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**Van Arnam et al.**

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(54) **ANTIFUNGAL COMPOUNDS**

(71) Applicants: **President and Fellow of Harvard College**, Cambridge, MA (US); **Wisconsin Alumni Research Foundation**, Madison, WI (US); **Universidad de Costa Rica**, San José (CR)

(72) Inventors: **Ethan Van Arnam**, Somerville, MA (US); **Clarissa Sit**, Brookline, MA (US); **Antonio Ruzzini**, Brookline, MA (US); **Jon Clardy**, Jamaica Plain, MA (US); **Cameron Currie**, Madison, WI (US); **Adrian Alberto Pinto-Tomas**, San José (CR)

(73) Assignees: **President and Fellows of Harvard College**, Cambridge, MA (US); **Wisconsin Alumni Research Foundation**, Madison, WI (US); **Universidad de Costa Rica**, San José (CR)

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§ 371 (c)(1),

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PCT Pub. Date: **Dec. 7, 2017**

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**Related U.S. Application Data**

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(51) **Int. Cl.**

**C07H 17/08** (2006.01)

**C12P 19/62** (2006.01)

**C12N 15/52** (2006.01)

**A61P 31/10** (2006.01)

(52) **U.S. Cl.**

CPC ..... **C07H 17/08** (2013.01); **A61P 31/10** (2018.01); **C12N 15/52** (2013.01); **C12P 19/62** (2013.01)

(58) **Field of Classification Search**

CPC ..... **C07H 17/08**

USPC ..... **549/415**

See application file for complete search history.

(56) **References Cited**

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International Search Report and Written Opinion for International Application No. PCT/US2017/035697 dated Oct. 19, 2017.

*Primary Examiner* — Taofiq A Solola

(74) *Attorney, Agent, or Firm* — Foley Hoag LLP

(57) **ABSTRACT**

Compounds of formula (I) or formula (II), compositions and methods useful for treating and/or preventing a fungal infections are provided. wherein the substituents are as defined in the appended claims.

