containing the desired compound were pooled and lyophilized.

292.7 mg (~27% yield, based on the loading of the starting resin) of white amorphous powder was obtained. HPLC: Rt = 16.7 min, gradient: 5% B for 0.5 min., 5→30% B in 0.5 min, 30→50% B over 20 min and 100% B for 5 min., t = 40°C, solvent A 0.01% TFA (aq), solvent B 70% CH$_3$CN, 0.01% TFA (aq); Purity: 100.0%; MS (M+H$^+$): expected 976.5, observed 976.3.

The other compounds were prepared by variation of these synthetic procedures.

Table 1a. Additional pharmacological data for reference compounds **1-3, AVP and dDAVP** and initial leads **4-8**.

Compound	*In vitro* biological activity					Rat PK
	EC_{50} receptor (nM) (pEC_{50}±SEM)				IC_{50} (nM)[a] (pIC_{50}±SEM)	CL±SEM (mL/min/kg)
	hOT	hV_2	hV_{1a}	hV_{1b}	hV_{1a}	
1	2.3 (8.63±0.03)	7.3 (8.14±0.09)	10 (7.98±0.18)	240 (6.62±0.19)	>10000[b] (N/A)	21±3.8
2	0.70 (9.15±0.01)	170 (6.76±0.09)	41[c] (7.39±0.17)	>10000[d] N/A)	>10000[b] (N/A)	22±1.7
3	0.10 (10.0±0.07)	3.5 (8.46±0.09)	21[c] (7.67±0.04)	180 (6.76±0.18)	>10000[b] (N/A)	27±3.8
4	0.98 (9.01±0.20)	690 (6.16±0.42)	>10000[d] (N/A)	>10000[d] N/A)	1300 (5.88±0.24)	21±1.9
5	0.82 (9.09±0.20)	670[c] (6.17)	>1000[e] (N/A)	>10000[d] (N/A)	670 (6.17±0.12)	38±4.6
6	0.06 (10.2±0.09)	40 (7.40±0.10)	>1000[e] (N/A)	1100 (5.94±0.20)	17 (7.77±0.22)	25±1.2
7	0.21 (9.68±0.17)	450 (6.35±0.13)	>100 (N/A)	>10000[d] (N/A)	55 (7.26±0.10)	20±4.6
8	0.37 (9.43±0.11)	450[c] (6.35±0.16)	>1000[e] (N/A)	>10000[d] (N/A)	1400 (5.84±0.06)	45±5.9
AVP	22 (7.65±0.06)	0.05 (10.26±0.04)	0.23 (9.63±0.02)	4.0 (8.40±0.02)	NT[f]	NT[f]
dDAVP	72[c] (7.14±0.24)	0.20 (9.70±0.01)	>1000[e] (N/A)	6.5[c] (8.19±0.09)	NT[f]	7.5±0.3

[a] hV_{1a} receptor stimulated with 2 nM AVP; [b] no significant antagonism up to 10000 nM, the highest concentration tested; [c] partial agonist, efficacy < 70%; [d] no significant agonism up to 10000 nM, the highest concentration tested; [e] no significant agonism up to 1000 nM, the highest concentration tested; [f] not tested.

Table 2a. Additional pharmacological data for disulfide bridge compounds **9-36**.

