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Supporting Information

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Supporting Information

for

Identification of Protein Fold Topology Shared between Different Folds Inhibited by Natural Products

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Table S-1 Result of data-mining for natural product inhibitors of the Zincin-like fold

NP/*derivative*[a]	NP type/ mode	Inhibits	Potency	PDB	Fold	Doesn't Inhibit	Fold
actinonin		peptide deformylase[41, 42]	K_i = 0.28 nM[41] IC_{50} = 0.8 nM[41] K_i = 0.3 nM[42] K_i = 0.012 -0.025 µM[43]	1q1y[44] 1ix1[44] 1g2a[45] 1lqw[46] 1lqy[46] 1lru[46] 1lry[46]	Peptide deformylase	ACE[45] *(IC_{50} > 100 µM)*	Zincin-like
						aminopeptidase P (3.4.11.9)[101]	Creatinase/ aminopeptidase
		meprin A	Kis = 0.135 µM[94] Kii = 1.57 µM[94]	no pdb	?Zincin-like *(homology with astacin)*	glutamyl aminopeptidase (3.4.11.7)[96]	?*homology with TET*
		astacin	Kis = 130 µM[94] Kii = 9500 µM[94]		Zincin-like	aminopeptidase W (3.4.11.16)[96]	?*no pdb no sequence*
		alanyl aminopeptidase (N/M) (3.4.11.2)[87-91]	IC_{50} = 25 nM[95] IC_{50} = 2 µM[96] IC_{50} = 0.4 µg/mL[97]	no pdb	?Zincin-like *(homology with LTA4H)*	aminopeptidase A (?EC) [97]*IC_{50}>100µg/mL*	?
		human neutrophil collagenase (MMP-8)	K_i = 1.4 mM[98] IC_{50} = 0.3 µM[99]		Zincin-like	arginine aminopeptidase (B) (3.4.11.6)[97] *IC_{50} > 100 µg/mL*	?Zincin-like *(homology with LTA4H)*
		collagenase (MMP-1)	IC_{50} = 0.19 µM[99] IC_{50} = 1 µM[45]		Zincin-like		

			IC_{50} = 0.33 µM[99]				
		gelatinase B (MMP-9)			Zincin-like		
			IC_{50} = 1.7 µM[99]				
		stromelysin (MMP-3)	IC_{50} = 6 µM[45]		Zincin-like		
			IC_{50} = 3 µM[45]				
		gelatinase A (MMP-2)			Zincin-like		
			IC_{50} = 7 µM[45]				
		neprilysin			Zincin-like		
			strongly [92]				
		cytosol alanyl aminopeptidase (3.4.11.14)[92, 93]			Phosphorylase / hydrolase like		
			IC_{50} = 1 µg/mL [97]				
		leucine aminopeptidase (3.4.11.1)[51]	IC_{50} = 0.40 µg/mL [100]	no pdb	Phosphorylase / hydrolase like		
		glutamyl aminopeptidase (3.4.11.7)			?*homology with TET*		
aclacinomycin A	anthracycyline	bacterial collogenase[102] (3.4.24.3)	IC_{50} = 9.9 µM[48]		CUB-like	elastase[48]	*?(depends on type)*
	independent of chelate effect ?[102]					trypsin [48]	Trypsin-like serine proteases
		aclacinomycin methylesterase *(RdmC) (biosynthetic enzyme)*[47]		1q0z[47]	Alpha/beta hydrolase		
adriamycin (doxorubicin)	anthracycyline	gelatinase A (MMP-2)	K_i = 49 µM[103]		Zincin-like	elastase[48]	*?(depends on type)*
	chelation	prolidase (3.4.13.9)	IC_{50} = 10 µM[104]		Creatinase/ aminopeptidase	trypsin[48]	Trypsin-like serine proteases
	independent of chelate effect ?[102]	bacterial collogenase[102] (3.4.24.3)	IC_{50} = 1.1 µM[48]		CUB-like		
		bontoxilysin[49]		1i1e[49]	Zincin-like		
amastatin		leucine aminopeptidase IV(3.4.11.22)	?IC_{50} = 1 µM[63]		Phosphorylase/ hydrolase like	LTA4H *(IC_{50} > 10 mM)*[3]	Zincin-like
	slow and tight[52]	leucine aminopeptidase (3.4.11.1)[50, 51]	K_i = 30 nM[52] K_i = 200 nM[53]	1bll[54]	Phosphorylase/ hydrolase like	aminopeptidase P (3.4.11.9)[101, 112, 113]	Creatinase/ aminopeptidase
		tetrahedral			?Phosphorylase/	arginine aminopeptidase (B) (3.4.11.6)[114]	?Zincin-like *(homology with LTA4H)*

		aminopeptidase (TET)		1y0y[55](no SCOP)	hydrolase like (*homology with leucine aminopeptidase*[55])	picornain 2A (3.4.22.29) (*IC_{50} > 0.1 mM)*[115]	Tryspin-like serine protease
		alanyl aminopeptidase (N/M) (3.4.11.2)[53, 91, 105-107]	K_i = 190 µM[53] IC_{50} = 1.5 – 2 µM[96] K_i = 52 nM[52] K_i = 20 nM[53]	no pdb	?Zincin-like *(homology with LTA4H)*	cystinyl aminopeptidase (3.4.11.3)[106]	Phosphorylase/ hydrolase like
	slow and tight[52]	cystinyl aminopeptidase (3.4.11.3)[50]			Phosphorylase/ hydrolase like	meprin A[116]	?Zincin-like *(homology with astacin)*
		glutamyl aminopeptidase (3.4.11.7)[96, 106]	IC_{50} = 1.5 – 2 µM[96]	no pdb	?*homology with TET*	glutamate carboxypeptidase II (3.4.17.21)[117] *(200 µM, 88 % activity)*	?Phosphorylas/ hydrolase like *(homology with 1cx8)*
		aminopeptidase W (3.4.11.16)[96]	IC_{50} = 1.5 – 2 µM[96]	?no pdb no sequence			
		cytosol alanyl aminopeptidase (3.4.11.14)[92, 93]	strongly[92]		Phosphorylase/ hydrolase like		
		aminopeptidase Y (3.4.11.15)[108]	0.02 mM, 10% activity[108]	no pdb	?Zincin-like *(homology with LTA4H)*		
	slow and tight[52]	bacterial leucyl aminopeptidase (3.4.11.10)	K_i = 0.26 nM[52]		Phosphorylase/ hydrolase like		
		pyroglutamyl aminopeptidase (3.4.19.3)	IC_{50} = 1 µg/ml[111]		Phosphorylase/ hydrolase like		
		mitochondrial intermediate peptidase (3.4.24.59)[109]		No pdb	?Zincin-like *(homology with neurolysin)*		
		X-his dipeptidase (3.4.13.3)[110]		No pdb	?Phosphorylase /hydrolase like *(homology with peptidase T)*		
ancovenin		ACE	IC_{50} = 0.87 µM[118]		Zincin-like		
antibiotic A 58365A	competitive[119]	ACE[119]	IC_{50} = 0.0018 µM[119]		Zincin-like		
antibiotic A 58365B	competitive[119]	ACE[119]	IC_{50} = 0.004 µM[119]		Zincin-like		
antibiotic I5B1/K4	non-competitive[119]	ACE	K_i = 0.18 µM[120]		Zincin-like	Trypsin[119]	Trypsin-like serine protease