**9 Claims, 54 Drawing Sheets**

Figure 1

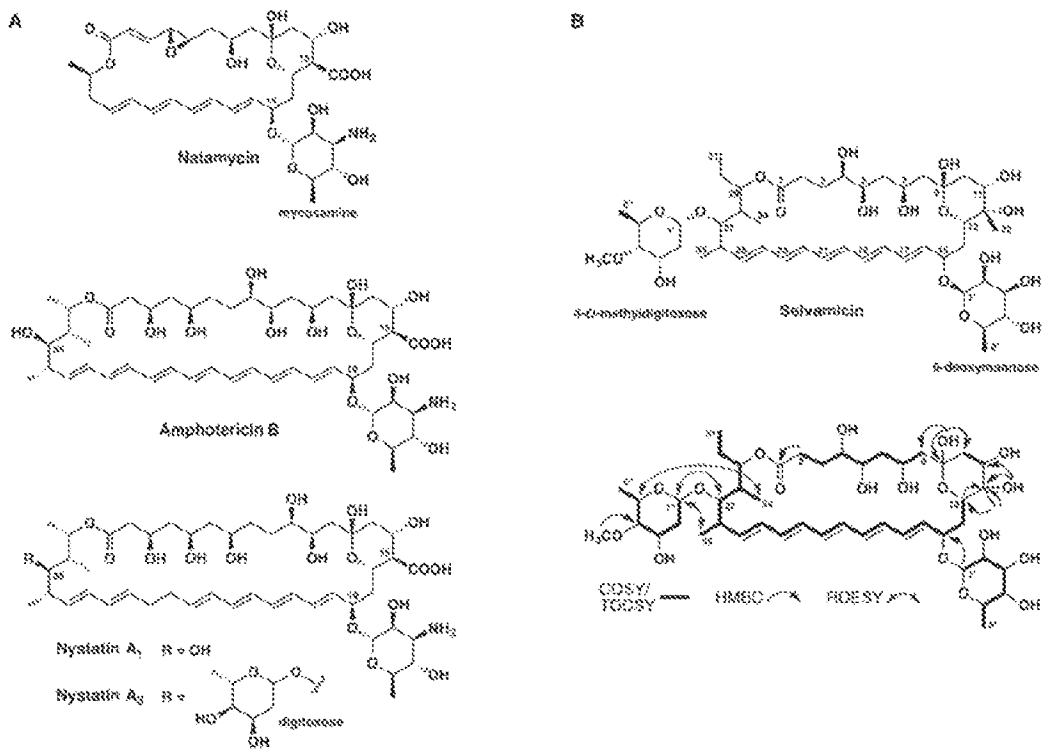


Figure 2

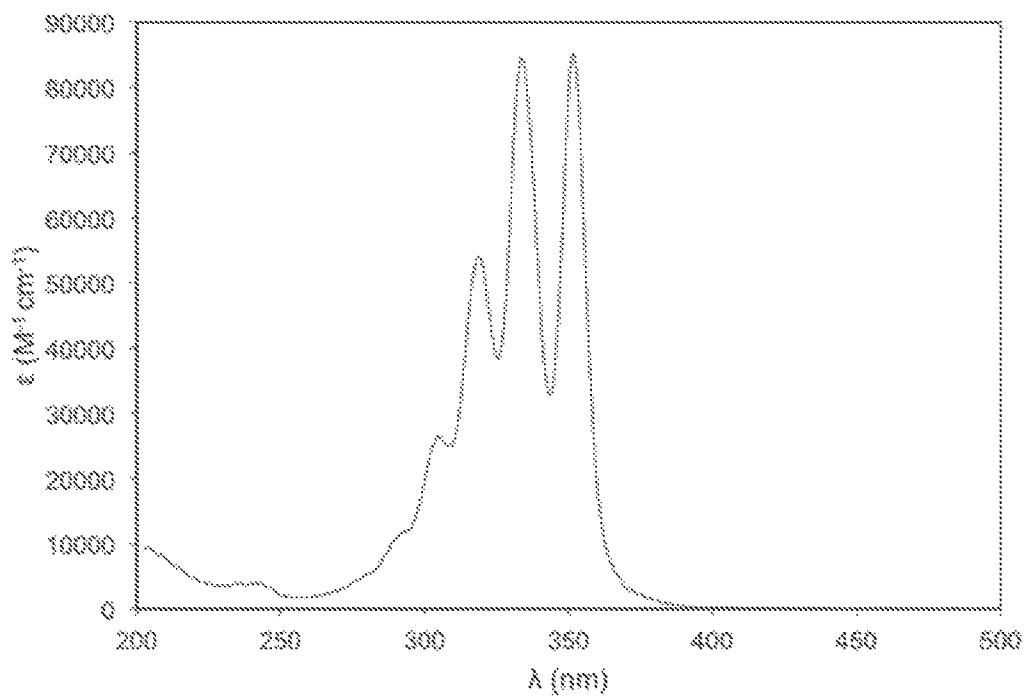