Compound	*In vitro* biological activity					Rat PK
	EC_{50} receptor (nM) (pEC_{50}±SEM)				**IC_{50} (nM)[a] (pIC_{50}±SEM)**	**CL±SEM (mL/min/kg)**
	hOT	hV_2	hV_{1a}	hV_{1b}	hV_{1a}	
9	0.05 (10.3±0.09)	4.2 (8.38±0.09)	>10000[b] (<5.00)	700 (6.16±0.18)	>10000[c] (N/A)	36±4.5
10	0.01 (11.2±0.09)	9.9 (8.01±0.06)	>10000[b] (N/A)	660 (6.18±0.06)	>10000[c] (N/A)	59±6.5
11	0.06 (10.2±0.11)	35 (7.46±0.04)	>10000[b] (N/A)	1000[d] (5.98±0.11)	>10000[c] (N/A)	63±8.4
12	0.16 (9.81±0.08)	1.8 (8.75±0.03)	85[d] (7.07±0.27)	500 (6.30±0.24)	>10000[c] (N/A)	NT[e]
13	0.01 (11.3±0.09)	77 (7.11±0.07)	19[d] (7.72±0.04)	370 (6.43±0.04)	>10000[c] (N/A)	94±7.3
14	0.13 (9.87±0.05)	11 (7.94±0.01)	>10000[b] (<5.00)	980[d] (6.01±0.17)	>10000[c] (N/A)	61±11
15	0.01 (10.9±0.05)	100 (6.99±0.06)	12[d] (7.94±0.28)	470 (6.32±0.09)	>10000[c] (N/A)	46±4.6
16	1.3 (8.90±0.12)	57 (7.25±0.08)	>10000[b] (N/A)	>10000[b] (N/A)	2300 (5.65±0.01)	NT[e]
17	0.03 (10.5±0.18)	80 (7.10±0.07)	>10000[b] (N/A)	2800[d] (5.56±0.04)	1800 (5.74±0.11)	47±4.1
18	0.39 (9.41±0.09)	100 (6.99±0.13)	>10000[b] (N/A)	>10000[b] (N/A)	3400 (5.47±0.24)	28±3.2
19	0.11 (9.95±0.09)	34 (7.47±0.03)	>10000[b] (N/A)	260 (6.58±0.24)	>10000[c] (N/A)	83±15
20	0.12 (9.92±0.10)	68 (7.17±0.07)	>10000[b] (N/A)	290 (6.55±0.10)	1900 (5.72±0.13)	81±13
21	0.01 (10.9±0.12)	30 (7.53±0.22)	>10000[b] (N/A)	110 (6.95±0.09)	>10000[c] (N/A)	91±6.8

22	0.15 (9.83±0.05)	84 (7.08±0.07)	>10000[b] (N/A)	200 (6.70±0.13)	1400 (5.84±0.15)	67±3.8
23	0.01 (10.9±0.19)	82 (7.09±0.11)	>10000[b] (N/A)	140 (6.86±0.14)	880 (6.05±0.04)	24±3.3
24	0.06 (10.2±0.07)	78 (7.11±0.04)	>10000[b] (N/A)	440 (6.36±0.22)	970 (6.01±0.12)	73±16
25	1.3 (8.88±0.18)	180 (6.74±0.07)	>10000[b] (N/A)	1800[d] (5.75±0.24)	2500 (5.66±0.07)	NT[e]
26	1.3 (8.88±0.05)	170 (6.77±0.10)	>10000[b] (N/A)	1300[d] (5.89±0.09)	1300 (5.88±0.10)	NT[e]
27	0.46 (9.33±0.07)	380 (6.42±0.07)	>10000[b] (N/A)	2600 (5.59±0.12)	3200 (5.49±0.20)	43±2.2
28	0.12 (9.94±0.05)	66 (7.18±0.07)	>10000[b] (N/A)	590 (6.23±0.16)	270 (6.57±0.28)	94±19
29	0.12 (9.94±0.18)	180 (6.74±0.08)	>10000[b] (N/A)	770 (6.11±0.07)	730 (6.14±0.08)	63±13
30	0.02 (10.6±0.07)	47 (7.33±0.04)	>10000[b] (N/A)	720 (6.14±0.07)	350 (6.46±0.06)	48±5.0
31	0.01 (11.0±0.07)	57 (7.24±0.07)	>10000[b] (N/A)	240 (6.62±0.10)	1200 (5.90±0.08)	71±8.6
32	0.11 (9.94±0.07)	62 (7.21±0.08)	>10000[b] (N/A)	930[d] (6.03±0.14)	3900 (5.41±0.13)	67±11
33	0.02 (10.8±0.16)	86 (7.07±0.08)	>10000[b] (N/A)	600 (6.22±0.07)	280 (6.55±0.10)	65±7.7
34	0.07 (10.1±0.16)	230 (6.65±0.08)	>10000[b] (N/A)	>10000[b] (N/A)	1500 (5.83±0.14)	39±3.9
35	19 (7.72±0.15)	1400[d] (5.86±0.14)	>10000[b] (N/A)	>10000[b] (N/A)	1300 (5.89±0.09)	NT[e]
36	10 (7.99±0.07)	1400 (5.86±0.05)	>10000[b] (N/A)	>10000[b] (N/A)	>10000[c] (N/A)	NT[e]

