Flexible Cyclic Ethers/Polyethers as Novel P2-Ligands for HIV-1 Protease Inhibitors: Design, Synthesis, Biological Evaluation and Protein-ligand X-ray Studies

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HPLC (Table 1SI) and HRMS (Table 2SI) data of inhibitors **3a-m**. Crystallographic Data Collection and Refinement Statistics (Table 3SI).

Table 1. Purity of inhibitors **3a-m**

Inhibitor	Solvent system[a]	Retention Time (min)	Purity (%)	Column	Flow rate (mL/Min)
3a	A	12.2	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	10.3	99%	XDB-C18 5 µM 4.6 x 150mm	2.0
3b	A	12.3	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	10.4	99%	XDB-C18 5 µM 4.6 x 150mm	2.0
3c	A	12.7	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	10.6	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
3d	A	12.3	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	10.3	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
3e	A	13.7	99%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	13.5	99%	XDB-C18 5 µM 4.6 x 150mm	2.0
3f	A	13.6	97%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	13.1	96%	XDB-C18 5 µM 4.6 x 150mm	2.0
3g	A	16.9	99%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	15.4	99%	XDB-C18 5 µM 4.6 x 150mm	2.0
3h	A	11.8	97%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	9.8	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
3i	A	13.3	98%	XDB-C18 5 µM 4.6 x 150mm	2.0
	B	11.2	96%	XDB-C18 5 µM 4.6 x 150mm	2.0
3j	A	11.7	97%	XDB-C18 5 µM 4.6 x 150mm	2.0

	B	10.5	97%	XDB-C18 5 μM 4.6 x 150mm	2.0
3k	A	15.0	98%	XDB-C18 5 μM 4.6 x 150mm	2.0
	B	17.8	99%	XDB-C18 5 μM 4.6 x 150mm	2.0
3l	A	11.5	95%	XDB-C18 5 μM 4.6 x 150mm	2.0
	B	9.3	>99%	XDB-C18 5 μM 4.6 x 150mm	2.0
3m	A	8.1	>99%	XDB-C18 5 μM 4.6 x 150mm	2.0
	B	7.2	98%	XDB-C18 5 μM 4.6 x 150mm	2.0

[a]**A=** linear gradient from 20% acetonitrile, 80% water containing 0.05% trifluoroacetic acid to 80% acetonitrile, 20% water containing 0.05% trifluoroacetic acid in 20 min. **B=** linear gradient from 20% methanol, 80% water containing 0.05% trifluoroacetic acid to 100% MeOH in 20 min.

Table 2. HRMS for inhibitors **3a-m**

3a	HRMS (*m/z*) calcd for $C_{28}H_{40}N_2NaO_8S$ $[M+Na]^+$ 587.2403, found 587.2380
3b	HRMS (*m/z*) calcd for $C_{27}H_{38}N_2NaO_8S$ $[M+Na]^+$ 573.2247, found 573.2260
3c	HRMS (*m/z*) calcd for $C_{28}H_{40}N_2NaO_8S$ $[M+Na]^+$ 587.2403, found 587.2405
3d	HRMS (*m/z*) calcd for $C_{27}H_{38}N_2NaO_8S$ $[M+Na]^+$ 573.2247, found 573.2254
3e	HRMS (*m/z*) calcd for $C_{28}H_{40}N_2NaO_7S$ $[M+Na]^+$ 571.2454, found 571.2458
3f	HRMS (*m/z*) calcd for $C_{28}H_{40}N_2NaO_7S$ $[M+Na]^+$ 573.2454ound 571.2452
3g	HRMS (*m/z*) calcd for $C_{29}H_{42}N_2NaO_6S$ $[M+Na]^+$ 569.2661, found 569.2663
3h	HRMS (*m/z*) calcd for $C_{26}H_{36}N_2NaO_8S$ $[M+Na]^+$ 559.2090, found 559.2094
3i	HRMS (*m/z*) calcd for $C_{29}H_{42}N_2NaO_9S$ $[M+Na]^+$ 617.2509, found 617.2501
3j	HRMS (*m/z*) calcd for $C_{31}H_{46}N_2NaO_{10}S$ $[M+Na]^+$ 661.2771, found 661.2788
3k	HRMS (*m/z*) calcd for $C_{30}H_{44}N_2NaO_{10}S$ $[M+Na]^+$ 647.2615, found 647.2590
3l	HRMS (*m/z*) calcd for $C_{29}H_{42}N_2NaO_{10}S_2$ $[M+Na]^+$ 665.2179, found 665.2191
3m	HRMS (*m/z*) calcd for $C_{30}H_{46}N_3O_8S$ $[M+H]^+$ 608.3006, found 608.3009

Table 3. Crystallographic Data Collection and Refinement Statistics

Space group	$P2_12_12$
Unit cell dimensions: (Å)	
a	57.96
b	86.41
c	46.03
Resolution range (Å)	50-1.00
Unique reflections	110,362
R_{merge} (%) overall (final shell)	8.0 (41.1)
I/σ(I) overall (final shell)	16.5 (2.6)
Completeness (%) overall (final shell)	88.4 (52.6)
Data range for refinement (Å)	10-1.00
R (%)	14.9
R_{free} (%)	17.5
No. of solvent atoms (total occupancies)	173.2
RMS deviation from ideality	
Bonds (Å)	0.017
Angle distance (Å)	0.034
Average B-factors ($Å^2$)	
Main-chain atoms	11.4
Side-chain atoms	16.5
Inhibitor	12.9
Solvent	22.6
Residual density (max/min) ($eÅ^{-3}$)	0.40/-0.29