		carboxypeptidase A	Weak 2,3%[119]		Phosphorylase/ hydroalse	Carboxypeptidase B[119]	Phosphorylase/ hydrolase
antibiotic I5B2	competitive[119]	ACE	IC_{50} = 0.091 µM[119, 121]		Zincin-like		
antibiotic K 13	non-competitive[119]	ACE	K_i = 0.349 µM[122]		Zincin-like	trypsin[122]	Trypsin-like serine protease
		leucine aminopeptidase	6 % inhibition[122]		Phosphorylase/ hydrolase like	carboxypeptidase A[122]	Phosphorylase/ hydrolase
		aminopeptidas B	5,3 % inhibition[122]		?Zincin-like or phosphorylase/ hydrolase like		
antibiotic K 26	non-competitive[119]	ACE	K_i = 0.03 µM[119] IC_{50} = 6.7 ng/ml[123]		Zincin-like	trypsin[119]	Trypsin-like serine protease
		carboxypeptidase A	13,7 % inhibition[123]		Phosphorylase/ hydrolase like	papain[119]	Cysteine proteinase
						carboxypeptidase B[119]	Phosphorylase/ hydrolase
						leucine aminopeptidase[119]	Phosphorylase/ hydrolase
						thermolysin[119]	Zincin-like
						chymostrypsin[119]	?Zincin-like or phosphorylase/ hydrolase
antipain		MEP (3.4.24.20)	weak[165]		Zincin-like		
		serralysin[124]			Zincin-like		
		cytosol alanyl aminopeptidase (3.4.11.14)	0.1 mM, 39 % inhibition[93]		Phosphorylase/ hydrolase like		
		aminopeptidase Y (3.4.11.15)[125]	0.05 mg/ml, 19 % inhibition[125]	no pdb	?Zincin-like *(homology with LTA4H)*		
		alanyl aminopeptidase (N/M) (3.4.11.2)[107]	0.1 mM, 47 % inhibition[107]	no pdb	?Zincin-like *(homology with LTA4H)*		
		aminopeptidase P (3.4.11.9)[126]			Creatinase/ aminopeptidase		
		arginine aminopeptidase (B)		no pdb	?Zincin-like *(homology with*		

(3.4.11.6)[127]			*LTA4H)*
tissue kallkrein (3.4.21.B47)[128]		No pdb/no sequence	
renal tissue kallikrein (3.4.21.35)[128]			Trypsin-like serine protease
plasma kallikrein (3.4.21.34)[129, 130]			Trypsin-like serine protease
chymase (3.4.21.39)[131]	partial[166]		Trypsin-like serine protease
tryptase (3.4.21.59)[131, 132]	0.01 mM, 94 % inhibition[167]		Trypsin-like serine protease
lysyl endopeptidase (3.4.21.50)	slight[168]		Trypsin-like serine protease
u-plasminogenactivator (3.4.21.73)	IC_{50} = 43 nM[169]		Trypsin-like serine protease
granzyme B (3.4.21.79)[133]			Trypsin-like serine protease
enteropeptidase (3.4.21.9)[134]			Trypsin-like serine protease
picornain 2A (3.4.22.29)[135]	IC_{50} = 0.065 mM[115]		Trypsin-like serine protease
dipeptidyl aminopeptidase (3.4.14.1)[136, 137]			Cysteine proteinase
cathepsin B (3.4.22.1)[138-148]	1 µM, 93 % inhibition[170]		Cysteine proteinase
cathepsin L (3.4.22.15)[149-151]	strongly [149]		Cysteine proteinase
cathepsin H (3.4.22.16)[152]	0.1 mM, 91 % inhibition[152] 0.01 mM, 53 % inhibition[171]		Cysteine proteinase
papain (3.4.22.2)[153]			Cysteine proteinase
	0.05 µM, complete		?Cysteine

		V-cath endopeptidase (3.4.22.50)[154]	inhibition[154]		proteinase *(homology with cathepsin F)*		
		calpain-1 (3.4.22.52)[155]	0.01 mM, 80 – 90 % inhibition[155]	No pdb	Cysteine proteinase		
		calpain-2 (3.4.22.53)[156, 157]	0.01 mM, 80 - 90 % inhibition[155] 0.02 mM, 82 – 87 % loss of activity[172] 0.05 mM, complete inhibition[173] K_i = 2.06 µM[174]		Cysteine proteinase		
		subtilisin (3.4.21.62)[158]			Subtilisin-like		
		thermitase (3.4.21.66)[159]			Subtilisin-like		
		furin (3.4.21.75)[160, 161]	moderately[160] 1 mM, 35.9 - 45.7 % activity[175]		Subtilisin-like		
		carboxypeptidase D (3.4.16.6)[56]		1bcr[56]	Alpha/beta hydrolase		
		tripeptidase aminopeptidase (3.4.11.4)[162]		no pdb	?Phosphorylase /hydrolase like *(homology with Peptidase T)*		
		oligopeptidase B (3.4.21.83)[163, 164]		no pdb	?Alpha/beta hydrolase *(homology with prolyloligopeptidase)*		
aranciamycin	anthracycline	bacterial collagenase (3.4.24.3)	IC_{50} = 0.37 µM[48]		CUB-like	elastase[48]	?*(depends on type)*
						trypsin[48]	Trypsin-like serine proteases
arphamenine A		arginine aminopeptidase (B) (3.4.11.6)[176]	IC_{50} = 0.007 µg/mL[178] IC_{50} = 0.005 µg/mL[178] K_i = 2.5 nM[179]	No pdb	?Zincin-like *(homology with LTA4H)*	leucine aminopeptidase (EC.?)	?
		carboxypeptidase A[177] *(inhibited by*			Phosphorylase/ hydrolase like	aminopeptidase A (EC. ?)	?

	derivatives)					
	alanyl aminopeptidase (N/M) (3.4.11.2)[91]	0.5 mM, 42 % inhibition[91]	no pdb	?Zincin-like *(homology with LTA4H)*		
	cystinyl aminopeptidase (3.4.11.3)[50]			Phosphorylase/ hydrolase like		
	leucine aminopeptidase (3.4.11.1)[50]			Phosphorylase/ hydrolase like		
	dipeptidyl aminopeptidase (3.4.14.4)[176]		No pdb No sequence match			
	ACE[176]			Zincin-like		
	carboxypeptidase (3.4.17.19)[176]		No pdb	?Zincin-like *(homology search)*		
	cytosol alanyl aminopeptidase (3.4.11.14)	0.1 mM, 80 % inhibition[93]		Phosphorylase/ hydrolase like		
arphamenine B	arginine aminopeptidase (B) (3.4.11.6)[87]	K_i = 0.84 nM[179]	No pdb	?Zincin-like *(homology with LTA4H)*	leucine aminopeptidase (EC.?)	?
	carboxypeptidase A [177] *(inhibited by derivatives)*			Phosphorylase/ hydrolase like	aminopeptidase A (EC. ?)	?
	cystinyl aminopeptidase (3.4.11.3)[50]			Phosphorylase/ hydrolase like	alanyl aminopeptidase (N/M) (3.4.11.2)[87]	?Zincin-like *(homology with LTA4H)*
	leucine aminopeptidase (3.4.11.1)[50]			Phosphorylase/ hydrolase like		
	pyroglutamyl aminopeptidase (3.4.19.3)[111]			Phosphorylase/ hydrolase like		
p-hydroxybenzylmalic acid *(Arphamenine B intermediate)*	carboxypeptidase A [180]			Phosphorylase/ hydrolase like		
	carboxypeptidase B[180]			Phosphorylase/		

