Supporting Information

Design of HIV-1 Protease Inhibitors with C3-Substituted Hexahydrocyclopentafuranyl Urethane as P_2-Ligands: Synthesis, Biological Evaluation, and Protein-Ligand X-Ray Crystal Structure.

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HPLC Analytical Purity

Table 1. Analytical Purity of Inhibitors **21** to **31** determined by HPLC.

Inhibitor	Method A		Method B	
	R_t (min)	Purity (area %)	R_t (min)	Purity (area %)
21	12.87	95.1	15.3	95.8
22	11.54	99.1	15.03	99.3
23	9.17	95.1	12.25	95.2
24	8.82	97.2	12.96	96.4
25	13.64	97.9	16.31	97.9
26	10.45	99.9	14.54	99.9
27	8.25	98.1	11.75	98.3
28	12.92	96.8	15.97	99.9
29	14.80	95.2	17.30	95.0
30	15.04	97.7	17.55	95.7
31	8.97	97.0	12.8	99.2

HPLC conditions:

Method A = Agilent Eclipse XDB-C18 (4.6 x 150 mm, 5 µm); t = 0-1 min (MeCN:H_2O:TFA 20:80:0.05), t = 1-20 min (*gradient to* MeCN:H_2O:TFA 90:10:0.05), t = 20-25 min (MeCN:H_2O:TFA 90:10:0.05); Flow = 1.5 mL/min; single detection wavelength λ = 215 nm, T = 25 °C, injection volume 30 µL, 10 min equilibration time between run.

Method B = Agilent Eclipse XDB-C18 (4.6 x 150 mm, 5 µm); t = 0-1 min (MeOH:H_2O:TFA 25:75:0.05), t = 1-20 min (*gradient to* MeOH:H_2O:TFA 95:5:0.05), t = 20-25 min (MeOH:H_2O:TFA 95:5:0.05); Flow = 1.5 mL/min; single detection wavelength λ = 215 nm, T = 25 °C, injection volume 30 µL, 10 min equilibration time between run.

Mass Spectrometry Data

Table 2. High and Low Resolution Mass Spectrometry Data for Inhibitors **21** to **31**.

Inhibitor	Molecular Formula	HRMS Technique	Ion	Calculated	Found
21	$C_{29}H_{38}N_2O_8S$	ESI	$[M+Na]^+$	597.2247	597.2251
22	$C_{29}H_{40}N_2O_8S$	LRMS-ESI	$[M+Na]^+$	599.2	599.3
23	$C_{28}H_{39}N_3O_7S$	ESI	$[M+Na]^+$	584.2406	584.2410
24	$C_{29}H_{40}N_2O_8S$	ESI	$[M+Na]^+$	599.2403	599.2401
25	$C_{30}H_{42}N_2O_8S$	ESI	$[M+H]^+$	591.2740	591.2742
26	$C_{29}H_{40}N_2O_8S$	ESI	$[M+H]^+$	577.2584	577.2572
27	$C_{28}H_{39}N_3O_7S$	ESI	$[M+Na]^+$	584.2406	584.2398
28	$C_{30}H_{42}N_2O_8S$	ESI	$[M+Na]^+$	613.2560	613.2555
29	$C_{28}H_{39}N_3O_7S$	LRMS- ESI	$[M+H]^+$	575.3	575.1
30	$C_{29}H_{40}N_2O_8S$	LRMS- ESI	$[M+H]^+$	575.3	575.1
31	$C_{31}H_{45}N_3O_7S$	LRMS-ESI	$[M+H]^+$	604.8	604.3

Crystallographic Data Collection and Refinement Statistics

Table 3. Crystallographic Data Collection and Refinement Statistics

	PR-GRL-0489A
Space group	$P2_12_12$
Unit cell dimensions: (Å)	
A	58.39
B	86.55
C	45.85
Resolution range (Å)	50-1.45
Unique reflections	41,487
R_{merge} (%) overall (final shell)	7.2 (41.8)
I/σ(I) overall (final shell)	16.0 (2.0)
Completeness (%) overall (final shell)	98.4 (88.5)
Data range for refinement (Å)	10-1.45
R (%)	16.0
R_{free} (%)	21.9
No. of solvent atoms	142
RMS deviation from ideality	
Bonds (Å)	0.010
Angle distance (Å)	0.029
Average B-factors ($Å^2$)	
Main-chain atoms	17.4
Side-chain atoms	23.6
Inhibitor	14.1
Solvent	26.2