Figure 3

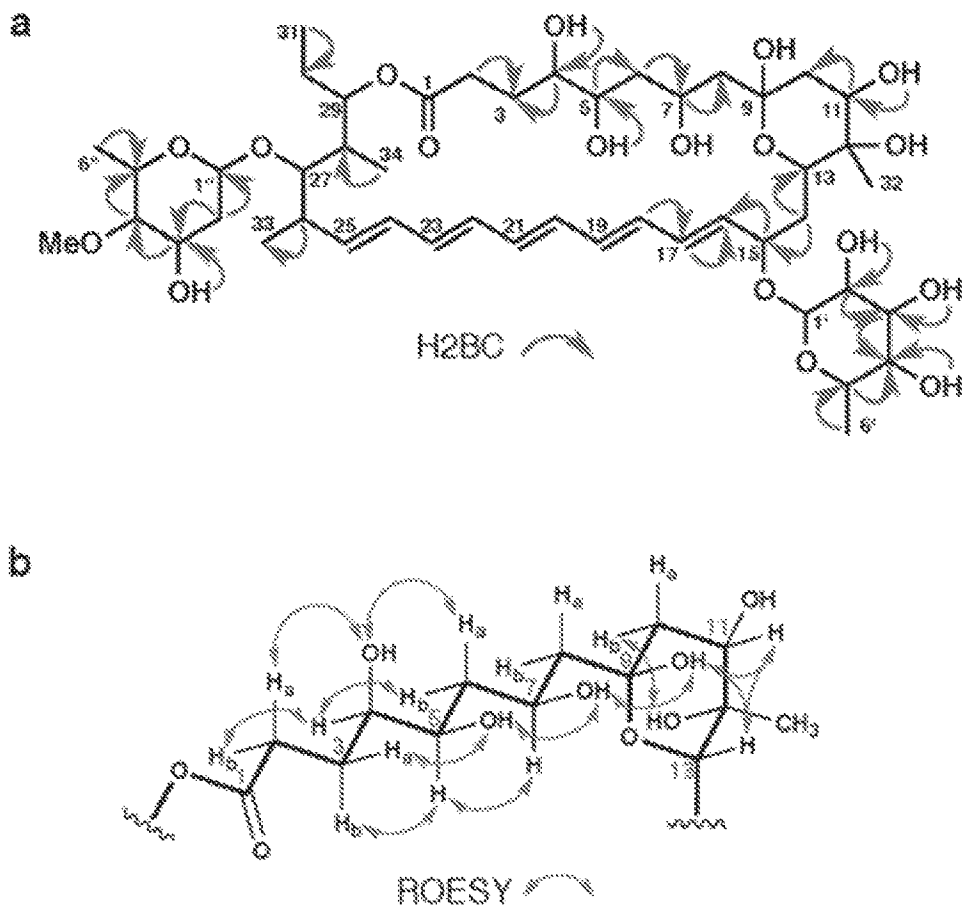


Figure 4

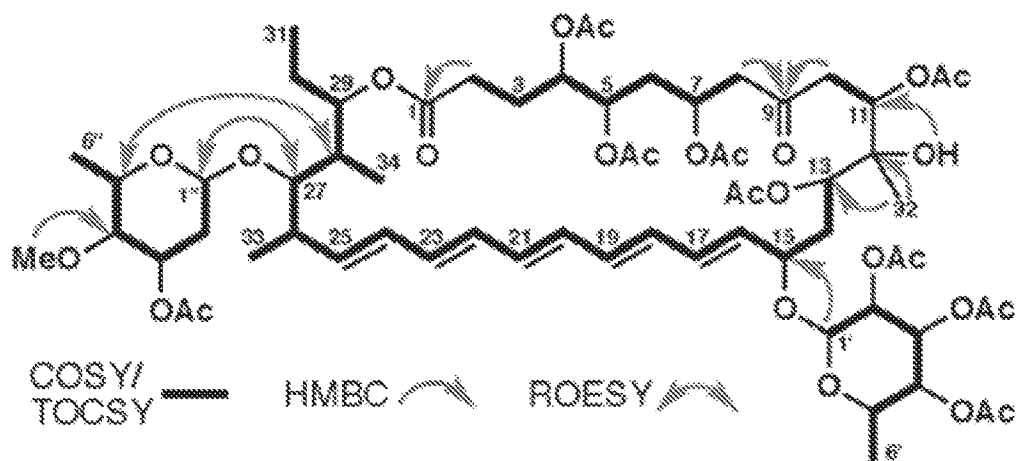


Figure 5