					hydrolase like		
P-hydroxybenzylsuccinic acid *(Arphamenine B intermediate)*		carboxypeptidase A [180]			Phosphorylase/ hydrolase like		
		carboxypeptidase B[180]			Phosphorylase/ hydrolase like		
		arginine aminopeptidase (B)[180] (3.4.11.6)		no pdb	?Zincin-like *(homology with LTA4H)*		
aspergillomarasmine A	competitive[119]	ACE[119, 181]	IC_{50} = 1.2 μM[183]		Zincin-like	alanyl aminopeptidase (N/M) (3.4.11.2) *(lower)*[183]	?Zincin-like *(homology with LTA4H)*
		ECE[182]	IC_{50} = 3.4 μM[184]	no pdb	?Zincin-like *(homology with neprilysin)*		
						carboxypeptidase A *(lower)*[183]	Phosphorylase/ hydrolase like
aspergillomarasmine B	competitive[119]	ACE[119]	IC_{50} =1.0 μM[183]		Zincin-like	alanyl aminopeptidase (N/M) (3.4.11.2) *(lower)*[183]	?Zincin-like *(homology with LTA4H)*
		ECE[182]	IC_{50} = 2.5 μM[184]	no pdb	?Zincin-like *(homology with neprilysin)*		
						carboxypeptidase A *(lower)*[183]	Phosphorylase/ hydrolase like
BE16627B		gelatinase B (MMP-9)[185]			Zincin-like	trypsin chymotrypsin	Trypsin-like serine proteases
		stromelysin (MMP-3)[185]			Zincin-like	papain	Cysteine proteases
		gelatinase A (MMP-2)[186]			Zincin-like	pepsin	Acid protease
		thermolysin[186]			Zincin-like	elastase	*?(depends on type)*
		bacterial collagenase[186] (3.4.24.3)			CUB-like		
		leucine aminopeptidase [186](E.C.?)			Phosphorylase/ hydrolase like		
bestatin		LTA4H	IC_{50} = 4 μM[3] K_i = 201 ± 95 nM[3]	1hs6[28]	Zincin-like	neprilysin[173]	Zincin-like
						ECE[201]	?Zincin-like *(homology with neprilysin)*
		lethal factor	IC_{50} = 700 μM[197]		Zincin-like		
	competitive[57] *rapidly reversible*	alanyl aminopeptidase (N/M) (3.4.11.2)[25, 57, 87,	IC_{50} = 89 μM[96] K_i = 4.1 μM[53]	No pdb	?Zincin-like *(homology with*	aminopeptidase P	Creatinase/

process[52]	91, 189]	K_i = 1.4 µM[52] IC_{50} > 100[95] K_i = 4 µM[198]		*LTA4H)*	(3.4.11.9)[101, 112, 113]	aminopeptidase
	arginine aminopeptidase (B)[25] (3.4.11.6) *(inhibited by analogs)*[2, 179]	K_i = 14 nM[179] K_i = 60 nM[199]	No pdb	?Zincin-like *(homology with LTA4H)*	glutamyl aminopeptidase (3.4.11.7)[96]	?*homology with TET*
competitive [57] *Slow and tight*[52]	leucine aminopeptidase[50, 57] (3.4.11.1)*(inhibited by analogs)* [2]	K_i = 1.3 nM[58] K_i = 0.58 nM[52] K_i = 20 nM[59]	Can't find pdb [60] *(have emailed authors)*	Phosphorylase/ hydrolase like	picornain 2A (3.4.22.29) (*IC_{50} > 0.1 mM)*[115]	Trypsin-like serine protease
	cystinyl aminopeptidase (3.4.11.3)[50]			Phosphorylase/ hydrolase like	meprin A[116]	?Zincin-like *(homology with astacin)*
	aminopeptidase W (3.4.11.16)[96]	IC_{50} = 7.9 µM[96]	?no pdb no sequence			
	cytosol alanyl aminopeptidase (3.4.11.14)[92, 93]	strongly [92]		Phosphorylase/ hydrolase like		
competitive[187]	aminopeptidase Y (3.4.11.15)[108, 187]	0.02 mM, 48 - 52 % activity[108]	no pdb	?Zincin-like *(homology with LTA4H)*		
slow and tight[52]	bacterial leucyl aminopeptidase (3.4.11.10)	K_i = 18 nM[52]	1txr[27]	Phosphorylase/ hydrolase like		
	pyroglutamyl aminopeptidase (3.4.19.3)	IC_{50} = 0.1 µmol/L[111]		Phosphorylase/ hydrolase like		
	prolidase (3.4.13.9)[190]	1 mM, 100 % inhibition[190]		Creatinase/ aminopeptidase		
	chymase (3.4.21.39)[131]			Trypsin-like serine protease		
	cathepsin H (3.4.22.16)[171]	1 mM, 62 % inhibition[171]		Cysteine proteinase		
competitively[162, 188]	tripeptide aminopeptidase (3.4.11.4)[191-194]	1 mM, 100 % inhibition[200] K_i = 1 µM[162] K_i = 0.5 µM[188]	No pdb	?Phosphorylase/ hydrolase like *(homology with Peptidase T)*		

		glutamate carboxypeptidase II (3.4.17.21)[117]	290 µM, 41 % activity[117]		?Phosphorylas/ hydrolase like *(homology with 1cx8)*		
		PepB aminopeptidase (3.4.11.23)[195]	1 mM, 100 % inhibition[195]		?Phosphorylase/ hydrolase *(homology with leucine aminopeptidase)*		
		X-his dipeptidase (3.4.13.3)[196]	strongly [110, 196]		?Phosphorylase /hydrolase like *(homology with peptidase T)*		
betulinic acid	triterpene compound	stromelysin (MMP-3)	K_i = 2.2 µM[204]		Zincin-like	trypsin[203]	
		collagenase (MMP-1)	K_i = 1.3 µM[204]		Zincin-like	thrombin[203]	
		alanyl aminopeptidase (N/M) (3.4.11.2)	IC_{50} = 7.3 µM[205]	no pdb	?Zincin-like *(homology with LTA4H)*		
		HIV-1(*derivatives)*[202]			Acid protease		
		prolyl endopeptidase[203]			Alpha/beta hydrolase		
captopril		ACE[37, 61, 62, 206]	?IC_{50}= 1 µM[64] K_i = 1.3 nM[64]	1uzf[31] 1j37[32]	Zincin-like	neprilysin[73, 74] *(IC_{50} > 1 mM[75])*	Zincin-like
		peptide deformylase[207]	IC_{50}= 11 µM[3, 65]	xray paper[66] *(waiting for release)*	Peptide deformylase	ECE[218-220] *(IC_{50} > 100 µM)*[220]	?Zincin-like *(homology with neprilysin)*
		LTA4H			Zincin-like	lethal factor*(poorly)*[221]	Zincin-like
		prolidase (3.4.13.9)	K_i = 90 µM[215] K_i = 25 – 35 µM[216] IC_{50} = 110 µM[217]		Creatinase/ aminopeptidase		
		aminopeptidase P (3.4.11.9)[112]	K_i = 400 µM[30]	1jt1[30]	Creatinase/ aminopeptidase		
		metallo-β-lactamase *(FEZ-1 subclassB3)*	K_i = 8 µM[30]		Metallo-hydrolase/ oxidoreductase		

		metallo-β-lactamase *(L-1 subclassB3)*			Metallo-hydrolase/ oxidoreductase		
		metallo-β-lactamase *(GOB-1 subclassB3)*	K_i = 70 - 100 μM[29]	1m2x[29]	Metallo-hydrolase/ Oxidoreductase		
		tentoxilysin[208, 209]		no pdb	?Zincin-like *c.domian has homology with bentoxilysin*		
		bentoxilysin[208-212]		No pdb	Zincin-like		
		dipeptidyl carboxypeptidase (3.4.15.5)[213]	partial[214]	No pdb	?Zincin-like *(homology with neurolysin)*		
		meprin A[116]	K_i = 1 μM[162]	No pdb	?Zincin-like *(homology with astacin)*		
		saccharolysin (3.4.24.37)[214]		No pdb	?Zincin-like *(homology with neurolysin)*		
		tripeptide aminopeptidase (3.4.11.4)[162]			?Phosphorylase/ hydrolase like *(homology with Peptidase T)*		
daunorubicin	anthracycyline	gelatinase A (MMP-2)	K_i = 92 μM[103]		Zincin-like	human neutrophil elastase[48]	Trypsin-like serine protease
	chelation	prolidase (3.4.13.9)	IC_{50} = 0.3 μM[104]		Creatinase/ aminopeptidase	trypsin[48]	Trypsin-like serine protease
	independent of chelate effect ?[102]	bacterial collogenase[102] (3.4.24.3)	IC_{50} = 1.9 μM[48]		CUB-like		
emodin	anthraquinone	bacterial collogenase (3.4.24.3)	IC_{50} = 40 μM[222]		CUB-like		
	independent of chelate effect?[222]						
(-)-epicatechin gallate	Catechin	collagenase [223] *(no effect from catechins without gallate moiety)*			Zincin-like		
(-)-epigallocatechin gallate	catechin	collagenase[223] *(no effect from*			Zincin-like		

