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Functional conservation of HIV-1 gag: implications for rational drug design

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Table S1, The summary of experimental gag inhibitors published to date.

	Inhibitor names	Target protein	Binding sites in target protein	Detected effect	HIV strain	PDB	Clinical trial	Year	Ref
Peptide inhibitors	Matrix1	Matrix	?	Inhibit assembly and maturation	B			1994	[1]
	Capsid1	Capsid	?	Inhibit assembly and maturation	B			1994	[1]
	CAI	Capsid	D166,Y169,K182,N183,E187,E212,M215	Inhibit capsid CTD interaction	Cell-free	2BUO		2005	[2]
	CAC1/CAC1M,H8	Capsid	I150,R154,Q155,R168,L173,Q179,N184,W185,M186,T189,L191,V192,C199,T201,I202,L203,K204,A205,L212,E213,M215,M216,A218,C219,Q220,V166,L173,E181,N194,D198,K200,G209,A210,T211,V222	Inhibit capsid assembly	B			2011	[3]
	NYAD series	Capsid	V165,F168,Y169,L172,R173,K182,N183,T186,L211,E212,M215[4]	Inhibit capsid CTD interaction	A,B,C,F,G,01A E	2L6E		2011	[5]
	P-1, P-2, P-3, P-4	Capsid	L151,R154, R184, M185, T188, K203(note that only the largest changes of NMR in the presence of peptides were notified)	Inhibit CA polymerization	B			2011	[6]
	CP4	Capsid	T148, I150, L151, D152, V181, A185, T186, Q192, A208, L211, E212, T216	Inhibit CA-hLysRS interaction	Cell-free			2011	[7]
	HAGPIA	CypA	H54,R55,G72,Q63,N102,H126,W121	Inhibit CA-CypA interaction	Cell-free	1AWR		1997	[8]
	Gagp6 (p6:346-354)	TSG101	T58,Y63,R64,Y68,N69,I70,T92,M95,K98,V141,F142,S143	Inhibit TSC101 UEV domain binding with gag	Cell-free	3OBU		2010	[9]
Small organic molecule	Compound14	Matrix	?	Inhibit PI(4,5)P ₂ -matrix interaction	A,B,C,D,E,F,G			2012	[10]
	Compound7	Matrix	L21,R22,W36,R76,T81,K98	Inhibit PI(4,5)P ₂ -matrix interaction	A,B,C,D,E,F,G			2013	[11]
	TD1,TD2,TD3	Matrix	L21,R22,K26,K27,H33,W36,E73,L75,R76,S77	Inhibit MA-RNA interaction	B			2013	[12]
	Bevirimat	CA-SP1	?	Inhibit gag maturation	B		Phase IIb[13]	2003	[14]
	Bevirimat analogs (C-28, C-30)	CA-SP1	H358,L363,A364 A366,Q369,A370 T371	Inhibit gag maturation	B			2011	[15]
	Vivecon (MPC-9055)	CA-SP1	?	Inhibit gag maturation	A,B,C,D,E,F,G, group O and N		Phase IIa (discontinued)	2009	[16]
	PA1050040	CA-SP1	?	Inhibit gag maturation	-		Phase I [17]	2009	[18]
	MPI-461359	CA-SP1	?	Inhibit gag maturation	-			2010	[19]
	PF-46396	CA-SP1	?	Inhibit gag maturation	B,C,E[20]			2012	[21]
	Compound(16)	CA-SP1	A366, M367, Q369, V370, N372, I376	Inhibit gag maturation	B			2012	[22]
	I-XW-053	Capsid	S33,P34,E35,V36,V165,D166,F168,Y169,K170,T171,L172,R173,A174,E175,Q176,S178,Q179,E180,N183,T186	Inhibit NTD interaction	A,B,C,D,E,F,G, group O			2012	[23]
	PF-3450074	Capsid	N57,M66,Q67,K70,I73,T107	Inhibit capsid NTD interaction	A,B,C,D,E	2XDE		2010	[24]
	BM4	Capsid	W23,V27A/I,K30R,F32,S33G,T58I,H62	Inhibit capsid NTD interaction	B	4E92		2012	[25]
	BD3	Capsid	W23,V24,V27A/I,F32,V36T,T58I,V59,G61E,H62	Inhibit capsid NTD interaction	B	4E91		2012	[25]
	Inhibitor4	Capsid	W80,M96,E98,W117,H120,P122,P123,I124,I129,R132	Inhibit capsid NTD interaction	B	4E91		2013	[26]
	BMMP	Capsid	?	Inhibit gag-gag interaction	B			2011	[27]
	Compound3,4,5	Capsid	?	Inhibit capsid NTD interaction	Cell-free			2013	[28]
	Compound27	Capsid	?	Inhibit capsid NTD interaction	Cell-free			2013	[29]
	CAP-1	Capsid	W23,V27,E28,A31,F32,V59,H62,A64,A65,I141	Inhibit capsid CTD interaction	B	2JPR		2007	[30]
	CAI-compound series	Capsid	V165,Y169,N183,L211,M215	Inhibit capsid CTD interaction	A,B,C,D,F,G, group O			2011	[31]
	Benzodiazepine series 33	Capsid	V27,A31,F32,V59,H62,A65,Y146	Inhibit capsid NTD interaction	Cell-free			2012	[32]
	Inhibitor3	Capsid	W23,V24,V27,E28,K30,A31,F32,S33,P34,V36,I37,F40,K56,V59,G60,G61,H62,A65,M66,K69,I134,K138,N139,I141,V142	Inhibit capsid NTD interaction	B	4INB		2013	[33]
	CAA	NC	V13,K14,F16,I24,A25,K26,R32,G35,W37,K38,Q45,M46,K47	Inhibit NC-RNA/DNA interaction	B	2M3Z		2013	[34]
	WDO-217	NC	?	Zinc ejection	B,HIV-2,SIV			2012	[35]

