SUPPLEMENTARY DATA

Synthesis of C781: N-((3S,6S)-1-furan-2-carbonyl)-6-isobutyl-4,7-dioxo-8-(piperidin-4-ylmethyl)octahydro-2H-pyrazino[1,2-a]pyrimidin-3-yl)-3-methylbutaneamide.

Chemical Materials:

N-α-Fmoc-protected amino acids, TCFH, DIC, and HOBt were purchased from SynPep (Dublin, CA) or from Novabiochem (San Diego, CA). Bromoacetal, 2-Chloro-chlorotrityl, and Wang resins were acquired from Rapp Polymere (Tubingen, Germany). Aloc group was used as a side chain protecting groups for the *N*α-Fmoc-Dap(N$^{\beta}$-Aloc). Reagent grade solvents, reagents, and acetonitrile for HPLC were acquired from VWR (West Chester, PA) or Sigma-Aldrich (St. Louis, MO) and were used without further purification unless otherwise noted. Chemicals and reagents were obtained from Sigma-Aldrich or TCI (Portland, OR). The solid-phase synthesis was performed in fritted syringes using a Domino manual synthesizer obtained from Torviq (Niles, MI).

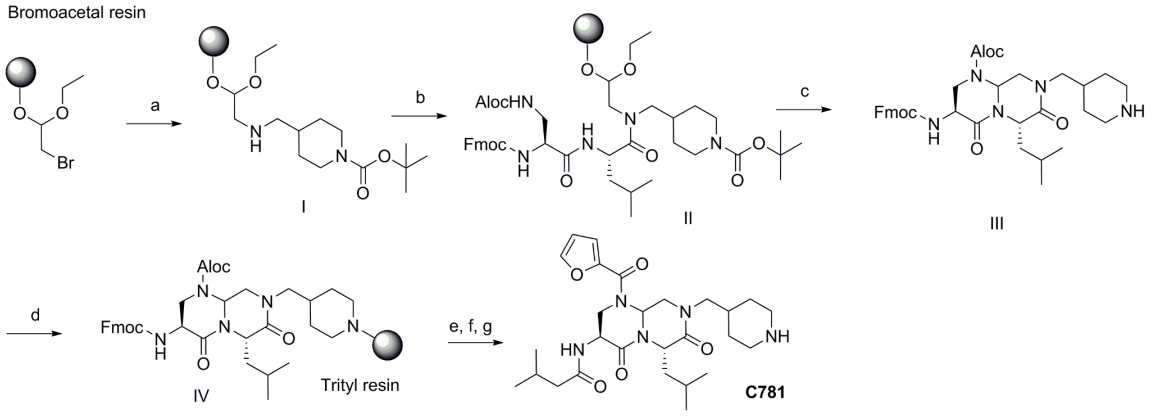
General Synthesis:

All solution phase reactions were conducted under Argon atmosphere using oven-dried glassware. ^{1}H NMR spectra were recorded on a Bruker-DRX-300 MHz instrument with chemical shifts reported relative to tetramethylsilane (TMS; 0.0 ppm) and residual dimethyl sulfoxide (DMSO; 2.50 ppm). Proton-decoupled ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm) as well as DMSO (39.51 ppm). Low resolution mass spectra were obtained on a Bruker AmaZon SL Ion Trap Mass Spectrometer with ESI source (Madison, WI). High resolution mass spectra (HRMS) were recorded on a Bruker SolariX Fourier-transform Ion Cyclotron Resonance Mass Spectrometer, 9.4T magnet, with ESI source (Madison, WI).

Quality control and purification:

The purity of products was checked by analytical reverse phase HPLC using a Waters Alliance 2695 Separation Model (Milford, MA) with a Waters 2487 dual wavelength detector (220 and 280 nm) on a reverse phase column (Waters Symmetry C18, 4.6 × 75 mm, 3.5 μm). Crude compounds were eluted with a linear gradient of aqueous CH_3CN/0.1% CF_3CO_2H at a flow rate of 1.0 mL/min. Purification of compounds was achieved on a Waters 600 HPLC using a reverse phase column (Vydac C18, 15–20 μm, 22 × 250 mm). Compounds were eluted with a linear gradient of CH_3CN/0.1% CF_3CO_2H at a flow rate of 5.0 mL/min. Separation was monitored at 230 and 280 nm. Flash chromatography was performed on a borosilicate glass column (2.6 × 250 mm, Sigma-Aldrich, St. Louis, MO) filled with 60A silicagel (Sigma-Aldrich,). The compounds were eluted with a step gradient flow of hexane/EtOAc/MeOH mixtures.