		catechins without gallate moiety)					
epirubicin		gelatinase A (MMP-2)	K_i = 40 μM[103]		Zincin-like		
FMPI	competitive[119]	ACE	IC_{50} = 0.008 μM[224]		Zincin-like	trypsin[224]	Trypsin-like serine protease
		thermolysin	moderate[224]		Zincin-like	papain[224]	Cysteine proteinase
						carboxypeptidase A[224]	Phosphorylase/ hydrolase
						carboxypeptidase B[224]	Phosphorylase/ hydrolase
						leucine aminopeptidase[224]	Phosphorylase/ hydrolase
foroxymithine		ACE[119]	IC_{50} = 0.0121 μM[119]		Zincin-like	picornain 2A (3.4.22.29) (*IC_{50} > 0.2 mM)*[115]	Trypsin-like serine protease
		trypsin	*(weak)*[119]		Trypsin-like serine protease		
		papain	*(weak)*[119]		Cysteine proteinase		
		carboxypeptidase A	*(weak)*[119]		Phosphorylase/ hydrolase		
		carboxypeptidase B	*(weak)*[119]		Phosphorylase/ hydrolase		
		thermolysin	*(weak)*[119]		Zincin-like		
		aminopetidase A aminopeptidase B chymotrypsin	*(weak)*[119] *(weak)*[119] *(weak)*[119]		?Zincin-like or Phosphorylase/ hydrolase		
fumagillin		methionine aminopeptidase 2 (3.4.11.18)[67-69]		1boa[70]	Creatinase/ aminopeptidase		
futoenone *and derivatives*	neolignan	stromelysin (MMP-3)	IC_{50} = 0.6 μM[225]		Zincin-like		
		collagenase [225] (MMP-1)			Zincin-like		
		gelatinase B[225] (MMP-9)			Zincin-like		
		platelet activating			Flavodoxin-like		

	factor (PAF)[226]			fold		
glycyrrhetinic acid	MMPs	weakly[227]				
homocarnosine	X-his dipeptidase (3.4.13.3)[228]	0.8 mM, 20 % inhibition[229]	No pdb	?phosphorylase /hydrolase like *(homology with peptidase T)*		
L-681,176	ACE	IC_{50} = 3.7 µM[230]		Zincin-like		
laccaridiones A and B	trypsin[231]			Trypsin-like serine proteases		
	papain[231]			Cysteine proteinases		
	thermolysin[231]			Zincin-like		
	collagenase (MMP?)[231]			Zincin-like		
	zinc protease[231]			?*(not sure which protein is meant)*		
lapstatin	leucine aminopeptidase (3.4.11.1)	IC_{50} = 0.3 - 2.4 µM[232]		Phosphorylase/ hydrolase like	alanyl aminopeptidase (N/M) (3.4.11.2) *IC_{50} > 122 µM*[232]	?Zincin-like *(homology with LTA4H)*
					arginine Aminopeptidase (B) (3.4.11.6) *IC_{50} > 1600 µM*[232]	?Zincin-like *(homology with LTA4H)*
					proline aminopeptidase (?EC) *IC_{50} > 1600 µM*[232]	
					dipeptidyl aminopeptidase (3.4.14.4) *IC_{50} > 1200 µM*[232]	No pdb No sequence match
leuhistin	alanyl aminopeptidase (N/M) (3.4.11.2)[87, 91, 233]	IC_{50} = 29.9 µM[95] strongly [233]	no pdb	?Zincin-like *(homology with LTA4H)*		
	arginine Aminopeptidase (B) (3.4.11.6)[233]	weakly[233]	no pdb	?Zincin-like *(homology with LTA4H)*		
	leucine aminopeptidase (?3.4.11.1)[233]	weakly[233]	no pdb	?Phosphorylase/ hydrolase like		

		cytosol alanyl aminopeptidase (3.4.11.14)[92, 93]	strongly [92]	no pdb	Phosphorylase/ hydrolase like		
		glutamyl aminopeptidase (3.4.11.7)	IC_{50} = 0.2 µg/mL [100]		*?homology with TET*		
matlystatin A	novel piperazic acid moiety	gelatinase B[234, 235] (MMP-9)	IC_{50} = 0.3 µM[236]		Zincin-like	thermolysin *(IC_{50} = 7-11 fold >)*	Zincin-like
		gelatinase A (MMP-2)	IC_{50} = 0.56 µM[236]		Zincin-like	alanyl aminopeptidase (N/M) *(IC_{50} = 7-11 fold >)*	?Zincin-like *(homology with LTA4H)*
		alanyl aminopeptidase (N/M) (3.4.11.2)[87]		no pdb	?Zincin-like *(homology with LTA4H)*		
matlystatin B		gelatinase B (MMP-9)[234, 237]	IC_{50} = 0.57 µM[238]		Zincin-like		
matlystatin Analogs		peptide deformylase [42]	K_i = 0.3 nM[42]		Peptide deformylase		
		peptide deformylase [42]	K_i = 60 nM[42]	*Have emailed author about pdb[42] going to release pending confidentiality agreement*	Peptide deformylase		
microginin		ACE[239]	IC_{50} = 7.0 µg/mL [239]		Zincin-like	papain*(IC_{50} > 100 µg/mL)*[239]	Cysteine proteases
						trypsin chymotrypsin *(IC_{50} > 100 µg/mL)*[239]	Trypsin-like serine proteases
						elastase*(IC_{50} > 100 µg/mL)*[239]	?*(depends on type)*
microginins (1) 478 (2) 51-A (6) 91-C (7) 91-D (8) 91-E		(1) ACE	IC_{50} = 13.5 µM[95]		Zincin-like	(1-8)papain[95]	Cysteine proteases
		(1,2 and 6-8) alanyl aminopeptidase (N/M) (3.4.11.2)	Refer to paper[95]	no pdb	?Zincin-like *(homology with LTA4H)*	(1-8)trypsin[95] (1-8)thrombin[95] (1-8)plasmin[95] (1-8)chymotrypsin[95]	Trypsin-like serine proteases
						(1-8)elastase[95]	?*(depends on type)*

