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Heterologous expression of bacterial natural product biosynthetic pathways

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Table S1. Selected examples of heterologous expression of bacterial BGCs from 2013 to 2018

§Method: Heterologous expression method/s employed. Plas, Self-replicating plasmid; Hom, homologous recombination with insertion locus indicated in brackets; Tnps, Transposition; Int, Phage integration. *S. Streptomyces*; *Sti. Stigmatella*; *Ps. Pseudomonas*. †Yield: Yields relative to the native producer, ∞ indicates the compound was unable to be isolated from the native host. Actual yield from heterologous host in brackets. Comments: Promoters listed replaced the native promoter of the cluster. Where yields from the native producer were not reported in the expression paper, the approximate levels were determined from the literature

	Compound	Native host	Size	Cloning method	Heterologous host	Method§	Yield†	Comments *	Ref.
Known									
	Abyssomicin / Neoabyssomicin	*S. koyangensis* SCSIO 5802	62.9	PAC library	*S. coelicolor* M1152	Int	n.d.	Native cluster	1
	Actinoallolides	*Actinoallomurus fulvus* K09-0307	53	Cosmid library	*S. coelicolor* M1152	Int	n.d.	P_{ermE*} promoter	2
	Actinorhodin	*S. coelicolor* M145	26	Fosmid library	*S. albus* J1074	Int	n.d.	Gene deletion of *pfk* gene encoding phosphofructokinase, overexpression of *crp* gene encoding cAMP receptor protein from *S. coelicolor*	3
	Aloesaponarin II	*Frankia* sp. CcI3		Fosmid library	*S. albus* Del14	Int	n.d.	Engineered heterologous host	4
	Alterochromides (A **22**)	*Pseudoalteromonas piscicida* JCM 20779	34	TAR	*E. coli* BL21	Plas	n.d.	PPTase from *Pseudoalteromonas luteoviolacea* 2ta16 coproduced, KBr supplemented in media	5
	Amicoumacin A **24**	*Bacillus subtilis* 1779	47.4	TAR	*B. subtilis* JH6421	Hom (*amyE*)	similar	*lac* repressor *lacI* and an IPTG-inducible promoter, *sfp* (PPTase) co-expression	6
	Alpiniamides	*S.* sp. 2014/011-12	47.6	TAR	*S. lividans* TK24 and *S. albus* Del14	Int	n.d.	Native cluster	7
	Avermectins	*S. avermitilis ATCC* 31267	81	BAC library	*S. lividans*	Int	n.d.	Native cluster	8
	Bacillomycin	*B. amyloliquefaciens* FZB42	37.2	LLHR	*B. subtilis* 1A751	Hom (*amyE*)	n.d.	Sfp (PPTase) rescued in host	9
	Bengamides	*Myxococcus virescens* ST200611	25	Cosmid library	*Myxococcus xanthus* DK1622	Int	similar	Native cluster	10
	Bhimamycin A	*Frankia* sp. CcI3		BAC library	*S. albus* Del14	Int	n.d.	Engineered heterologous host	4
	Bicyclomycin	*Ps. aeruginosa* SCV20265 / *S.*	7	PCR + Gibson assembly	*Pseudomonas fluorescens* SBW25 / *S.*	Plas / Int	n.d.	Synthetic P_{tac} promoter / P_{ermE*} promoter	11