Compound6,Compound8	NC	F16,R32,K34,W37,Q45,M46,K47	Inhibit NC(11-55)-RNA interaction	B			2012	[36]
Compound45	NC	C49,T50,E51	Inhibit NC-oligonucleotide	B			1999	[37]
SL3ligands	NC	zinc fingers(15-28,36-49)	Inhibit NC-RNA/DNA interaction	B			2012	[38]
mONs	NC	zinc fingers	Inhibit NC-DNA interaction	Cell-free			2011	[39]
SAMT	NC	zinc fingers	Inhibit NC-RNA/DNA	B			2010	[40]
NV038	NC	zinc fingers	Zinc ejection	B,HIV-2,SIV			2010	[41]
CO7	NC	zinc fingers	Inhibit NC-DNA interaction	Cell-free			2009	[42]
Thioesters	NC	zinc fingers	Inhibit NC-RNA interaction	B			2004	[43]
YS1332D	NC	zinc fingers	Inhibit NC-RNA interaction	B			2003	[44]
DIBA	NC	zinc fingers	Zinc ejection	B,HIV-2,SIV			2001	[45]
PATeS	NC	zinc fingers	Target zinc fingers	B			2001	[44]
NSC 624151	NC	zinc fingers	Target zinc fingers	A,B,C,D,F,HIV-2,SIV			1996	[46]
SRR-SB3	NC	zinc fingers	Target zinc fingers	B,HIV-2,SIV			1996	[47]
NOBA	NC	zinc fingers	Target zinc fingers	Cell-free			1998	[48]
Enantiomers	NC	zinc fingers	Inhibit NC-RNA interaction	Cell-free			2003	[49]
2-Mercaptobenzamide Thioesters	NC	zinc fingers	Target zinc fingers	Cell-free			2005	[50]
thiolcarbamates (TICAs),	NC	zinc fingers	Target zinc fingers	B			2002	[51]
Azodicarbonamide (ADA)	NC	zinc fingers	Target zinc fingers	B,HIV-2		PhaseI/II (discontinued[52])	2000	[53]