microginins 299-A (1) 299-B (2) 299-C (3) 299-D (4) 99-A (5) 99-B (6)		(1)leucine aminopeptidase (3.4.11.1) (2)leucine aminopeptidase (3.4.11.1) (3)leucine aminopeptidase (3.4.11.1) (4)leucine aminopeptidase (3.4.11.1)	IC_{50} = 4.6 µg/mL[240] IC_{50} = 6.5 µg/mL[240] IC_{50} = 2 µg/mL[241] IC_{50} = 6.4 µg/mL[241]		Phosphorylase/ hydrolase like Phosphorylase/ hydrolase like Phosphorylase/ hydrolase like Phosphorylase/ hydrolase like	(1-6)ACE[240, 241] (1-6)papain[240, 241] (1-6)trypsin[240,241] (1-6)thrombin[240, 241] (1-6)plasmin[240, 241] (1-6)chymotrypsin[240, 241] (1-6)elastase[240, 241] (5,6)leucine aminopeptidase (3.4.11.1)	Zincin-like Cysteine proteases Trypsin-like serine proteases *?(depends on type)* Phosphorylase/ hydrolase like
MR-387A MR-387B	slow and tight binding irreversible[242]	(A and B) alanyl aminopeptidase (N/M) (3.4.11.2)	(A) K_i = 0.22 nM[242]	no pdb	?Zincin-like *(homology with LTA4H)*		
muracein A	competitive[119]	ACE[119, 181, 243]	IC_{50} = 0.28 µM[244] K_i = 1.5 µM[244]		Zincin-like	carboxypeptidase A (IC_{50} >150 µM)[244] alcoholdehydrogenase (% <5)[244]	Phosphorylase/ hydrolase like NAD(P)-binding rossman-fold domain
muracein B	competitive[119]	ACE[119, 181, 243, 244]	IC_{50} = 12 µM[244]		Zincin-like	carboxypeptidase A (IC_{50} > 150 µM)[244] alcoholdehydrogenase (% < 5)[244]	Phosphorylase/ hydrolase like NAD(P)-binding rossman-fold domain
muracein C	competitive[119]	ACE[119, 181, 243, 244]	IC_{50} = 170 µM[244]		Zincin-like	carboxypeptidase A (IC_{50} > 150 µM)[244] alcoholdehydrogenase (% <5)[244]	Phosphorylase/ hydrolase like NAD(P)-binding rossman-fold domain
nicotianamine		getatinase	weakly[245]		Zincin-like		
ovalicin		methionine aminopeptidase 2 (3.4.11.18)[68, 69]		1b59[70]	Creatinase/ aminopeptidase		
5-demethylovalicin		methionine aminopeptidase 2 (3.4.11.18)	IC_{50} = 17.7 nM[246]		Creatinase/ aminopeptidase		

phenacein	competitive[119]	ACE[181, 247]	K_i = 0.58 µM[248]		Zincin-like	*other zinc containing enzymes*[248]	
		carboxypeptidase B	(%) 11[119]				
					Phosphorylase/ hydrolase	carboxypeptidase A (%) < 5[119]	Phosphorylase/ hydrolase
						alcoholdehydrogenase (%) < 5[119]	NAD(P)-binding Rossman-fold domain
phosphoramidon		thermolysin[71, 72, 249]	?IC_{50} = 1 µM[258] K_i = 0.032 µM[76]	1tlp[77-79]	Zincin-like	LTA4H[3]	Zincin-like
						ACE[62]	Zincin-like
		neprilysin[73-75]	IC_{50} = 39 nM[73] IC_{50} = 94 nM[75]	1dmt[80]	Zincin-like		
						picornain 2A (3.4.22.29) (*IC_{50} > 0.15 mM)*[115]	Trypsin-like serine protease
		ECE[201, 218, 250-254]	IC_{50} = 2.5 µM[259] IC_{50} = 1.8 - 2.7 µM[252] IC_{50} = 4 µM[219] IC_{50} = 0.35 µM[220]	no pdb	?Zincin-like *(homology with neprilysin)*		
						aminopeptidase Y (3.4.11.15) *(0.02 mM, 84 – 86 % activity)*[108]	?Zincin-like *(homology with LTA4H)*
		MEP (3.4.24.20)	weak[165]		Zincin-like		
		atrolysin C[255, 256]	weak[256]		Zincin-like	meprin A[116]	?Zincin-like *(homology with astacin)*
		atrolysin A[255]		?*no pdb no sequence*			
		cytosol alanyl aminopeptidase (3.4.11.14)	0.1 mM, 17 % inhibition[93]		Phosphorylase/ hydrolase like	glutamate carboxypeptidase II (3.4.17.21) *(1 µM. 99 %* activity)[117]	?Phosphorylas/ hydrolase like *(homology with 1cx8)*
		aminopeptidase P (3.4.11.9)[112]			Creatinase/ aminopeptidase		
		granzyme B (3.4.21.79)	0.05 mM/mL, 65 ± 5 % inhibition[260]		trypsin-like serine protease		
		pseudolysin/ elastase (3.4.24.26)[257]	K_i = 0.055 µM[76]		Zincin-like		
probestin	*competitive*[261]	alanyl aminopeptidase (N/M) (3.4.11.2)	IC_{50} = 50 nM[96] IC_{50} = 1.5 – 2 µM[96] IC_{50} = 0.023 µg/mL[97] K_i = 0.19 nM[261]	no pdb	?Zincin-like *(homology with LTA4H)*	aminopeptidase A (? EC) *IC_{50} > 100 µg/mL*[97]	?
		glutamyl aminopeptidase (3.4.11.7)[96]	IC_{50} = 1.5 – 2 µM[96] IC_{50} = 0.023 µg/mL[100]	no pdb	?*homology with TET*		
		aminopeptidase W	IC_{50} = 1.5 - 2 µM[96]	no pdb	?*no pdb*		

		(3.4.11.16)[96]			*no sequence*		
		leucine aminopeptidase (3.4.11.1)	IC_{50} = 0.081 µg/mL[97]		Phosphorylase/ hydrolase like		
		arginine aminopeptidase (B) (3.4.11.6)	IC_{50} = 36.7 µg/mL[97]	no pdb	?Zincin-like *(homology with LTA4H)*		
prostatin		glutamyl aminopeptidase (3.4.11.7)	IC_{50} = 0.028 µg/mL[100]	no pdb	?*homology with TET*		
		alanyl aminopeptidase (N/M) (3.4.11.2)	IC_{50} = 0.028 µg/mL[97]	no pdb	?Zincin-like *(homology with LTA4H)*		
		leucine aminopeptidase (3.4.11.1)	IC_{50} = 0.3 µg/mL[97]		Phosphorylase/ hydrolase like		
		aminopeptidase A (? EC)	IC_{50} = 91.1 µg/mL[97]		?		
		arginine aminopeptidase (B) (3.4.11.6)	IC_{50} = 60 µg/mL[97]	no pdb	?Zincin-like *(homology with LTA4H)*		
puromycin		cystinyl aminopeptidase (3.4.11.3)[50]			Phosphorylase/ hydrolase like	neprilysin[73]	Zincin-like
						aminopeptidase P (3.4.11.9)[101, 113]	Creatinase/ aminopeptidase
		leucine aminopeptidase (3.4.11.1)[50, 263]			Phosphorylase/ hydrolase like	alanyl aminopeptidase (N/M) (3.4.11.2)	?Zincin-like *(homology with LTA4H)*
		glutamyl aminopeptidase (3.4.11.7)[106]		no pdb	?*homology with TET*	*80-fold less sensitive then 3.4.11.14*	
	competitive[262]	alanyl aminopeptidase (N/M) (3.4.11.2)[91]	0.1 mM, 67 % inhibition[91] 1 mM, 93 % inhibition[106] K_i = 0.1 mM[198] K_i = 12.5 µM[262]	no pdb	?Zincin-like *(homology with LTA4H)*	meprin A[116]	?Zincin-like *(homology with astacin)*
		arginine aminopeptidase (B) (3.4.11.6)[264]		no pdb	?Zincin-like *(homology with LTA4H)*		