[a] hV_{1a} receptor stimulated with 2 nM AVP; [b] No significant agonism at the highest concentration tested – 10000 nM; [c] No significant antagonism at the highest concentration tested - 10000 nM; [d] partial agonist, efficacy < 70%; [e] Not tested

Table 3a. Additional pharmacological data for monocarba analogues **37-65**.

Compound	*In vitro* biological activity					Rat PK
	EC_{50} receptor (nM) (pEC_{50}±SEM)				IC_{50}[a] (nM) (pIC_{50}±SEM)	CL±SEM (mL/min/kg)
	hOT	hV_2	hV_{1a}	hV_{1b}	hV_{1a}	
37	0.11 (9.96±0.10)	70 (7.16±0.02)	>10000[b] (N/A)	3200 (5.49±0.19)	>10000[c] (N/A)	20±1.9
38	0.16 (9.80±0.36)	52 (7.29±0.04)	>10000[b] (N/A)	830 (6.08±0.06)	990 (6.00±0.23)	22±1.4
39	0.96 (9.02±0.04)	1100 (5.96±0.03)	>10000[b] (N/A)	>10000[b] (N/A)	>10000[c] (N/A)	32±4.9
40	0.85 (9.07±0.06)	1300 (5.90±0.05)	>10000[b] (N/A)	>10000[c] (N/A)	2500 (5.61±0.12)	21±1.5
41	0.01 (10.9±0.29)	500[d] (6.30±0.19)	>10000[b] (N/A)	>10000[b] (N/A)	1400 (5.86±0.05)	18±1.7
42	0.13[e] (9.90±0.18)	150 (6.83±0.10)	>10000[b] (N/A)	>10000[b] (N/A)	1800 (5.76±0.11)	13±0.53
43	0.86 (9.07±0.08)	2600 (5.59±0.05)	>10000[b] (N/A)	>10000[b] (N/A)	>10000[c] (N/A)	22±2.1
44	0.12 (9.91±0.45)	73 (7.14±0.07)	>10000[b] (N/A)	820 (6.08±0.04)	>10000[c] (N/A)	36±0.96
45	0.14 (9.85±0.43)	18 (7.76±0.07)	>10000[b] (N/A)	450 (6.35±0.09)	>10000[c] (N/A)	NT[e]
46	0.23 (9.64±0.14)	2000[d] (5.70±0.11)	>10000[b] (N/A)	>10000[c] (N/A)	2800 (5.56±0.05)	NT[e]
47	0.09 (10.1±0.11)	1200[d] (5.92±0.09)	>10000[b] (N/A)	>10000[b] (N/A)	740 (6.13±0.05)	61±4.6
48	0.11 (9.95±0.36)	110 (6.97±0.10)	86[d] (7.07±0.24)	500 (6.30±0.13)	>10000[c] (N/A)	45±0.75

