

MOL # 117663

Molecular Pharmacology

Modulators of CXCR4 and CXCR7/ACKR3 function

Ilze Adlere, Birgit Caspar, Marta Arimont, Sebastian Dekkers, Kirsten Visser, Jeffrey Stuijt, Chris de Graaf, Michael Stocks, Barrie Kellam, Stephen Briddon, Maikel Wijtmans, Iwan de Esch, Stephen Hill, Rob Leurs

Supplemental Table 1. Chemokines and peptides binding to CXCR4 and ACKR3

Group	Name	Type	Length ¹	CXCR4 pharmacology	CXCR4 reference(s)	Notes	ACKR3 pharmacology	ACKR3 reference(s)/notes
Chemokines								
	CXCL12 (SDF-1)	Endogenous chemokine	93	Full agonist, pKd 7.7-8.4*	Hesselgesser et al (9551924)		Agonist, pKd 9.39	Balabanian et al 2005 (16107333)
	CXCL11 (ITAC)	Endogenous chemokine	94				Agonist, pKd 9.39	Burns et al 2006 (16940167)
	CXCL10 (IP10)	Endogenous chemokine	98	No binding, pIC50 <6	Szpakowska et al 2017 (29272550)		No binding, pIC50 <6	Szpakowska et al 2017 (29272550)
	vCCL2 (vMIP-II)	Viral chemokine mimic	94	Antagonist, pIC50 8.2	Kledal et al (9287217)		Partial agonist, pIC50 7.3	Szpakowska et al 2016(27238288)
Chemokine mutants and/or truncations								
	CXCL12 1-8	Chemokine N-terminal mimic	8	Agonist, fold pEC50 -3.9	Loetscher et al 1998 (9712844)	Peptide ligands, lead discovery		Szpakowska et al 2017 (29272550)/ evaluate interaction mechanism to CXCR3,
	CXCL12 1-9	Chemokine N-terminal mimic	9	Full agonist, fold pEC50 -2.3	Loetscher et al 1998 (9712844)	Peptide ligands, lead discovery	Agonist, fold pEC50 -3.3	CXCR4, and ACKR3
	CXCL12 1-9[P2G]	Chemokine mutant N-terminal	9	Antagonist, fold pKd -2.4	Loetscher et al 1998 (9712844)	Peptide ligands, lead discovery		Szpakowska et al 2017 (29272550)/ evaluate interaction mechanism to CXCR3,
	CXCL12 1-17	Chemokine truncation	17	Full agonist, fold pKd -2	Loetscher et al 1998 (9712844)	Peptide ligands, lead discovery	Agonist, fold pEC50 -2.7	CXCR4, and ACKR3
						Evaluation of structural requirements for CXCL12 activities		
	CXCL12[K1R]	Chemokine mutant	93	Antagonist, fold pKd -0.56	Crump et al (9384579)	Evaluation of structural requirements for CXCL12 activities		
	CXCL12[P2G]	Chemokine mutant	93	Antagonist, fold pKd -0.4	Crump et al (9384579)	Evaluation of structural requirements for CXCL12 activities		
	CXCL12 2-67	Chemokine truncation	65	Antagonist, fold pKd -0.75	Crump et al (9384579)	Evaluation of structural requirements for CXCL12 activities		
	CXCL12 (3-9)-67	Chemokine truncations	58-64	Antagonists, fold pKd >(-1)	Crump et al (9384579)	Evaluation of structural requirements for CXCL12 activities		
	CXCL12 (XXXX)-17	Chemokine mutant truncations	17	Antagonists	Ehrlich et al 2013 (23973527)	CXCL12 SAR evaluation in CXCR4 and ACKR3	Agonists	Ehrlich et al 2013 (23973527)
	CXCL11 1-9	Chemokine truncations	9			Evaluate interaction mechanism to CXCR3, CXCR4, and ACKR3	Agonist, fold pEC50 -2.9	Szpakowska et al 2017 (29272550)
	CXCL11 1-17	Chemokine truncations	17			Evaluate interaction mechanism to CXCR3, CXCR4, and ACKR3	Agonist, fold pEC50 -2.25	Szpakowska et al 2017 (29272550)
	N15P (vMIP-II 1-15)	Chemokine truncation	15	Antagonist	Mo et al 2015 (25676435)	Antiinflammatory properties	vMIP-II 1-11, agonist, fold pEC50 -2.5	Szpakowska et al 2017 (29272550)
DV1 series (vMIP-II 1-21)		Chemokine truncations/mutations	15-21/1-21	Antagonists, pIC50 <5-7.7	Zhou et al 2002 (11880384)	Anti HIV-1 activity		