		cytosol alanyl aminopeptidase (3.4.11.14)[92, 265]	strongly [92] IC_{50} = 0.6 μM[93]		Phosphorylase/ hydrolase like		
		pyroglutamyl aminopeptidase (3.4.19.3)[266]			Phosphorylase/ hydrolase like		
		cathepsin H (3.4.22.16)[267]	1 mM, 20 % inhibition[171]		cysteine proteinase		
		pyroglutamyl-peptidase II (3.4.19.6)[268]	1 mM, 17 % inhibition[268]	No pdb	?Zincin-like *(homology with LTA4H)*		
		tripeptide aminopeptidase (3.4.11.4)[191]		No pdb	?phosphorylase/ hydrolase like *(homology with Peptidase T)*		
		glutamate carboxypeptidase II (3.4.17.21)[117]	0.5 mM, 45 % activity[117]	No pdb	?phosphorylase/ hydrolase like *(homology with 1cx8)*		
pycnidione	tropolone fungal metabolite	stromelysin (MMP-3)	IC_{50} = 31 μM[269]		Zincin-like	ACE[269]	Zincin-like
						human leucocyte elastase (hNE) [269]	Trypsin-like serine proteases
						papain[269]	Cysteine proteases
						HIV-1protease[269]	Acid protease
rifampicin		MMPs	weakly[270]				
SB236049		metallo-β-lactamase *(IMP-1 subclassB1)*	IC_{50} = 151 μM[81]		Metallo-hydrolase/ oxidoreductase	metallo-β-lactamase *(L-1 subclassB3)* IC_{50} > *1000 μM*[81]	Metallo-hydrolase/ oxidoreductase
		metallo-β-lactamase *(CfiA subclassB1)*	IC_{50} = 2 μM[81] K_i = 15 μM[81]		Metallo-hydrolase/ oxidoreductase	ACE *IC_{50} > 333 μM*[81]	Zincin-like
		metallo-β-lactamase *(BcII subclassB1)*	IC_{50} = 0.3 μM[81]		Metallo-hydrolase/ oxidoreductase		
SB236050		metallo-β-lactamase *(IMP-1 subclassB1)*	IC_{50} = 113 μM[81] K_i = 32 μM[81]		Metallo-hydrolase/ oxidoreductase Metallo-hydrolase/	metallo-β-lactamase *(L-1 subclassB3)* IC_{50} >	Metallo-hydrolase/ oxidoreductase

		metallo-β-lactamase *(CfiA subclassB1)*	IC_{50} = 29 μM[81] K_i = 10 μM[81]	1kr3[81]	oxidoreductase	*1000 μM*[81]	
		metallo-β-lactamase *(BcII subclassB1)*	IC_{50} = 389 μM[81] K_i = 88 μM[81]		Metallo-hydrolase/ oxidoreductase	ACE *IC_{50} > 1000 μM*[81]	Zincin-like
SB238569		metallo-β-lactamase *(IMP-1 subclassB1)*	IC_{50} = 26 μM[81] K_i = 17 μM[81]		Metallo-hydrolase/ oxidoreductase	metallo-β-lactamase *(L-1 subclassB3) IC_{50} > 1000 μM*[81]	Metallo-hydrolase/ oxidoreductase
		metallo-β-lactamase *(CfiA subclassB1)*	IC_{50} = 7 μM[81] K_i = 3.4 μM[81]		Metallo-hydrolase/ oxidoreductase		
		metallo-β-lactamase *(BcII subclassB1)*	IC_{50} = 13 μM[81] K_i = 79 μM[81]		Metallo-hydrolase/ oxidoreductase	ACE IC_{50} > *1000 μM*[81]	Zincin-like
SF2513A		ACE[271]			Zincin-like		
SF2513 B		ACE[271]			Zincin-like		
SF2513 C		ACE[271]			Zincin-like		
talopeptin	competitive[119]	ACE[119]	IC_{50} = 0.0016 μM[119]		Zincin-like	some metalloproteinases[119]	Zincin-like
		thermolysin[272]	strong[119]		Zincin-like		
		carboxypeptidase A	slight[273]		Phosphorylase/ hydrolase like	trypsin[119]	Trypsin-like serine protease
		glucose 6-phosphate dehydrogenase[273]			NAD(P)-binding Rossmann-fold domain	papain[119]	Cysteine proteinase
	For dehydrogenases Phosphate group binds to the same site as coenzyme	lactate dehydrogenase[273]			NAD(P)-binding Rossmann-fold domain		
		malate dehydrogenase[273]			NAD(P)-binding Rossmann-fold domain		
		glutamate dehydrogenase[273]			NAD(P)-binding Rossmann-fold domain		
		glycerol phosphate dehydrogenase[273]			NAD(P)-binding Rossmann-fold domain		
tetracycline *doxycyline minocycline*		collagenase (MMP-1)[274-276]	IC_{50} = 280 – 510 μM[280] IC_{50} = 15 – 350 μM[278]		Zincin-like	stomelysin (MMP-3)	Zincin-like

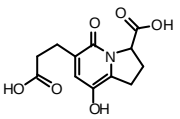
			IC_{50} > 200 µg/mL[281]			
		gelatinase B[275, 277] (MMP-9)		Zincin-like		
		gelatinase A[278, 279] (MMP-2)		Zincin-like		
		macrophage elastase (MMP-12)[278]		Zincin-like		
		human neutrophil collagenase (MMP-8)	IC_{50} = 15 – 30 µM[280] IC_{50} = 15 - 86 µg/mL[281]	Zincin-like		
		gelatinases	IC_{50} < 1µg/mL[281]	Zincin-like		
		MMP-13[275]				
doxycycline	tetracycline derivative	collagenase (MMP-1)	IC_{50} = 452 µM[282] IC_{50} = 280 µM[283]	Zincin-like		
		Gelatinase A (MMP-2)	IC_{50} = 56 µM[282]	Zincin-like		
		stromelysin (MMP-3)	IC_{50} = 32 µM[282]	Zincin-like		
		MMP-13	IC_{50} ~ 50 µM[284] IC_{50} = 2 µM[281]			
		human neutrophil collagenase (MMP-8)	IC_{50} ~ 50 µM[284] IC_{50} = 30 µM[283] IC_{50} = 26 µM[285] IC_{50} = 38 µg/mL[281]	Zincin-like		
		arginine-specific gingipain(RgpB)	IC_{50} = 3 µM[286]	Immunoglobulin-like beta-sandwich / Caspase-like		
minocycline	tetracycline derivative	stomelysin (MMP-3)	IC_{50} = 290 µM[282]	Zincin-like	collagenase (MMP-1)[282]	Zincin-like
					gelatinase A (MMP-2)[282]	Zincin-like
WF-10129		ACE	IC_{50} = 14 nM[287] IC_{50} = 0.008 µM[119]	Zincin-like		

[a] Compounds in Italics are derivatives of natural products

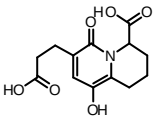
ancovenin

16 amino acid residues

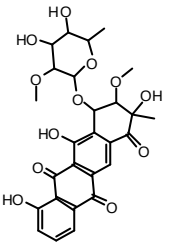
antibiotic A (58365A)



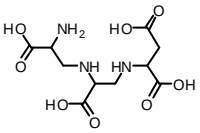
antibiotic A (58365B)



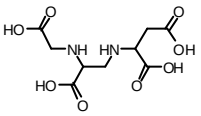
aranciamycin



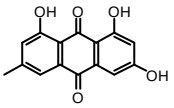
aspergillomarasmine A



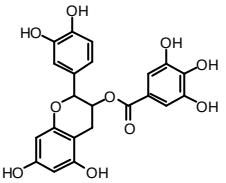
aspergillomarasmine B



emodin



epicatechin gallate



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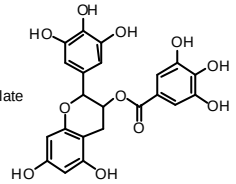
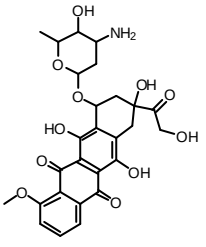
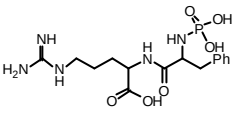