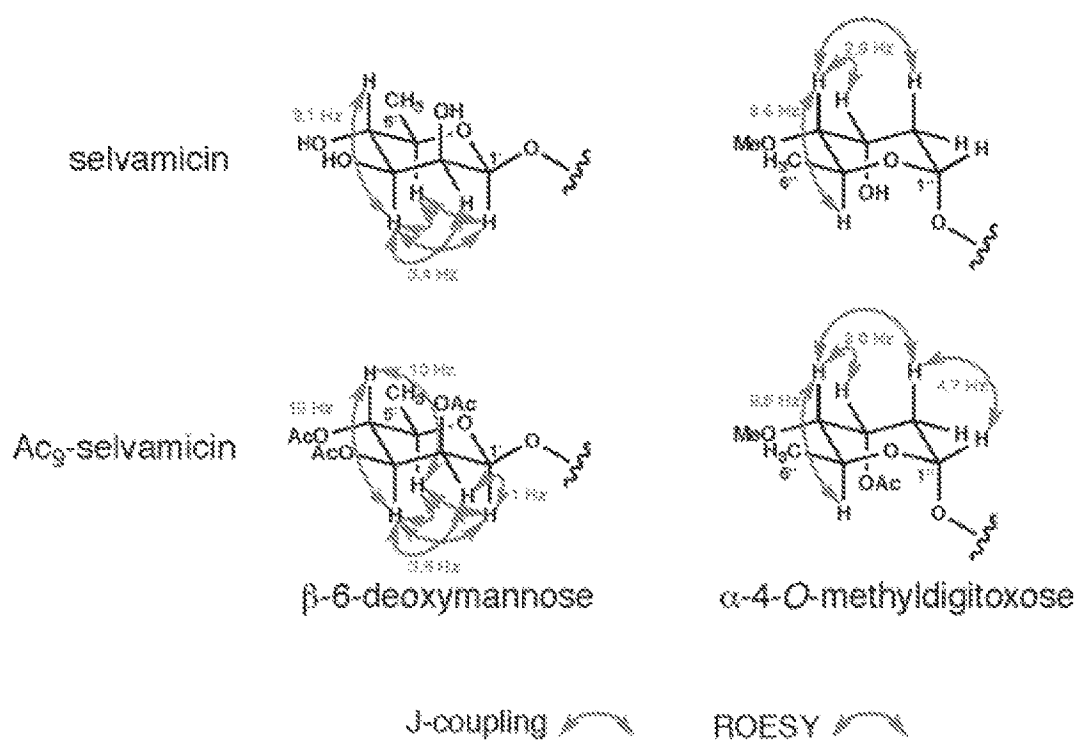


Figure 6

A

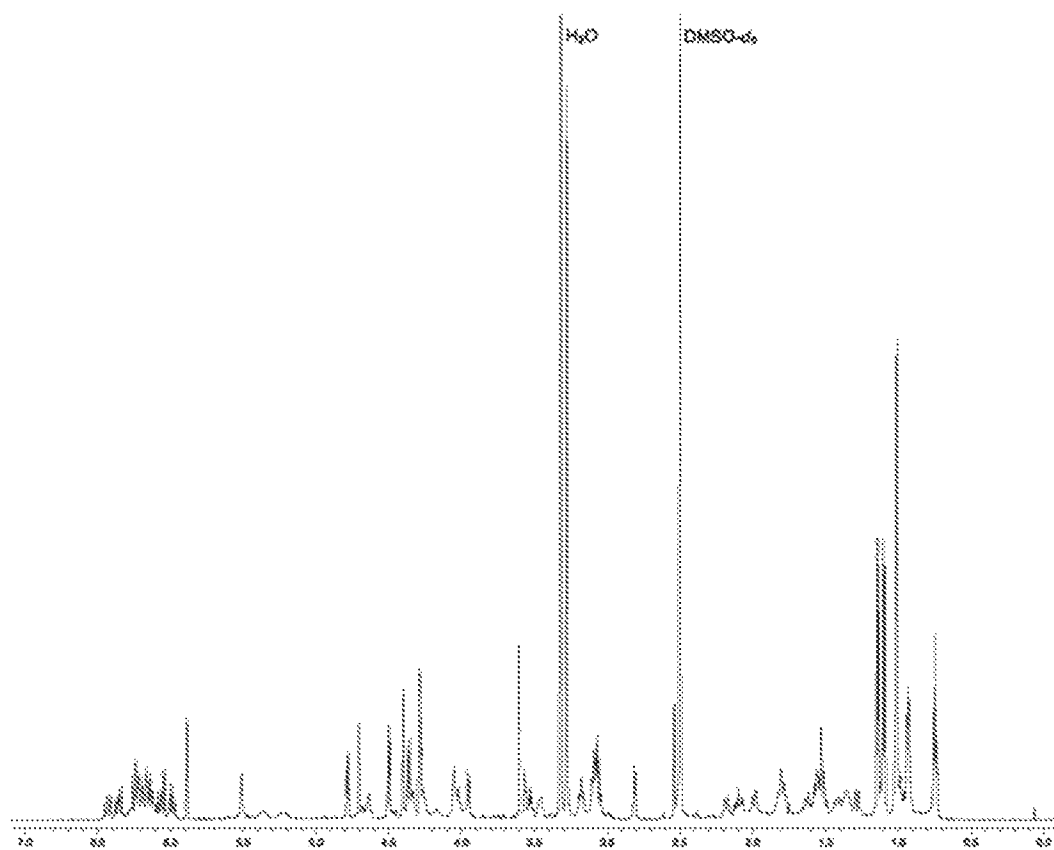


Figure 6 (Continued)