	DV1-K-(DV3)	Chemokine truncation	32/32	Antagonist, pIC50 8.4	Xu et al 2013 (23688427)	Anti HIV-1 activity, bivalent
Proteins and peptides						
β-defensins 2 and 3	Endogenous peptides	67	Antagonists	Quinones-Mateu et al (14571200); Feng et al (16818731)		
EPI-X4	Endogenous peptide	16	Antagonist, pKi 5.5	Zirafi et al 2015 (25921529)		
Ubiquitin	Endogenous protein	76	Agonist, pEC50 7.12	Saini et al 2010 (20228059)	No binding	Saini et al 2011(21757744)
Adrenomedullin	Endogenous peptide	52			Agonist, pKd 6.7	Klein et al 2014 (25203207)
T22	Synthetic peptide	18	Antagonist, pIC50 7.3	Murakami et al 1997 (9334379)	Anti X4-HIV-1 entry	
T22 series	Synthetic peptide	17-19	Paper not available	Tamamura et al 1998 (9730240)	SAR to build strategy for DD	
TW70	Synthetic peptide	14/1	Antagonist, pEC50 ³ 7.5	Tamamura et al 1998 (9597190)	Anti X4-HIV-1 entry	
T134	Synthetic peptide	14/1	Antagonist, pIC50 8.38	Tamamura et al 1998 (9547946)	Anti X4-HIV-1 entry (higher potency)	
T140	Synthetic peptide	14/2	Antagonist/Inverse agonist ⁴ , pIC50 8.6	Tamamura et al 1998 (9918823)/Zhang et al 2002 (11923301)	Anti X4-HIV-1 entry (higher potency)	
TZ14004 series ⁵	Synthetic peptides	14/2	Antagonists, pEC50 ³ 7.1-9.4	Tamamura et al 2001 (11459656)	Improved stability in serum	TC14012, agonist, pEC50 6.5
Ac-TE14011 series	Synthetic peptides	14/2	Antagonists, pEC50 ³ 4.8-7.8	Tamamura et al 2003 (14649896)	Improved biostability in liver	Gravel et al 2010 (20956518)
4F-benzoyl-TE14011-Me (TF14013-Me) series	Synthetic peptides	14/2	Antagonists pEC50 ³ 5.9-9.6	Tamamura et al 2003 (14649897)	Improved biostability in liver	
4F-benzoyl-TN14003/TE14011 N-terminal series	Synthetic peptides	3-4/1	Antagonists, pEC50 ³ <4-5.8	Tamamura et al 2006 (16763678)	Included tumor metastasis/progression inhibitory activity	
POL3026 series (CVX15)	Synthetic peptides	16/2	Antagonists, pIC50 7-8.9	DeMarco et al 2006 (17010618)	Improved ADME	
Ac-TZ14011 fluorescent series	Synthetic peptides	14/2	Antagonists, 6.6-7.9	Oishi et al 2008 (18412193)	Fluorescent probes	No binding
4F-benzoyl-TZ14011 series	Synthetic peptides	28/4 + linker	Antagonists, pIC50 7.6 - 7.9	Tanaka et al 2017 (28078743)	Cover CXCR4 dimer (inhibit chemotaxis)	
FC131 series	Synthetic peptides	5/2-3	Antagonists, pEC50 ³ <4 - 7.4	Fuji et al 2003 (12876735)	Lower molecular weight	Agonists, pEC50 5.7-7.5
FC131 series 2	Synthetic peptides	5/2	Antagonists, pEC50 ³ <4 - 6	Tamamura et al 2005 (15658852)	Reduced peptide character	Oishi et al 2015 (26042340)
FC131 series 3	Synthetic peptides	5/2-3	Antagonists, pIC50 <6 - 7.9	Tamamura et al 2005 (16327900)	Restrained conformation	
Bivalent FC131 series	Synthetic peptides	10/6 + linker	Antagonists, pKi/pIC50 7-8	Tanaka et al 2010 (20973474)	Molecular probes for oligomerization; antimetastatic effect	
ALX40-4C	Synthetic peptide	9/9	Antagonist, pIC50 8.5	O'Brien et al 1996 (8627756)	Anti HIV-1 activity	

CXCR4-ED-derived peptides	Synthetic peptides	22-32	HIV-entry inhibitors, pEC50 ³ <5-6	Hashimoto et al 2013 (24039179)	CXCR4 EC domain mimetics, anti HIV-1 activity
LY2510924	Synthetic peptide	8/5	Antagonist, pKi 10.1	Peng et al 2015 (25504752)	Metastasis-preventing candidates, mot polyphemusin-II derived
Peptides R, S, T, and I	Synthetic peptides	5-7	Antagonists	Portella et al 2013 (24058588)	No binding
Macrocyclic peptide-peptoid series	Synthetic peptides	6/2-5			Agonists, pKi 5.1-8.3
ECL2-X4	Synthetic peptide	27	Antagonist, pIC50 4.7	Chevigné et al 2014 (24480462)	CXCR4 ECL mimetics
T140-CXCL12 series	Chemokine/peptides chimeras	20-30/2	(Partial) Agonists, pIC50 6.7-8.9	Lefrançois et al 2011 (21841963); Mona et al 2016 (27434274)	Antagonist, pIC50 4
				Develop high affinity agonists	Chevigné et al 2014 (24480462)

Chimeras IT1t-CXCL12 Chemokine/small molecule chimera 10 Antagonists, pIC50 6.5-6.0 Mona et al 2016 (27752700)

*incl. α, β, [125I]

- 1) Natural AA/non-natural AA (including D-isomers)
- 2) Reconsidered
- 3) Antagonist EC50 > Anti HIV activity
- 4) Inverse agonist for constitutively active CXCR4 mutant N119^{3,35}S/A
- 5) Also available a series conjugated to AZT (11504655)