Supporting Information

Design and Synthesis of HIV-1 Protease Inhibitors Incorporating Oxazolidinones as P2/P2′ Ligands in Pseudosymmetric Dipeptide Isosteres

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Synthesis of Protease Inhibitors: General Procedures for the Coupling Reactions.

Coupling reactions of acid A1.[1] To an ice-cooled solution of the free amine (1.0 mmol) in a mixture of H_2O-CH_2Cl_2 (1:1) (10 mL) were added *N*-Ac-Val-OH (1.2 mmol) followed by HOBt (1.2 mmol) and solid EDCI (1.2 mmol) under dry N_2 atmosphere. The reaction mixture was stirred at 0–4 ºC until the reaction was complete (monitored by TLC). Small amount of CH_2Cl_2 was added and layers were separated. The organic extract was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using mixture of ethyl acetate/hexanes as eluent to provide the target compound as solid.

Coupling reaction of acid A2.[2] To an ice-cooled suspension of the acid **A2** (1.0 mmol) in THF (10 mL) was slowly added $SOCl_2$ (1.4 mmol). The reaction mixture was warmed to room temperature, stirred for 6 h and then dried under reduced pressure. Heptane (10 mL) was added to the residue, the slurry again dried under reduced pressure and the residual acyl chloride was dissolved in dry DMF (5 mL). To an ice-cooled solution of free amine (1.0 mmol) in EtOAc (5 mL) was added imidazole (3 mmol) followed by the addition of the above acyl chloride solution. The reaction mixture was stirred at 0 ºC for 1 h, warmed to room temperature and stirred overnight. The reaction was quenched with 0.5 N HCl, small amount of EtOAc was added and layers were separated. The organic extract was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using mixture of methanol/chloroform as eluent to provide the target compound as solid.

Coupling reactions of acid A3.[3] To an ice-cooled solution of the carboxylic acid (0.6 mmol) in a mixture of DMF-CH_2Cl_2 (1:1) (5 mL) were added EDCI (0.6 mmol) and HOBt (0.6 mmol) under dry N_2 atmosphere. After stirring 15 minutes, a solution of the deprotected amine (0.5 mmol) in DMF-CH_2Cl_2 mixture (1:1) (5 mL) was slowly added followed by the addition of DIPEA (1.2 mmol). The reaction mixture was warmed to room temperature and stirred until reaction was complete (monitored by TLC). Small amount of water and CH_2Cl_2 were added and layers were separated. The organic extract was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using mixture of ethyl acetate/hexanes as eluent to provide the target compound as solid.

Coupling reactions of acids A4 and A5.[2] $SOCl_2$ (0.8 mmol) was slowly added to the slurry of acid **A4** (0.6 mmol) in EtOAc (5 mL) followed by a drop of DMF. The resulting slurry was warmed to 50 ºC and stirred for 6 h providing a clear solution of the acyl chloride. The solution was cooled to room

temperature and used in the coupling step. The deprotected amine (o.6 mmol) was dissolved in EtOAc (15 mL) and a solution of $NaHCO_3$ (3.5 mmol) in water (5 mL) was added followed by the slow addition of the above acyl chloride solution. The reaction mixture was stirred at room temperature for 1h. The layers were separated, and the organic extract was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using mixture of ethyl acetate/hexanes as eluent to provide the target compound as solid.

Coupling reactions of phenyloxazolidinone-5-carboxylic acids.[4] Excess oxalyl chloride was added to solid phenyloxazolidinone-5-carboxylic acid (0.5 mmol) and the resulting mixture was stirred at room temperature overnight. Oxalyl chloride was removed by distillation under reduced pressure and residue dried under high vacuum for 30 minutes. A solution of the resulting acid chloride in dry THF (5 mL) was used in the coupling reaction. To an ice-cooled mixture of the Boc deprotected amine (0.5 mmol) in dry THF (5 mL) was added Et_3N (1.1 mmol) followed by the slow addition of the acid chloride solution. After 15 minutes the reaction mixture was warmed to room temperature and stirred until reaction was complete (monitored by TLC). Small amount of water and ethyl acetate were added and layers were separated. The organic extract was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered and evaporated. Flash chromatography on silica gel using mixture of ethyl acetate/hexanes (in some cases, methanol/chloroform mixture) as eluent, provided the target compound as solid.

References

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Purity of Target Compounds Determined by HPLC Using Two Different Systems

Compound	First System		Second System	
	R_t (min)	Purity (%)	R_t (min)	Purity (%)
12a	5.12	98.78	4.41	99.08
13a	5.17	97.92	4.45	98.94
13c	7.02	99.02	5.21	100.0
13d	5.60	100.0	4.79	100.0
13e	5.41	100.0	4.14	100.0
14a	6.10	95.03	4.56	96.05
15a	6.41	96.82	5.32	98.10
21a	8.13	100.0	6.79	100.0
22a	8.10	100.0	6.84	100.0
22d	9.0	95.59	7.66	97.21
23a	6.63	100.0	5.35	99.26
24a	6.38	100.0	4.86	100.0
25d	6.56	97.60	4.31	97.63
32	6.59	97.86	5.62	98.03
35	6.58	95.73	5.85	96.05
39	7.01	96.19	5.82	96.47
40	5.58	98.69	4.46	98.13

Analytical reversed-phase high performance liquid chromatography (HPLC) was performed on a Waters Separation Module 2695 system equipped with an auto sampler and a Waters 996 photodiode array detector. First system: column, Waters XTerra RP-C18 (3.5 μm, 4.6 mm × 150 mm); mobile phase A, 10 mM ammonium acetate in water; mobile phase B, acetonitrile. Using a flow rate of 0.8 mL/min, gradient elution was performed from 30% B to 90% B over 10 min. Second system: column, Zorbax 300SB-C8 (5 μm, 4.6 mm x 250 mm); mobile phase A, 0.1% trifluoroacetic acid in water; mobile phase B, 0.1% trifluoroacetic acid in acetonitrile. Gradient elution was performed from 40% B to 90% B over 10 min at a flow rate of 1 mL/min.