49	0.25 (9.60±0.20)	2100[d] (5.69±0.06)	>10000[b] (N/A)	3600[d] (5.45±0.10)	>10000[c] (N/A)	95±4.2
50	0.07 (10.2±0.10)	1000[d] (5.99±0.08)	>10000[b] (N/A)	1000 (6.00±0.13)	>10000[c] (N/A)	83±9.5
51	0.04 (10.4±0.10)	140 (6.85±0.11)	>10000[b] (N/A)	100 (7.00±0.34)	1400 (5.85±0.12)	51±5.9
52	0.05 (10.3±0.36)	36 (7.45±0.07)	>10000[b] (N/A)	100 (7.00±0.14)	>10000[c] (N/A)	68±5.0
53	0.40 (9.39±0.05)	720 (6.14±0.05)	>10000[b] (N/A)	440 (6.36±0.10)	1600 (5.79±0.12)	43±1.8
54	0.08 (10.1±0.28)	210 (6.67±0.08)	>10000[b] (N/A)	84 (7.08±0.20)	>10000[c] (N/A)	70±3.5
55	0.02 (10.6±0.06)	55 (7.26±0.13)	71[d] (7.15±0.48)	87 (7.06±0.13)	>10000[c] (N/A)	61±8.4
56	0.56 (9.25±0.31)	1600[d] (5.79±0.08)	>10000[b] (N/A)	620 (6.21±0.28)	480 (6.32±0.11)	63±12
57	0.08 (10.1±0.06)	330 (6.48±0.18)	>10000[b] (N/A)	180 (6.75±0.15)	1200 (5.93±0.04)	65±5.9
58	0.04 (10.4±0.12)	140 (6.85±0.19)	>10000[b] (N/A)	91[d] (7.04±0.24)	>10000[c] (N/A)	58±2.1
59	0.23 (9.64±0.08)	1400 (5.85±0.05)	>10000[b] (N/A)	750[d] (6.13±0.20)	1300 (5.89±0.03)	68±13
60	0.04 (10.3±0.08)	160 (6.79±0.05)	>10000[b] (N/A)	450 (6.35±0.09)	490 (6.31±0.05)	75±3.3
61	0.05 (10.3±0.19)	100 (7.00±0.04)	>10000[b] (N/A)	160 (6.81±0.08)	640 (6.19±0.13)	52±5.9
62	0.78 (9.11±0.07)	3000[d] (5.52±0.10)	>10000[b] (N/A)	1500 [d] (5.83±0.13)	330 (6.49±0.06)	62±6.9
63	0.09 (10.1±0.21)	250 (6.60±0.21)	>10000[b] (N/A)	420 (6.38±0.12)	2100 (5.67±0.26)	48±6.8
64	0.14	30	>10000[b]	190	380	53±7.8

	(9.86±0.32)	(7.52±0.11)	(N/A)	(6.73±0.13)	(6.42±0.02)	
65	0.30 (9.53±0.23)	760 (6.12±0.07)	>10000[b] (N/A)	850 (6.07±0.07)	1200 (5.91±0.17)	49±8.1

[a] hV_{1a} receptor stimulated with 2 nM AVP; [b] No significant agonism at the highest concentration tested - 10000 nM; [c] No significant antagonism at the highest concentration tested - 10000 nM; [d] partial agonist, efficacy < 70%; [e] Not tested.