Notations: (a) peptide inhibitors – amino acid sequences which were designed to inhibit HIV replication, (b) small organic molecule – low molecular weight organic compounds that were designed to bind gag proteins. Sequences of peptide inhibitors are:

- (1) Matrix1[matrix sites: 47-59]: NPGLLTSEGCQRQ,
- (2) Capsid1[capsid sites:124-133]: IPVGEIYKRW,
- (3) CAI: ITFEDLLDYGPK(Bio¹)CL,
- (4) CAC1M [capsid sites:175-193] SESAASSVKAWMTETLLVANTSS,
H8[capsid sites:158-176] KEPFRDYYVDRFYKTLRAEQ,
- (5) NYAD-201[capsid sites:178-192] AQEVKXWMTXTLLVA
(X= (S)-alpha- (2'-pentenyl)alanine),
- (6) P-1[capsid sites: 181-192] VKNWMTETLLRQ,
- (7) CP4: cyclo(D-Ala-Ile-Fpa-Arg-Tyr-Trp-D-Ala-D-Ala-Glu)-Lys
- (8) HAGPIA [capsid sites:87-92] HAGPIA
- (9) Gagp6[p6 sites:5-13]: PEPTAPPEE

Table S2. The summary of natural variants at drug binding sites of known gag inhibitors.

Inhibitors	Ref	Target	HIV-1 subtypes							
			B(n=4131)	A1(n=1648)	C(n=2780)	D(n=443)	F1(n=35)	G(n=49)	01_AE(n=1714)	02_AG(n=62)
CAI	[2]	Capsid		F169Y1.2,G183A1.2,G183N20.9,G183S2.4,E187D11.7	D187E14.1	N183A4.8,N183G7.0,N183T7.0,E187K2.7	G183N30.3,G183S3.0,D187E8.8,	G183N37.5,G183H2.1,G183S12.5,D187E10.4	Y169F1.3,N183H2.9	N183G4.9,N183H1.6,E187D14.8