Preparation of the cyclized azabicycloalkane analog C781 (Scheme S1).



Scheme S1. Solid-phase synthesis of **C781.**
(a) 0.5M solution of Boc-protected diamine in DMSO, 60°C, overnight. **(b)** (i) Fmoc-Leu coupling, TCFH/collidine (II) 10% piperidine in DMF, 20 minutes (iii) Fmoc-Dap(Aloc), DIC/HOBt, 3hrs. **(c)** (i) 60 % a. formic acid, 4 hrs (ii) column purification. **(d)** attachment to the 2-Chloro-chlorotrityl resin, 2.5 eq. in DCM, DIEA. **(e)** 10% piperidine in DMF, 20 minutes (ii) 0.5 M acid chloride, DCM, collidine, overnight. **(f)** (i) deprotection of Aloc: Pd(0), DCM, dimethylbarbituric acid. (ii) 2-furoic acid, TCFH, DIEA, DCM. **(g)** (i) 94% TFA in DCM, 3% water, 3% EDT, 1 hr. (ii) HPLC purification.

Intermediate I: The bromoacetal resin (0.2g, 0.25 mmol) was swelled for 2 hours by the addition of DCM. The swollen resin was carried out through the solid-phase procedure. The resin was washed successively with dimethylformamide (DMF; 3 × 2 min), dichloromethane (DCM' 3 × 2 min), DMSO (5 × 2 min). Amine displacement of bromine was accomplished with 0.5M solution of 1-*N*-Boc-4-(aminomethyl)piperidine (0.214 g, 1mmol, 4 equiv.) in DMSO at 60°C overnight. The reaction mixture was removed by filtration and the resin was washed successively with DMSO (5 × 2 min) and DCM (3 × 2 min). Before coupling of Fmoc-Leu, the resin was neutralized with 10% diisopropylethylamine (DIEA) in DCM (2 × 3 min), followed by washing successively with DCM (3 × 2 min) and DMF (5 × 2 min).

Intermediate II:

The intermediate resin I from above (0.2g, 0.25 mmol) was coupled with Fmoc-Leu. The coupling was performed by adding Fmoc-Leu (0.353g, 1 mmol, 4 equiv) and coupling reagents [tetramethylchloroformamidium hexafluorophosphate (TCFH) 0.28g, 1mmol, 4 equiv and; diisopropylethylamine (DIEA) 0.35 mL, 2 mmol, 8 equiv] in DMF (2 mL) to the resin and stirring the mixture overnight. A second TCFH coupling was performed for 3 hour. The reaction mixture was removed by filtration and the resin was washed with DMF (5 × 2 min) and DCM (3 × 2 min). The N^{α}-Fmoc protecting group was removed with 1:10 piperidine in DMF (1 × 2 min and 1 × 20 min). The resin was washed successively with DMF (5 × 2 min), DCM (3 × 2 min), a solution of 0.05 mM solution of Bromophenol Blue in 0.2 M N-hydroxybenzotriazole HOBt in DMF, then DMF (3 × 2 min). The N^{α}-Fmoc-Dap(Aloc) was coupled using pre-activated 0.3 M HOBt esters in DMF-DCM mixture (3 equiv of N^{α}-Fmoc-Dap(Aloc), 3 equiv of HOBt, and 3 equiv of DIC). The resin slurry was stirred for 2 h or until the bromophenol test became negative (yellow). The resin was washed with DMF (3 × 2 min). A second coupling was performed by the HCTU/2,4,6-lutidine procedure (0.3 M solution of 3 equiv of N^{α}-Fmoc-Dap(Aloc), 3 equiv of HCTU, and 6 equiv of 2,4,6-lutidine in DMF. The reaction mixture was removed by filtration and

the resin was washed with DMF (5 × 2 min), DCM (3 × 2 min), and then MeOH (3 x 2 min). The reactor was placed in vacuum oven to remove solvents.

Intermediate III:

The dry intermediate resin II from above (0.2g, 0.25 mmol) was treated with 60% formic acid (2 mL) for 4 hrs. The resin was filtrated and washed with water (2 x 2 min). Acid filtrate and washes were collected and lyophilized. The crude intermediate III was purified using column chromatography to yield pure III (74 mg, 53%, $(M+H)^+$ 559.3, HPLC >95%).

Intermediate IV:

The dry intermediate III from above (74 mg, 132 μmol) was added to dry 2-Chloro-chlorotrityl resin (250 mg, 430 μmol, 2.5 equiv.). Dry DCM (2.0 mL) and DIEA (171 μL, 1.0 mmol) were injected into the resin and the mixture was agitated at room temperature for overnight. The reaction was quenched by adding MeOH (0.2 mL, 30 min). The reaction mixture was removed by filtration and the resin was washed with DMF (3 × 2 min), DCM (5 × 2 min), and then DMF (2 x 2 min).