Table 4. Physicochemical properties of compounds **1-65**

Compound	HPLC Purity	HPLC ret time (min)[a]	k'	log k'	MH+ expected	MH+ observed
1	99.7	2.25	4.63	0.67	1007.4	1007.8
2	100.0	6.18	14.48	1.16	988.5	988.5
3	99.4	4.49	10.23	1.01	992.4	992.2
4	97.0	6.00	14.00	1.15	1018.5	1018.4
5	100.0	6.82	16.05	1.21	1034.5	1034.3
6	98.9	6.80	16.00	1.20	1002.5	1002.2
7	97.0	7.71	18.28	1.26	1016.5	1016.5
8	100.0	5.59	12.98	1.11	948.5	948.2
9	99.4	5.13	11.83	1.07	992.4	992.3
10	100.0	5.61	13.03	1.11	1006.4	1006.3
11	99.3	6.26	14.65	1.17	1008.5	1008.3
12	100.0	5.61	13.03	1.11	1006.5	1006.3
13	99.5	7.16	16.90	1.23	1022.5	1022.5
14	97.2	6.33	14.83	1.17	1020.5	1020.3
15	99.3	8.06	19.15	1.28	1036.5	1036.1
16	99.1	6.79	15.98	1.20	1034.5	1034.5
17	99.8	4.74	10.85	1.04	1010.4	1010.3
18	99.6	3.44	7.60	0.88	1010.4	1010.3
19	99.4	6.62	15.55	1.19	1042.5	1042.5
20	100.0	7.17	16.93	1.23	1056.5	1056.4

21	100.0	7.41	17.53	1.24	1056.5	1056.2
22	100.0	7.40	17.50	1.24	1056.5	1056.2
23	100.0	6.91	16.28	1.21	1060.4	1060.0
24	99.4	6.64	15.20	1.18	1072.5	1072.1
25	98.3	3.52	7.80	0.89	1043.5	1043.3
26	98.4	2.85	6.13	0.79	1043.5	1043.3
27	99.9	2.91	6.28	0.80	1043.4	1043.4
28	100.0	7.24	17.10	1.23	1056.5	1056.5
29	100.0	3.28	7.20	0.86	1057.5	1057.4
30	100.0	3.01	6.53	0.81	1057.5	1057.3
31	99.1	6.31	14.78	1.17	1048.4	1048.3
32	99.0	5.82	13.55	1.13	1032.4	1032.5
33	100.0	6.89	16.23	1.21	1062.4	1062.0
34	100.0	5.23	12.08	1.08	1036.5	1036.1
35	99.5	3.28	7.20	0.86	1049.5	1049.5
36	98.1	3.13	6.83	0.83	1065.5	1065.7
37	100.0	4.20	9.77	0.99	992.5	992.1
38	100.0	4.06	9.41	0.97	992.5	992.1
39	100.0	6.25	14.63	1.17	976.5	976.1
40	100.0	6.12	14.30	1.16	976.5	976.3
41	100.0	2.86	6.33	0.80	992.5	992.1
42	100.0	2.69	5.90	0.77	992.5	992.1
43	99.8	5.01	11.53	1.06	976.5	976.1
44	100.0	5.91	14.15	1.15	990.5	990.3
45	100.0	5.72	13.30	1.12	990.5	990.3
46	99.3	7.66	18.15	1.26	974.5	974.1
47	100.0	7.58	17.95	1.25	974.5	974.1
48	98.8	6.84	16.54	1.22	1004.5	1004.3
49	100.0	8.68	20.70	1.32	988.5	988.1
50	100.0	8.47	20.18	1.30	988.5	988.1

51	99.4	6.19	14.87	1.17	1024.5	1024.2
52	98.9	6.07	14.56	1.16	1024.5	1024.2
53	100.0	7.95	18.88	1.28	1008.5	1008.5
54	99.1	7.01	16.97	1.23	1038.5	1038.1
55	99.4	6.91	16.72	1.22	1038.5	1038.0
56	100.0	8.75	20.88	1.32	1022.5	1022.3
57	96.1	6.47	15.59	1.19	1042.5	1042.2
58	99.0	6.33	15.23	1.18	1042.5	1042.0
59	98.7	8.20	19.50	1.29	1026.5	1026.3
60	98.7	6.90	16.69	1.22	1038.5	1038.2
61	100.0	6.65	16.05	1.21	1038.5	1038.0
62	99.9	8.51	20.28	1.31	1022.5	1022.4
63	98.7	5.82	13.92	1.14	1030.4	1030.2
64	100.0	5.75	13.74	1.14	1030.5	1030.1
65	99.4	7.70	18.25	1.26	1014.5	1014.0