	cinnamoneus DSM 41675			*coelicolor* M1146/1152				
BM1157/BM1300	*Lactobacillus crustorum* MN047	0.2	PCR and ligation	*E. coli* BL21	Plas	n.d.	T7 promoter	12
Brasilicardin	*Nocardia terpenica* IFM 0406	13.1	Fosmid library	*Amycolatopsis japonicum*	Int	n.d.	P_{ermE*} promoter	13
Bottromycin A2 **7**	*S.* sp. BC16019	16	Cosmid library	*S. albus* J1074 and *S. lividans* TK24	Int	5–50 fold higher	Optimized the expression of genes in operons and created a library of modified gene clusters	14
Cacibiocin A/B	*Catenulispora acidiphila* DSM 44928	16.6	Cosmid library	*S. coelicolor* M1152	Int	↑ 12 fold (60 mg L^{-1})	Native cluster	15
Chaxamycin	*S. leeuwenhoekii*	80.2	PAC library	*S. coelicolor* M1152	Int	n.d.	P_{ermE} promoter	16
Chuangxinmycin **25**	*Actinoplanes tsinanensis*	11	LLHR	*Streptomyces spp*	Int	n.d.	Strong artificial promoter Virolle-a1-14	17
Clethramycin/mediomycin A	*S. mediocidicus* ATCC23936	180	BAC library	*S. lividans* TK24	Int	n.d.	P_{ermE} promoter	18
Corallopyronin A **16** Corallopyronin B **17**	*Corallococcus coralloides* B035	65	Cosmid library	*Myxococcus xanthus* DK1622	Int	↑ ca. 30 fold (37 mg L^{-1})	P_{nptII} promoter and media optimization	19
Cosmomycin (C **23**)	*S.* sp. CNT-302	54	TAR	*S. coelicolor* M512	Int	n.d.	Native cluster	20
Dawenol **20**	*Sti. aurantiaca* DW4/3-1	21	Subcloning via plasmid recovery	*Myxococcus xanthus* DK1622	Int	n.d.	Native cluster	21
6-Deoxyerythronolide B	*Saccharopolyspora erythraea*	30	Cosmid library	*Bacillus subtilis* JK13	Int	↓ 2.6 µg L^{-1}	Optimized RBS, P_{acoA} promoter, deletion of the *prpBD* operon responsible for propionyl-CoA degradation, feeding propionate precursor, *sfp* (PPTase) co-expression	22
Desotamides	*S. scopuliridis* SCSIO ZJ46	39	Cosmid library	*S. coelicolor* M1152	Int	n.d.	Native promoter	23
2,4-Diacetylphloroglucinol	*Ps. protegens* Pf-5 / *Ps.* sp. G22	3.8	PCR and ligation	*Pseudomonas* sp. WS5	Plas	↑ 7-fold (12–14 µg m L^{-1})	P_{lac} promoter	24
Disorazol A1 Disorazol A2	*Sorangium cellulosum* So ce12	58	BAC library	*Myxococcus xanthus* DK1622	Tpns	↑ 12-fold (0.7 mg L^{-1})	P_{tet} promoter, synthetic P_{cp25} promoter	25

Enterocin A	*Enterococcus faecium* T136	0.5	PCR and ligation	*Lactobacillus* spp.	Plas	↑ 4.9-fold (9.3 μg mg^{-1} cell dry weight)	Signal peptide SP_{usp45} fused to EntA, inducible promoter	26
Enterocin	*Salinispora pacifica* CNT-150	18	TAR	*S. coelicolor* M1146 / *S. lividans* TK23	Int	n.d.	Native cluster	27
Epothilone A **9** Epothilone B **10**	*Sorangium cellulosum So ce90*	56	Cosmid library + LCHR assembly	Burkholderiales sp. DSM 7029	Tnps	↑ 75-fold (0.3 mg L^{-1})	$P_{Tn5\text{-}kan}$/P_{tet} promoter, introduction of propionyl-CoA carboxylase (PCC) encoding genes from *Streptomyces coelicolor* A3(2), introduction of rare tRNA genes	28
Epothilone A **9** Epothilone B **10**	*Sorangium cellulosum* So0157-2	56	Cosmid library + LCHR assembly	*Myxococcus xanthus*	Int	↑ (21.8 mg L^{-1})	Tandem repeat engineering on the original promoter P_{epo}	29, 30
FK506	*S. tsukubaensis* NRRL 18488	83.5	PAC library	*S. coelicolor* M1146	Int	n.d.	*ermE** promoter, overexpression of the LuxR regulatory gene *fkbN*	31
Fostriecin	*S. pulveraceus* ATCC 31906	48.4	Cosmid library + LCHR assembly	*S. lividans* TK24	(2 parts) Int and Plas	n.d.	$P_{act\ I}$ promoter	32
FR900359 **26**	*Burkholderia crenata*	11.7	BAC library	*E.coli* BL21 *and* BAP1	Plas	n.d.	Constitutive promoter *pS7*	33
Galbonolide	*S.* sp. LZ35	11.8	PCR and ligation	*S. coelicolor* ZM12	Int	n.d.	P_{ermE*} promoter	34
Glidobactin	Burkholderiales sp. DSM7029	25	LLHR	*E. coli* Nissle 1917	Plas	n.d.	P_{tet}/P_{BAD} promoter	35
Grecocycline	*S.* sp. Acta 1362	36	PCR + TAR assembly	*S. albus* J1074	Int	n.d.	Mutations in genes due to PCR, detect several biosynthetic intermediate	36
Haliangicin	*Haliangium ochraceum SMP-2*	47.8	Cosmid library	*M- xanthus*	Int	↑ 10-fold higher	Native cluster	37
Hapalosin **5**	*Fischerella sp. PCC 9431*	23	DiPaC + SLIC	*E. coli* BAP1	Plas	n.d.	T7 promoter, *sfp* (PPTase) co-expression	38
Herbicidin	*S.* sp. L-9-10	26	Cosmid library	*S. albus* J1074	Int	n.d.	Native cluster	39
Ikarugamycin A **21**	*S.* sp. Tü 6239	33	Fosmid library	*E. coli* BAP1	Plas	n.d.	T7 promoter, *sfp* (PPTase) co-expression	40
Kinamycin	*S. galtieri* Sgt26	75	BAC library	*S. albus* J1074	Int	n.d.	Native cluster	41
Kocurin **28**	*Kocuria flava* HO-9041	12	PCR and Gibson	*S. coelicolor* M1146	Int	n.d.	P_{ermE*} promoter	42