CAC1/CA C1M,H8	[3]	Capsid	R154K29.1, K199R6.0,T 216I2.4,T21 6S1.1,A194S 12.3,T200S2 .5,T210S2.7	K154R3.2,V1 91I17.1,K199 R1.5,R203K8 .1,A204G6.0, S200A3.7,S2 00G1.3,S200 T10.1,T210S 18.7	K154R26.3,V1 91I10.0,K199R 1.2,R203K16.2, A204G12.9,T2 00N4.4,T200I5. 0,T200S2.1,T2 00V2.4,T210S3 0.9,L211I1.4	R154K9.1,Q1 79T3.4,V191I 4.3,I201L3.2, A204G4.1,T2 16S3.4,T200I 4.1,T210S6.6	R154K33.3, V191I8.8,K1 99R2.9,K203 R5.9,A204G 5.9,L205M2. 9,Q219R2.9, G220E2.9,A 194S8.8,T20 0I2.9,A209G 2.9,T210S18. 2,L211I2.9	R154K46.8, Q179T2.1, V191I4.3,R 203K31.9, A204G4.2, A204S2.1,T 200N2.1,T2 00I2.1,T21 0S20.8	R154K12.7 ,V191I3.0, K199R1.2, K203R5.7, A204S2.7, S200A5.8, S200T3.4, T210S5.3	R154K27.9,V19 1I3.3,V191T1.6, K199R3.3,R203 K33.3,A204G3. 3,L205M3.3,T2 16S1.6,A194S3. 3,S200A13.1,S2 00H1.6,S200I1. 6,S200T14.8,T2 10S5.0
NYAD series	[5]	Capsid		F169Y1.2,G1 83A1.2,G183 N20.9,G183S 2.4	L211I1.4	N183A4.8,N1 83G7.0,N183 T7.0	G183N30.3, G183S3.0,L2 1I2.9	G183N37.5 ,G183H2.1, G183S12.5	Y169F1.3, N183H2.9	N183G4.9,N183 H1.6
P-1, P-2, P- 3, P-4	[6]	Capsid	R154K29.1	K154R3.2,R2 03K8.1	K154R26.3,R2 03K16.2	R154K9.1,	R154K33.3,T 188S5.9,K20 3R5.9	R154K46.8, T188S2.1,R 203K31.9	R154K12.7 ,K203R5.7	R154K27.9,R20 3K33.3
Bevirimat analogs (C-28, C-30)	[15]	Capsid	Q6H1.9,V7A 20.8,V7I1.7, V7M6.2,V7 T1.1,T8S1.3	Q6H1.8,V7A 16.5,V7I1.9, V7L1.4,Q8N 1.3,Q8H3.1	Q6R1.0,Q6L1. 7,A7T15.5,A7 V22.7,N8Q1.1, N8G14.1,N8S7 .1,N8T1.5	A1T2.3,A7V 18.8,T8N15.4 ,T8S8.8	Q6K5.9,A7I3 .0,A7L3.0,A 7T6.1,A7V4 2.4,T8A3.3,T 8N3.3,T8Q1 6.7,T8S6.7	Q6N2.1,Q6 H10.4,Q6K 2.1,A7I2.1, A7M2.1,A7 V10.4,S8N 2.1,S8T16. 7	Q6N7.5,Q6 H30.3,Q6K 1.3,Q6S2.7 ,A7T4.0,A 7V28.1	V7A31.1,V7T1. 6,Q8H16.4
CP4	[7]	Capsid	T148A2.1,T 148I2.5,T14 8S3.6,T148V 22.3,A208G 15.6,T216I2. 4,T216S1.1	G208A1.6	V148T1.8,G20 8A5.5,L211I1.4	A208Q2.0,A2 08G38.9,T21 6S3.4	V148T2.9,G 208A5.9,L21 1I2.9	V148T4.2, D152G2.1	V148I2.5, V148T10.2	V148T18.0,G20 8A1.6,T216S1.6
Compound 7	[11]	Matrix	K76R42.8,T 81A9.1,T81 L1.0,K98R1. 0	R76K36.7,T8 1A4.5	R22K5.0,R76I3 .8,R76K41.5,R 76V1.3	K76R7.2,K98 Q3.4	R22K8.8,W3 6R2.9,R76K 38.2,T81A3. 0,T81L6.1	L21M2.1,K 76R39.6,T8 1A12.5,T81 P2.1,K98Q 6.4,K98T4. 3	K76R17.4, T81A9.2,T 81L4.1,K9 8Q1.6	K76R18.0,T81A 3.3
TD1,TD2, TD3	[12]	Matrix	K26R8.2,K2 6N2.3,K26S 2.1,L75I4.9, L75F7.5,K76 R42.8	K26R6.6,K26 N1.8,K26S1. 1,L75I12.8,L 75F4.5,L75V 1.8,R76K36.7	R22K5.0,K26R 1.7,E73K5.1,L7 5I2.8,L75F8.5, R76I3.8,R76K4 1.5,R76V1.3	N26R6.7,N26 G3.0,N26H12 .0,N26K24.2, N26S24.2,K2 7Q2.0,E73K4 .8,I75L24.9,I 75M2.0,I75V 2.0,K76R7.2	R22K8.8,K2 6R2.9,W36R 2.9,L75I5.9, L75F2.9,R76 K38.2	L21M2.1,K 26R39.6,K2 7N4.2,E73 Q4.2,L75I4 2.6,K76R39 .6	K26R7.7,L 75I6.1,L75 F1.6,L75Y 1.2,L75V4. 2,K76R17. 4	K26R1.6,K26N 3.3,K26S3.3,L7 5I4.9,L75V1.6, K76R18.0
PF- 3450074	[24]	Capsid	T107S2.8			T107S2.9	T107A4.2,T1 07S6.2	T107S1.2		