Final product C781:

The intermediate resin IV from above was deprotected by piperidine. The N^{α}-Fmoc protecting group was removed with 1:10 piperidine in DMF (1 × 2 min and 1 × 20 min). The resin was washed with DMF (5 × 2 min) and then DCM (5 × 2 min). The isovaleric acid was coupled using 0.3 M acid chloride in DCM (isovaleryl chloride, 121 mg, 1 .0 mmol, 7.6 equiv; pyridine, 80 mL, 1.0 mmol, 7.6 equiv). The resin slurry was stirred for 3 h, the reaction mixture removed by filtration, the resin was washed with DCM (5 × 2 min) and the isovaleric acid was coupled again using 5 equiv. The reaction mixture was removed by filtration and the resin was washed successively with DMF (5 × 2 min), DCM (3 × 2 min). The N^{α}-Aloc protecting group was removed with Palladium catalyzed cleavage (Tetrakis(triphenylphosphine)palladium(0) (Pd(PPh3)4), 11.5 mg, 0.01 mmol; 1,3-dimethylbarbituric acid, 78 mg, 0.5 mmol) in 0.5 mL DCM then repeated (2 × 30 min). The resin was washed successively with DCM (3 × 2 min), DMF (5 × 2 min), with a solution of 0.5 M Sodium diethyldithiocarbamate trihydrate (113 mg in 1 mL) in DMF (2 × 20 min), then washed with DMF (5 × 2 min). The resin was neutralized by 0.5 M diisopropylethylamine DIEA in DMF (5 × 2 min), then washed with DMF (5 × 2 min) and DCM (5 x 2 min). The final coupling was performed by adding 2-furoic acid (112 mg, 1 mmol, 7.6 equiv) and coupling reagents [TCFH (0.28g, 1mmol, 7.6 equiv) and DIEA (0.35 mL, 2 mmol, 15.2 equiv)] in DCM (2 mL) to the resin and stirring the mixture overnight. The coupling was repeated for 3 hours using 5 equiv of 2-furoic acid. The reaction mixture was removed by filtration and the resin was washed successively with DMF (5 × 2 min), DCM (7 × 2 min), then cleaved by strong acid. A cleavage cocktail (2.0 mL) consisting of CF_3CO_2H (94%), H_2O (3%), and 1,2-ethylenedithiol EDT (3%) was injected into the resin and the mixture was agitated at room temperature for 4 h. The solution was filtered, the resin was washed with CF_3CO_2H (2 × 3 min), the liquid phases were collected and concentrated under a stream of nitrogen, and the product was precipitated using cold diethyl ether/hexane [(Et_2O)/hexane]. The crude product was washed three times with cold Et_2O/hexane, lyophilized, purified by HPLC, and characterized as described above. The desired product was 25 mg of C781 as a white lyophilizate (yield 19%).

Analytical data:

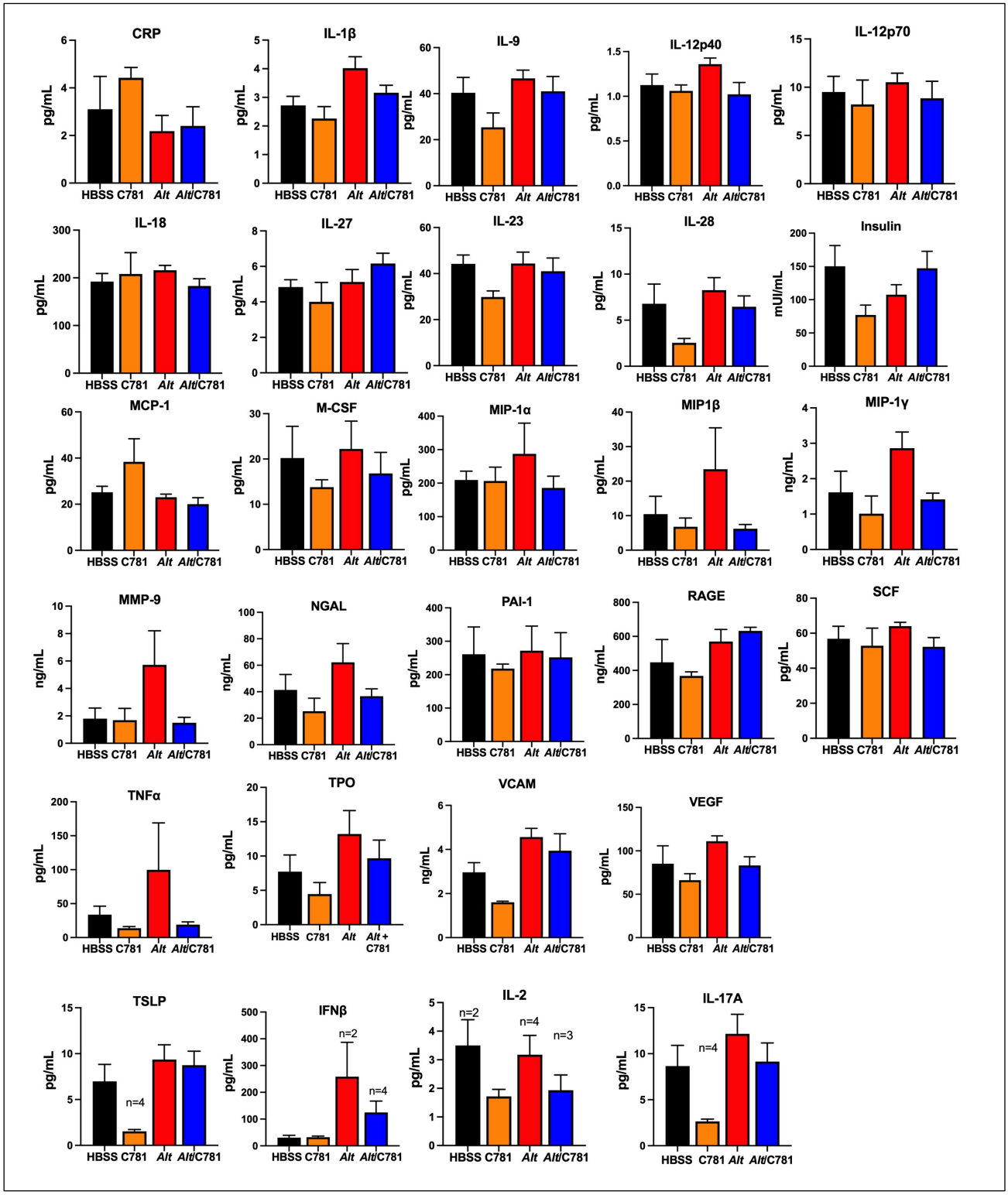
$(M+H)^+$ 515.30, HPLC >95%).

^{1}H NMR: 0.86 (d, 6H), 0.90 (d, 6H), 1.30 (m, 4H), 1.60 (m, 1H), 1.74 (t, 2H), 1.97 (m. 1H), 2.0 (d, 2H), 2.02 (m. 1H), 2.81(m, 4H), 3.3 (t, 2H), 3.50 (t, 2H), 3.70(m, 2H), 4.5 (t, 1H), 5.0 (t, 1H), 6.10 (t, 1H), 6.7(t, 1H), 7.30 (d, 1H), 7.92 (d, 1H), 8.25(d, 1H).

13C NMR: 26.8 (CH3), 27.5 (CH3), 28.3 (CH), 29.5 (CH), 30.7 (CH2), 32.0 ((CH), 32.5 (CH), 48.2 ((CH2), 49.5 (CH2), 52.3 (CH2), 52.8 (CH2), 54.1 (CH2), 58.5 (CH), 114.1 (CH), 117.3 (ArCH), 150.5 (ArCH), 151.5 (ArCH), 164.1 (CO), 170. 07 (CO), 172.3 (CO), 177.6 (CO)

Non-standard abbreviations for medicinal chemistry:

Alloc	**allyloxycarbonyl**
Boc	**t-butyloxycarbonyl**
Dap	**diaminopropionic acid**
DCM	**dichloromethane**
DIC	**N,N'-diisopropylcarbodiimide**
DIEA	**diisopropylethylamine**
DMF	**N,N'-dimethylformamide**
EDT	**1,2-ethylenedithiol**
ESI-MS	**electrospray ionization - mass spectrometry**
EtOAc	**ethyl acetate**
Et_2O	**diethylether**
Fmoc	**(9H-fluoren-9-ylmethoxy)carbonyl**
HBTU	**2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate**
HOBt	**N-hydroxybenzotriazole**
HPLC	**high performance liquid chromatography**
OBt	**O-benzotriazolyl**
MeOH	**methanol**
NMR	**Nuclear magnetic resonance**
$Pd(TPP)_4$	**Palladium (0) tetrakistriphenylphoshine**
SPE	**solid-phase extraction**
SPPS	**solid-phase peptide synthesis**
TCFH	**tetramethylchloroformamidium hexafluorophosphate**
THF	**tetrahydrofuran**
TFA	**trifluoroacetic acid**
TMS	**tetramethylsilane**



Supplementary Figure 1: Cytokine and signalling molecule measurements from bronchoalveolar lavage fluid (BALF). The top 24 panels represent cytokines and signalling molecule concentrations from BALF that did not show significant changes in response to *A. alternata*. Trends are shown in the bottom four panels that did not have sufficient measurements to perform statistical evaluations and thus represent preliminary findings.