			assembly					
Lactococcin Z	*Lactococcus lactis* QU 7	5.1	PCR and ligation	*Lactococcus lactis* NZ9000	Plas	n.d.	Native cluster	43
Lasso peptides	Marine *Actinobacteria*	2–3	PCR and Gibson assembly	*Streptomyces* spp.	Int	n.d.	$P_{A127\text{-}LP}$ promoter, co-expression of gene encoding *Streptomyces* antibiotic regulatory protein (SARP)	44
Lyngbyatoxin A **12**	*M. producens*	11.3	TAR/Red-ET recombineering	*Anabaena* sp. PCC 7120	Plas	↑ 13-fold	P_{glnA} promoter and media optimization	45
Matlystatin	*Actinomadura atramentaria* DSM 43919	24.1	Fosmid library	*S. coelicolor* M1154	Int	n.d.	Native cluster	46
Microcystin-LR [d-Asp^3]microcystin-LR	*Microcystis aeruginosa* PCC 7806	55	Fosmid library/LCHR	*E. coli* GB05-MtaA	Plas	↑ ca. 2–3 fold	P_{tetO} promoter, *mtaA* (PPTase) co-expression	47
Mithramycin A **13**	*S. argillaceus* ATCC12956	45	TAR	*S. lividans* TK24	Int	↑ ca. 20 fold (3 g L^{-1})	Deletions of secondary metabolite gene clusters from *S. lividans* TK24	48
Mycosporine-2-(4-deoxygadusolyl-ornithine)	*Nostoc flagelliforme* CCNUN1	8.19	PCR and ligation	*Anabaena* sp. PCC 7120	Plas	n.d.	Native cluster	49
Mycosporine-Ornithine / Mycosporine-Lysine	*Cylindrospermum stagnale* PCC 7417	6.23	PCR and ligation	*E. coli* BL21(DE3)	Plas	n.d.	T7 promoter, rare tRNA genes co-expresssed	50
Myxopyronin A **14** Myxopyronin B **15**	*Myxococcus fulvus* Mxf50	53	Subcloning via plasmid recovery	*Myxococcus xanthus* DK1622	Int	↑ ca. 20-fold (156 mg mL^{-1})	P_{nptII} promoter and media optimization	19
Napsamycin	*S.* sp. DSM5940	38.6	Cosmid library	*S. coelicolor* M1154	Int	n.d.	Native cluster	51
Nataxazole / AJ9561	*S.* sp. Tü 6176	68.4	TAR	*S. lividans* JT46	Int	n.d.	Native cluster	52
Nematophin	*Xenorhabdus nematophila* ATCC 19601	4.1	PCR + Gibson assembly	*E. coli* DH10BMtaA	Plas	~ 1 mg L^{-1}	P_{BAD} promoter, precursor feeding	53
Oxytetracycline	*S. rimosus* M4018	29	Fosmid library	*S. venezuelae* WVR2006	Int	Similar (431 mg L^{-1})	Engineering two cluster-situated regulators (CSR) OtcR and OtrR and feeding precursor, P_{ermE*} and *kasOp** promoter	54
Plantaricyclin A	*Lactobacillus plantarum* NI326	3.17	PCR and ligation	*Lactococcus lactis* NZ9000	Plas	n.d.	Native cluster	55