I-XW-053	[23]	Capsid	K170R4.5,T171V2.6,S178T10.4,E180D36.1	S33N4.7,F169Y1.2,T171A4.7,T171C9.8,T171I1.2,T171V7.7,T178S17.4,E180D25.5,E180P1.1,G183A1.2,G183N20.9,G183S2.4	S33N15.9,V36I11.4,K170R3.2,T171A1.2,T171V4.0,T178S15.1,D180E38.4	S33N7.7,T171V8.8,S178T5.0,Q179T3.4,D180N2.7,D180E11.1,N183A4.8,N183G7.0,N183T7.0	S33N2.9,V36I2.9,K170R9.1,T171A9.1,T171C3.0,T171V6.1,T178S26.5,E180D11.8,G183N30.3,G183S3.0	S33N6.2,T171A4.2,T171C2.1,T171V2.1,T178S10.4,Q179T2.1,E180D29.2,G183N37.5,G183H2.1,G183S12.5	N33S2.7,Y169F1.3,T178S16.1,E180D1.6,N183H2.9	E35K1.6,T171A1.6,T171V1.6,T178S3.3,E180D13.1,N183G4.9,N183H1.6
BM4	[25]	Capsid	V27I25.1,	I27V2.3,K30R13.3,S33N4.7,I58V6.4	I27V13.9,S33N15.9	I27V17.0,S33N7.7	W23M2.9,I27V33.3,K30R2.9,S33N2.9	V27I16.7,K30N2.1,S33N6.2	V27I7.0,N33S2.7	I27V3.3,K30R1.6,I58V1.6
BD3	[25]	Capsid	V27I25.1,	I27V2.3,I58V6.4,V59I1.9	I27V13.9,V36I11.4,V59I3.0	I27V17.0	W23M2.9,I27V33.3,V36I2.9	V27I16.7	V27I7.0,G61D2.0	I27V3.3,I58V1.6
Inhibitor4	[26]	Capsid	M96I8.6,M96L3.4,M96V3.5,E98D11.0,N120H17.9,N120S23.2,P123A1.8,I124V3.6,R132K5.8	M96I8.9,M96L12.2,S120N7.5,S120G16.0,I124F1.8,I124V2.4,R132G2.0,R132K5.5	M96I20.2,M96L5.1,M96S1.1,E98D6.0,S120A3.1,S120N16.6,S120G19.4,S120H1.2,P123A2.2,I124V35.7	M96I15.2,E98D7.0,S120A2.5,S120N38.0,S120G1.1,S120H2.3,I124V6.3,R132K7.3	M96I32.4,M96L2.9,E98D2.9,S120A2.9,S120G14.7,P122Q2.9,V124I2.9,I129M2.9,R132G2.9,R132K2.9	I96M2.1,E98D20.8,E98G2.1,W117R2.1,S120N10.6,S120G6.4,P123A2.1,I124V10.4	M96I13.5,M96L8.5,E98D2.1,N120G10.8,N120S35.8,P123A8.4,P123S4.1,I124V1.8	M96I1.6,M96L1.6,E98D1.6,S120N1.6,S120G4.9,I124T1.6,I124V14.8,I129M1.6,
CAP-1	[30]	Capsid	V27I25.1,	I27V2.3,A31G24.5,V59I1.9,I141L5.6	I27V13.9,A31N5.6,A31G16.2,V59I3.0	I27V17.0,E28K2.9,A31G6.3	W23M2.9,I27V33.3,E28G2.9,A31G2.9	V27I16.7,A31G2.1,A31S2.1	V27I7.0,G31S1.1,A64G1.5	I27V3.3,A31N1.6,A31G11.5
CAI-compound series	[31]	Capsid		F169Y1.2,G183A1.2,G183N20.9,G183S2.4	L211I1.4	N183A4.8,N183G7.0,N183T7.0	G183N30.3,G183S3.0,L211I2.9	G183N37.5,G183H2.1,G183S12.5	Y169F1.3,N183H2.9	N183G4.9,N183H1.6
Benzodiazepine series 33	[32]	Capsid	V27I25.1	I27V2.3,A31G24.5,V59I1.9,S146N1.9	I27V13.9,A31N5.6,A31G16.2,V59I3.0	I27V17.0,A31G6.3	I27V33.3,A31G2.9	V27I16.7,A31G2.1,A31S2.1,S146C4.2	V27I7.0,G31S1.1,S146R1.9,S146K1.6	I27V3.3,A31N1.6,A31G11.5
Inhibitor3	[33]	Capsid		K30R13.3,A31G24.5,S33N4.7,V59I1.9,N139H5.6,I141L5.6	A31N5.6,A31G16.2,S33N15.9,V36I11.4,V59I3.0	E28K2.9,A31G6.3,S33N7.7,I134V1.4	W23M2.9,E28G2.9,K30R2.9,A31G2.9,S33N2.9,V36I2.9	K30N2.1,A31G2.1,A31S2.1,S33N6.2,N139H2.1	G31S1.1,N33S2.7,G61D2.0,N139H1.2	K30R1.6,A31N1.6,A31G11.5
CAA	[34]	NC	V13I15.3,I24L11.6,I24T1.5,I24V1.8,K26R48.5	R26K6.0	V13I33.7,F16Y1.7,I24L22.7,R26K25.0	I13L13.2,I13V9.1,I24L14.5,I24T13.3,K26R31.7	V13I35.3,I24L11.8,I24V2.9,K26R42.4	K14R2.1,F16Y2.1,L24I2.1,R26K2.1,Q45L2.1,M46I2.1,K47R18.8	R26K3.6	I13L1.6,I13V1.6,L24V1.6,R26K1.6,Q45L1.6
Compound 6,Compound 8	[36]	NC	K34R17.9	F16Y1.7,K34R11.9	R34K40.1	K34R2.9	F16Y2.1,K34R6.2,Q45L2.1,M46I2.1,K47R18.8	K34R2.9	R34K29.3,Q45L1.6	