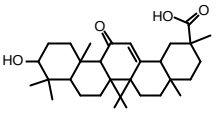
epirubicin



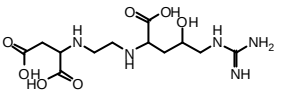
FMPI



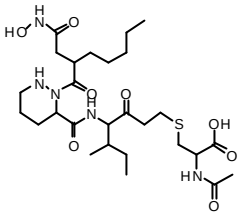
glycyrrhetinic acid



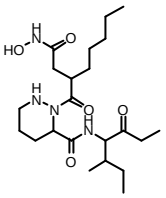
L-681,176



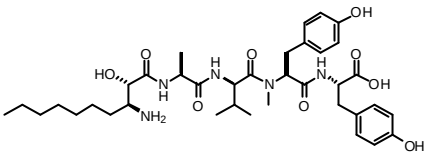
matlystatin A



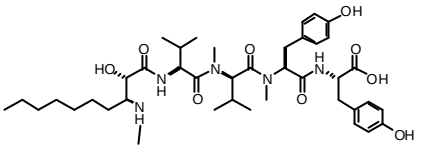
matlystatin B



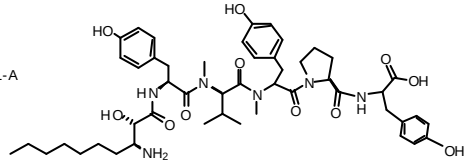
microginin



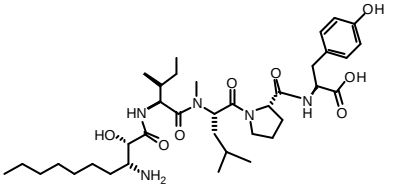
microginin 478



microginin 51-A



microginin 91-C



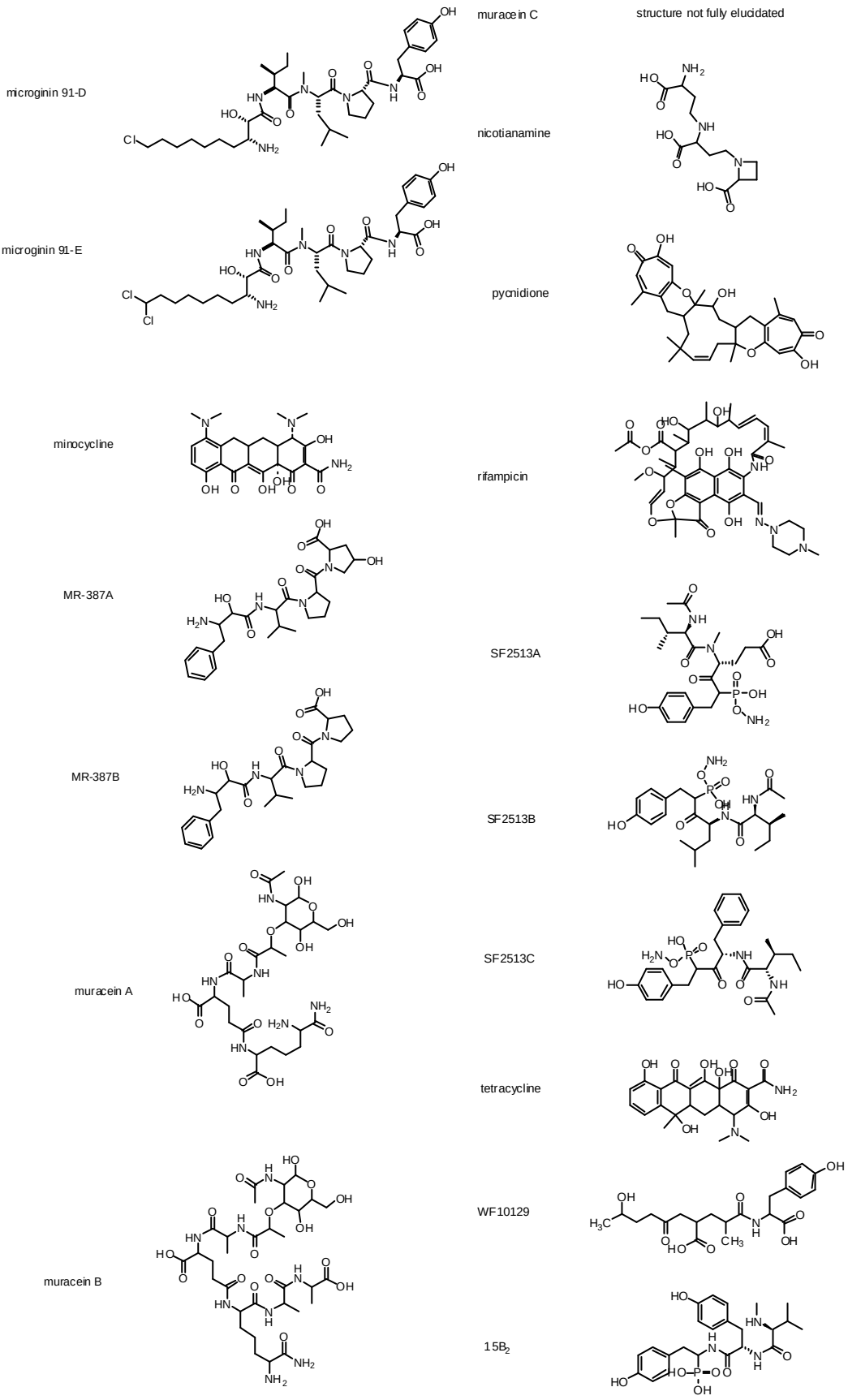
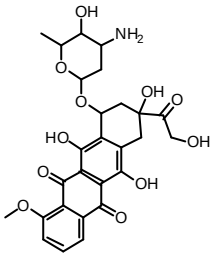
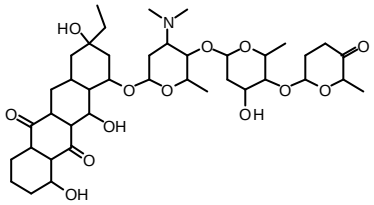


Figure S1. Structures of the 36 natural products known only to inhibit Zincin-like fold proteins.