Pikromycin	*S. venezuelae* ATCC15439	60	Ligation-based plasmid rescue	*S. lividans / S. coelicolor*	Int	↑ 2.1 fold (333.7 mg L^{-1})	Tandem repeat of the *pik* gene cluster	56
Pyridinopyrone A **27**	*S. albus* subsp. *Chlorinus* NRRL B-24108		BAC library	*S. albus* Del14	Int	n.d.	Solid medium, engineered heterologous host	4
Salinomycin	*S. albus* DSM41398	106	LLHR + LCHR	*S. coelicolor A3(2)*	Int	n.d.	Assembly of native BGC from three DNA fragments into a BAC vector	57
Septacidin **1**	*S. fimbriatus* CGMCC 4.1598	24	CATCH	*S. albus* J1074	Int	n.d.	Native cluster	58
Spinosad	*Saccharopolyspora spinosa* NRRL 18395	80	BAC library	*S.albus* J1074 *and S. lividans* TK24	Int	1.46 mg L^{-1}	*kasOp**, *rpsL-TP* and *rpsL-cf* promoter	59
Spinosad	*Saccharopolyspora spinosa* ATCC 49460	80	Cosmid library and iterative recombination to replace erythromycin PKS genes with the spinosad BGC	*Saccharopolyspora erythraea* ATCC 40137	Int	↑ 40 fold (830 mg L^{-1})	Native erythromycin polyketide synthase (PKS) genes in *S. erythraea* were replaced by the assembled spinosad gene cluster, overexpression of the rhamnosyltransferase, duplication of rhamnose biosynthesis genes, UV mutagenesis, *sfp* (PPTase) co-expression	60
Streptoseomycin	*S. seoulensis* A01	76	BAC library	*S. chartreusis* 1018	Int	n.d.	Native cluster	61
Streptothricin	*S.* sp. strain fd1-xmd	41.8	Plasmid rescue	*S. coelicolor* M1146	Int	n.d.	Native cluster	62
Syringolin	*Ps. syringae* pv. *syringae* (Pss) B728a	22	LLHR	*S. coelicolor* M145 / *S. lividans* TK24	Tnps	n.d.	P_{snpA} promoter	63
Tautomycetin	*S. sp.* CK4412	80	Ligation-based plasmid rescue	*S. coelicolor* M145	Int	↑ 5.4 fold (13.31 mg L^{-1})	Tandem repeat of the *tmc* gene cluster	64
Telomestatin	*S. anulatus* 3533-SV4	19	BAC library	*S. avermitilis* SUKA	Int	n.d.	$P_{sav2794}$ promoter	65
Telomycin	*S. canus* ATCC 12646	80.5	BAC library	*S. albus* J1074	Int	n.d.	Native promoter	66
Thaxtomins	*S. scabiei* 87.22	18	TAR	*S. albus* J1074	Int	↑10-fold (222 mg L^{-1})	Medium optimization	67
Thaxtomins	*S. scabiei*	18	Gibson	*S. albus*	Int	n.d.	Biotransformation step utilizing	68