Compound 45	[37]	NC	T50N4.7,T50I2.2,T50S4.0,E51G1.6	T50D1.3,T50E1.4,E51D1.2	T50N3.1		T50N2.9,T50E2.9,T50P2.9	T50M2.1,T50S2.1,E51D2.1,E51Q2.1	T50N4.6	T50N3.3,E51V1.6
Bevirimat	[14]	CA-p2	Q6H1.9,V7A20.8,V7I1.7,V7M6.2,V7T1.1,N9Q1.6,N9G8.4,N9S6.7,N9T2.6,I13M2.3,I13V14.1	Q6H1.8,V7A16.5,V7I1.9,V7L1.4,H9N11.5,H9Q29.5,H9G1.1,I13V7.8	Q6R1.0,Q6L1.7,A7T15.5,A7V22.7,N9Q4.9,N9H6.0,N9S20.7,M13L12.2	A7V18.8,N9Q3.4,N9G13.6,N9K12.7,N9S14.7,N9T2.3,N9V4.8,I13A1.6,I13L6.3,I13M3.6,I13V18.8	Q6K5.9,A7I3.0,A7L3.0,A7T6.1,A7V4.2.4,N9G3.0,N9H12.1,N9K6.1,N9S21.2,V13I44.1,V13L2.9	Q6N2.1,Q6H10.4,Q6K2.1,A7I2.1,A7M2.1,A7V10.4,G9N4.3,G9D2.1,G9S2.1,G9T2.1,I13A2.2,I13M2.2,I13V17.8	Q6N7.5,Q6H30.3,Q6K1.3,Q6S2.7,A7T4.0,A7V28.1,H9N5.6,H9Q35.9,H9G2.6,H9P1.3,H9S1.5,I13M1.3,I13V15.4	V7A31.1,V7T1.6,Q9N3.3,I13V34.4

Inhibitor names, references and targets are indicated in the first three columns. The proportions of natural variations for subtype B, A1, C, D, F1, G, 01AE and 02AG were summarized from the 4th to 11th columns. Natural polymorphisms for each inhibitor are summarized for each subtype and they are annotated in the form of “wildtype+position+mutation+proportion”. For instance, “R154K29.1” indicates the most prevalent amino acid R at position 154 switches to amino acid K, with the proportion 29.1% in sequence dataset. Note that the most prevalent amino acid is defined as wildtype in our analysis.

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