Cytokine/Signaling Molecule	Abbr.	LDD	LLOQ	Units
Chemokine (C-C motif) ligand 6	**CCL6**	0.0096	0.021	pg/mL
C-Reactive Protein	**CRP**	1.1	6.5	ng/mL
Eotaxin	**Eotaxin**	1.8	5.0	pg/mL
Granulocyte Chemotactic Protein 2	**GCP-2**	0.091	0.096	ng/mL
Granulocyte-Macrophage Colony-Stimulating Factor	**GM-CSF**	0.20	0.46	pg/mL
Interferon beta	**IFNβ**	4.8	11.0	pg/mL
Interferon gamma	**IFNγ**	0.057	0.090	pg/mL
Interleukin 10	**IL-10**	0.63	1.0	pg/mL
Interleukin 12p40	**IL-12p40**	0.085	0.23	ng/mL
Interleukin 12 p70	**IL-12p70**	2.2	2.5	pg/mL
Interleukin 17A	**IL-17A**	1.9	3.4	pg/mL
Interleukin 18	**IL-18**	17	36	pg/mL
Interleukin 1 alpha	**IL-1α**	6.3	11	pg/mL
Interleukin 1 beta	**IL-1β**	0.35	0.53	pg/mL
Interleukin 2	**IL-2**	0.93	1.6	pg/mL
Interleukin 23	**IL-23**	6.7	11	pg/mL
Interleukin 27	**IL-27**	2.1	3.5	pg/mL
Interleukin 28	**IL-28**	1.2	2.1	pg/mL
Interleukin 4	**IL-4**	0.14	0.30	pg/mL
Interleukin 5	**IL-5**	4.2	14	pg/mL
Interleukin 6	**IL-6**	0.71	2.3	pg/mL
Interleukin 9	**IL-9**	10	14	pg/mL
Insulin	**Insulin**	4.3	7.7	mUI/mL
Interferon Gamma Inducible Protein	**IP-10**	0.58	1.7	pg/mL
Growth-Regulated Protein alpha	**KC/GRO**	0.66	1.1	pg/mL
Monocyte Chemotactic Protein 1	**MCP-1**	5.4	6.9	pg/mL
Macrophage Colony-Stimulating Factor	**M-CSF**	0.0011	0.0021	ng/mL
Macrophage Derived Chemokine	**MDC**	2.1	10	pg/mL
Macrophage Inflammatory Protein 1 alpha	**MIP-1α**	72	86	pg/mL
Macrophage Inflammatory Protein 1 beta	**MIP-1β**	0.36	0.51	pg/mL
Macrophage Inflammatory Protein 1 gamma	**MIP-1γ**	0.0020	0.0081	ng/mL
Matrix Metalloproteinase 9	**MMP-9**	0.12	0.25	ng/mL
Neutrophil Gelatinase-associated Lipocalin	**NGAL**	0.041	0.11	ng/mL
Plasminogen Activator Inhibitor-1	**PAI-1**	0.0050	0.0066	ng/mL
Receptor for Advanced Glycation End product	**RAGE**	11	11	ng/mL
Stem Cell Factor	**SCF**	7.3	13	pg/mL
Tissue Inhibitor of Metalloproteinases 1	**TIMP-1**	0.069	0.073	ng/mL
Tumor Necrosis Factor alpha	**TNFα**	2.2	3.7	pg/mL
Thrombopoietin	**TPO**	0.0057	0.0071	ng/mL
Thymic Stromal Lymphopoietin	**TSLP**	0.65	1.3	pg/mL
Vascular Cellular Adhesion Protein 1	**VCAM-1**	0.037	0.052	ng/mL
Vascular Endothelial Growth Factor	**VEGF-A**	0.40	0.86	pg/mL

Table 1: Sensitivity of cytokines and signalling molecules in the Rodent MAP array (AmpersandBio, Lake Clear, NY). Abbr.: abbreviations used in text; LDD: least detectable dose; LLOQ: lower limit of quantification; Units: units of measurement.