				assembly				promiscuous tryptophan synthase (TrpS) from *Salmonella typhimurium* to produce 4-substituted L-tryptophans, and fed to a *S. albus* strain possessing the NRPS TxtA and TxtB to established a *de novo* biosynthesis of unnatural thaxtomin derivatives	
	Thiolactomycin	*Lentzea* sp. ATCC 31319	13.7	PCR + Gibson assembly	*S. lividans* TK24	Int	Similar	Native cluster	[69]
	Thiolactomycin	*S. pacifica* CNS-863	22	TAR	*S. coelicolor* M1152	Int	n.d.	Native cluster	[70]
	Thiostreptamide S4	*S.* sp. NRRL S-4	19	TAR	*S. coelicolor* M1146	Int	n.d.	Native cluster	[71]
	Thioviridamide	*S. olivoviridis* NA05001	16.5	PCR and ligation	*S. lividans* TK23	Int	n.d.	Native cluster	[72, 73]
	Tilivalline	*Klebsiella oxytoca*	17	TAR	*E. coli* BL21	Plas	n.d.	P_{tet} and P_{BAD} promoter, tryptophanase TnaA of *K. oxytoca,* precursor feeding	[74]
	Tilivalline	*Xenorhabdus indica*	17	TAR	*E. coli* DH10B-MtaA	Plas	n.d.	P_{BAD} promoter, *mtaA* (PPTase) co-expression, precursor feeding	[75]
	Vancoresmycin	*Amycolatopsis* sp. ST 101170	141	PAC library	*S. coelicolor* M1152	Int	n.d.	Native cluster	[76]
	Violacein	*Pseudoalteromonas luteoviolacea* 2ta16	8	TAR	*Pseudomonas putida* KT2440 *Agrobacterium tumefaciens* LBA4404	Plas	~15 mg L^{-1} 10 mg L^{-1}	Native cluster	[77]
	Vioprolides A **11**	*Cystobacter violaceus* Cb vi35	56	Cosmid library + LCHR assembly	*Myxococcus xanthus* DK1622 Burkholderiales strain DSM7029 *Pseudomonas putida* KT2440	Hom (*tetR* site) Tnps	↑ ca. 100 fold (500 mg L^{-1})	P_{tn5} promoter	[78]
	YM-216391	*S. nobilis*	13	Cosmid library	*S. coelicolor* M1146-M1546	Int with multiple *attB* sites	36.4 mg L^{-1}	One integrase-multiple *attB* sites (up to four)	[79]
Novel									
	8D1-1 **29**, 8D1-2 **30**	*S. rochei*	81	LEXAS	*S. lividans* SBT5	Int	n.d.	Native cluster	[80]
	Ambactin **44**	*Xenorhabdus miraniensis* DSM	20	ExRec	*E. coli* DH10B	Plas	n.d.	*mtaA* (PPTase) co-expression, T7 promoter	[81]

	17902							
Burrioglumin A **42** Burrioglumin B **43**	*Burkholderia glumae* PG1	41	LLHR	*E.coli* GB05-MtaA	Plas	n.d.	P_{tet} promoter, MtaA (PPTase) in heterologous host	82
Clifednamide C **53**	*S.* sp. JV178		PCR and ligation	*Streptomyces* sp. strain NRRL F-2890	Int	n.d.	P_{ermE*} promoter, *cftA* heterologous expression	83
Combamides (E **39**, F **40**)	*S.* sp. S10	15	Fosmid library	*Streptomyces* sp. SR111	Int	n.d.	*kasOp** promoter	84
Fluostatin L **31**/difluostatin A **32**	*Micromonospora rosaria* SCSIO N160	40	Cosmid library	*S. coelicolor* YF11	Int	n.d.	Native cluster	85
Fontizine A **5**	*Serratia fonticola* DSM 4576	9.7	DiPaC	*E. coli* BAP1	Plas	n.d.	T7 promoter	86
Fralnimycin **8**	*Frankia alni* strain ACN14a		Fosmid library	*S. albus* Del14	Int	n.d	Native cluster, engineered host	4
Lavendiol **46**	*S. lavendulae* FRI-5	55.1	Cosmid library	*S. avermitilis* SUKA22	Int	n.d.	Native cluster	87
Neothioviridamide **48**	*S. olivoriridis* NA05001	13	BAC library	*S. avermitilis* SUKA22	Int	n.d.	Native cluster	88
Nevaltophins (A **47**)	*Xenorhabdus* PB62.4 / *Xenorhabdus* mirianensis DSM17902	12.6	PCR + Gibson assembly	*E. coli* DH10B-MtaA	Plas	~ 1 mg L^{-1}	P_{BAD} promoter, precursor feeding	53
Pactamides (A **38**)	*S. pactum* SCSIO 02999	14.8	Cosmid library	*S. lividans* TK64,	Int	n.d.	P_{ermE*} promoter	89
Pepteridines (A B)	*Photorhabdus luminescens* TT01		PCR + ligation	*E. coli* BAP1	Plas	n.d.	T7 promoter	90
Polycyclic tetramate macrolactam (SGR810–815)	*S. griseus*	18	DNA assembler	*S. lividans*	Int	n.d.	Six constitutive promoters inserted upstream of SGR genes	91
Pyxidicyclines (B **4**)	*Pyxidicoccus fallax An d48*	33.7	PCR + TAR assembly	*Myxococcus xanthus* DK1622, *Sti. aurantiaca* DW4/3-1	Int	n.d.	P_{tn5} promoter, P_{van} promoter	92
Sevadicin **41**	*Paenibacillus larvae*	11.6	LLHR	*E. coli* GB05-MtaA	Plas	n.d.	P_{BAD} promoter, swap start codon from TTG to ATG along with RBS insertion, *mtaA* (PPTase) co-expression	93
Taromycin A **2**	*Saccharomonospora* sp. CNQ-490	67	TAR	*S. coelicolor* M512	Int	n.d.	Native cluster	94
Taromycin B **3**	*Saccharomonospora* sp. CNQ-490	67	TAR	*S. coelicolor* M1146	Int	n.d.	Native cluster	95
Thiotetroamides	*S. afghaniensis* NRRL 5621	29	TAR	*S. coelicolor* M1152	Int	n.d.	Native cluster	70
Violapyrones (**33-37**)	*S. somaliensis* SCSIO	1.2	PCR and	*S. coelicolor* M1146	Int	n.d.	P_{gapDH} promoter	96