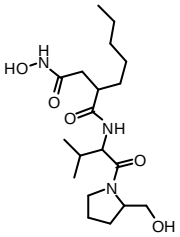
adriamycin



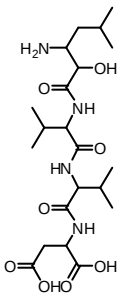
aclacinomycin A analog



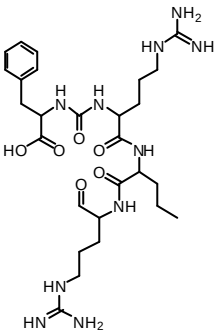
actinonin



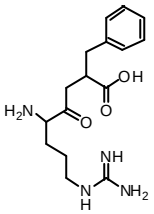
amastatin



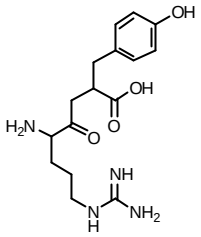
antipain



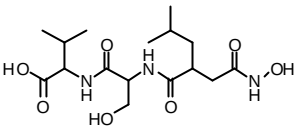
arphamenine A



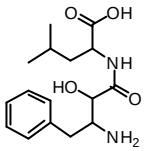
arphamenine B



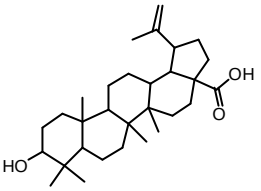
BE16627B



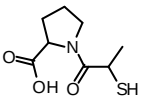
bestatin



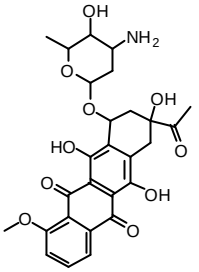
betulinic acid



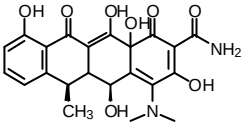
captopril



daunorubicin



doxycycline



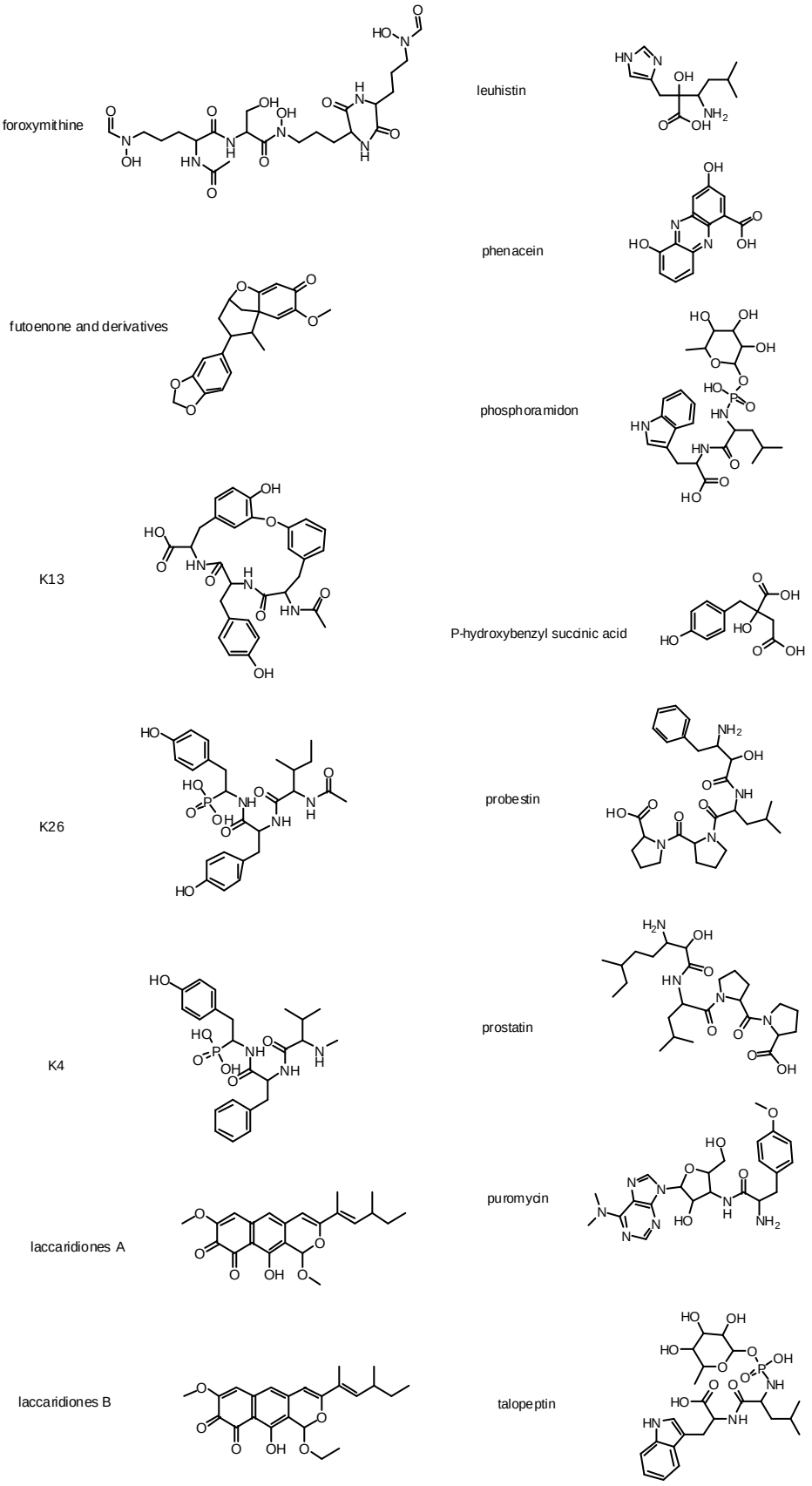


Figure S2. Structures of 28 natural products known to inhibit members of other fold types.

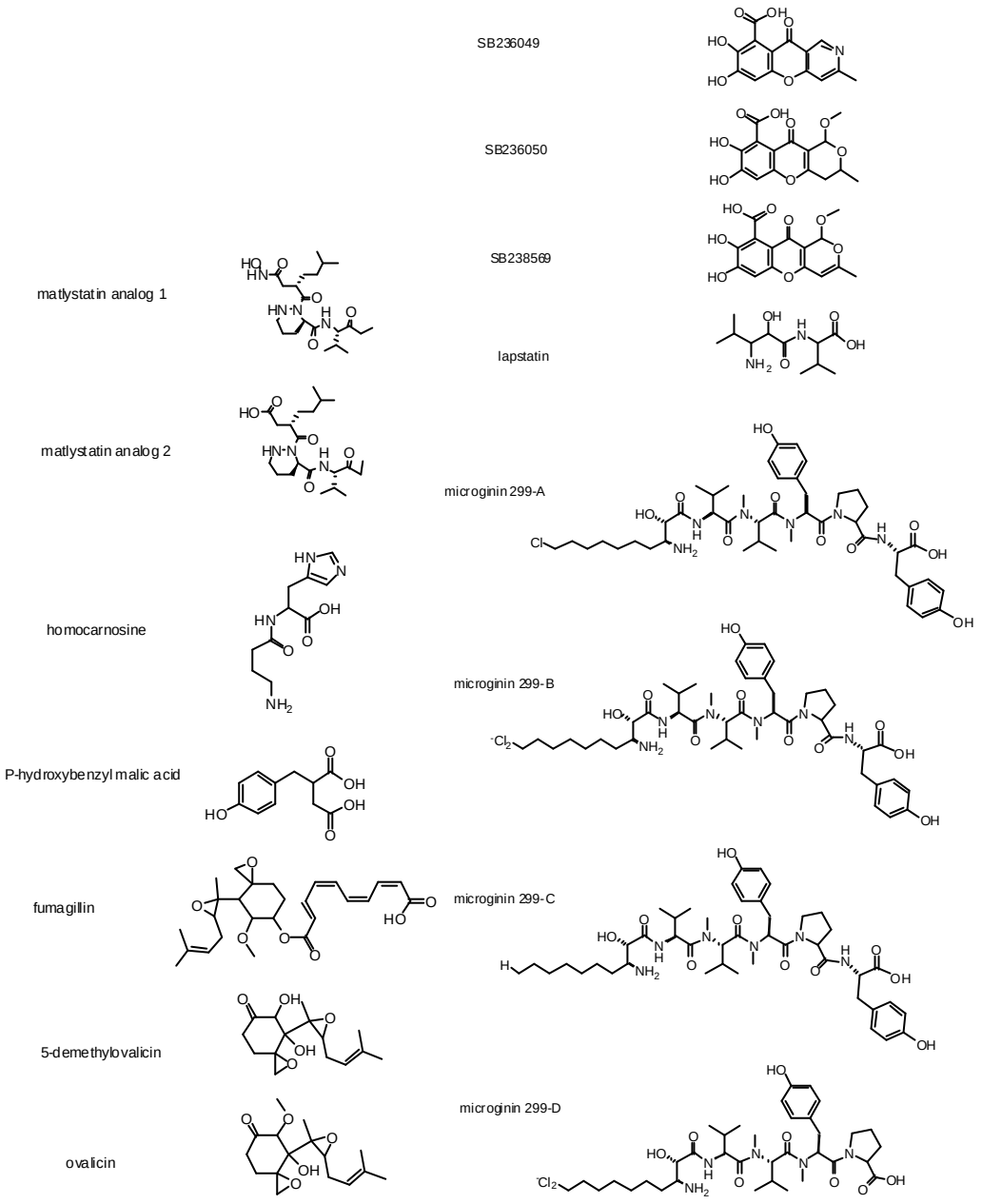


Figure S3. Natural products related to other fold types known not to inhibit some protein members of the Zincin-like fold (left). Natural products related to other fold types with no known Zincin-like fold activity (right).

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