		ZH66		ligation					
	Xenolindicin A **45**	*Xenorhabdus indica* DSM 17382	20	ExRec	*E. coli* DH10B-MtaA	Plas	n.d.	*mtaA* (PPTase) co-expression, T7 promoter	81
Metage-nomics									
	Arenimycin C **58** Arenimycin D **59**	eDNA collection	40	Cosmid library + TAR assembly	*S. albus*	Int	n.d.	Native cluster	97
	Arimetamycin A **60**	eDNA collection	40	Cosmid library	*S. albus*	Int	n.d.	P_{ermE*} promoter	98
	Arixanthomycin A **57**	eDNA collection	33	Cosmid library + TAR assembly	*S. albus*	Int	n.d.	Native cluster	99
	Calixanthomycin A	eDNA collection	50	Cosmid library + TAR assembly	*S. albus*	Int	n.d.	Native cluster	97
	Clarepoxcins A–E (A **61**)	eDNA collection	25	Cosmid library	*S. albus*	Int	n.d.	Native cluster	100
	Divamide A **66**	eDNA collection	12	Illumina library	*E. coli* DH10β	Plas	n.d.	Native cluster	101
	Hydroxysporine **55**	eDNA collection	3.2	Cosmid library	*S. albus*	Int	n.d.	Native cluster	102
	Landepoxcin A **62** and B	eDNA collection	25	Cosmid library	*S. albus*	Int	n.d.	Native cluster	100
	Lazarimides A and B	eDNA collection	25	Cosmid library + TAR assembly	*S. albus*	Int	n.d.	Promoter engineering	103
	Malacidin A **64** Malacidin B **65**	eDNA collection	69.2	Cosmid library + TAR assembly	*S. albus* J1074	Int	n.d.	Native cluster	104
	Metatricycloene **63**	eDNA collection	n.d.	Cosmid library	*S. albus*	Int	n.d.	Native cluster	105
	Methylarcyriarubin **54**	eDNA collection	5	Cosmid library	*E. coli* BL21	Plas	n.d.	T7 promoter, indole-3-pyruvic acid (IPA) imine synthase *vioA* co-expression	106
	Polybrominated diphenyl ether	eDNA collection	n.d.	Metagenomic library	*Synechococcus elongatus* PCC 7942	Int	n.d.	Introduction of synthetic promoter–riboswitch system	107
	Reductasporine **56**	eDNA collection	n.d.	Cosmid library	*S. albus*	Int	n.d.	Native promoter	102

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