B

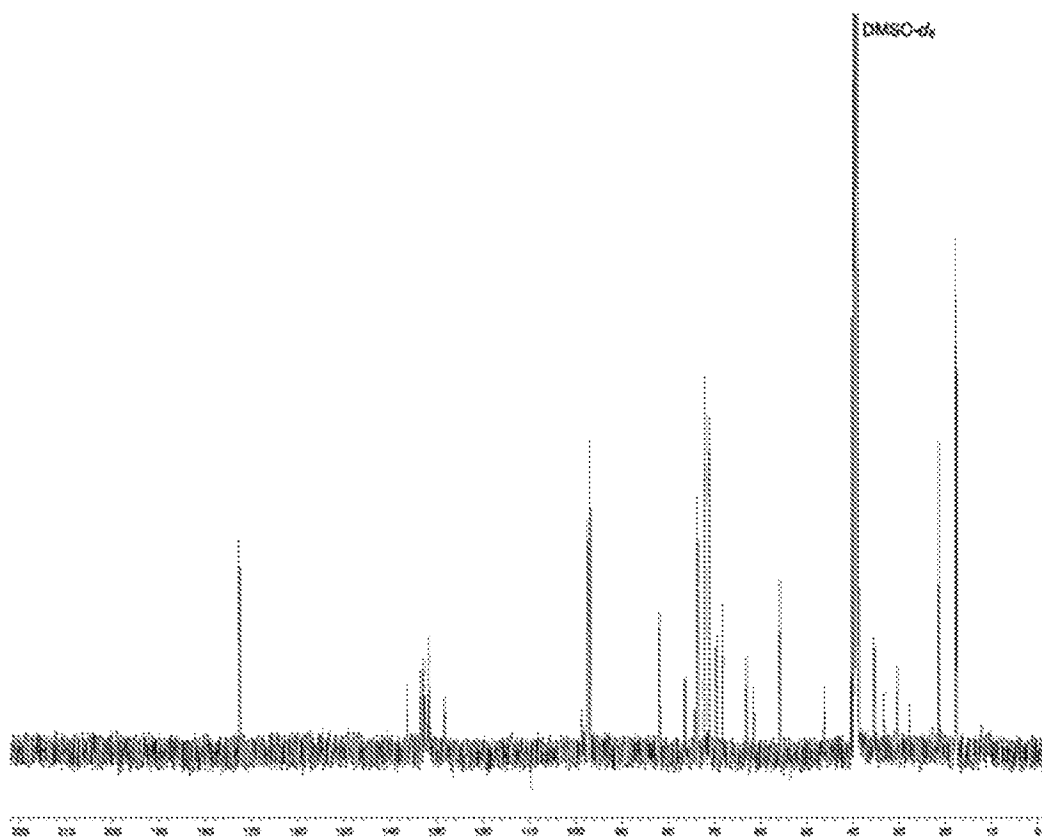




Figure 6 (Continued)

C

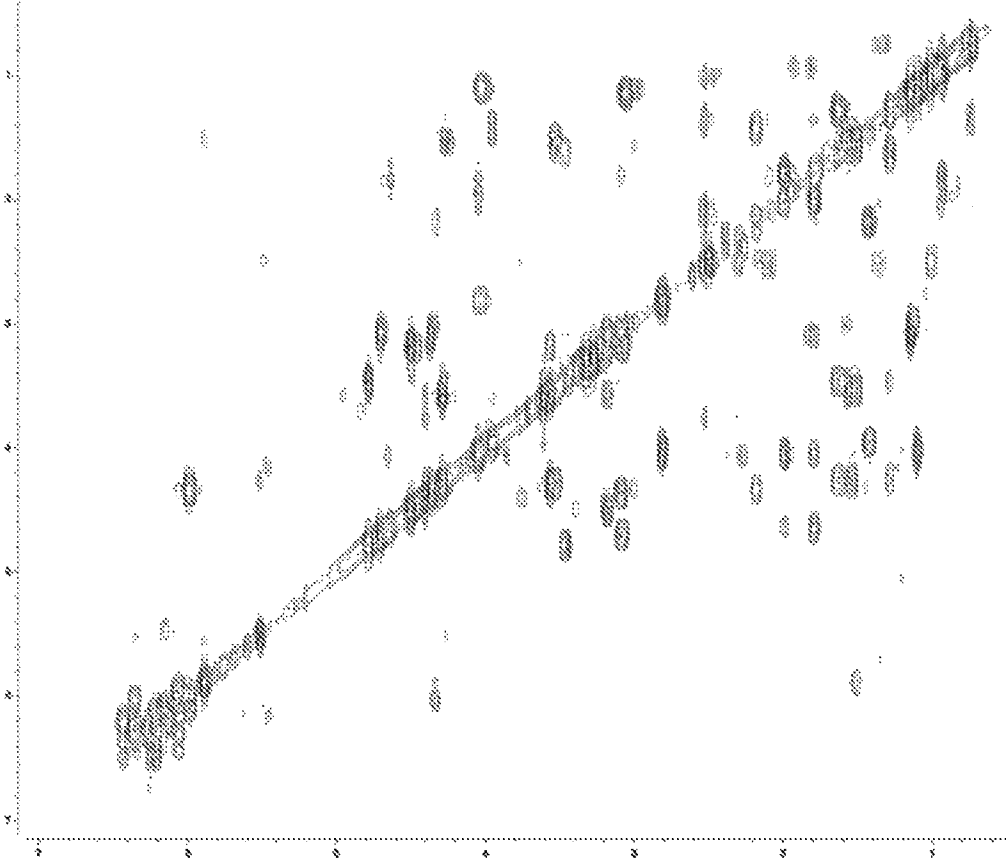


Figure 6 (Continued)

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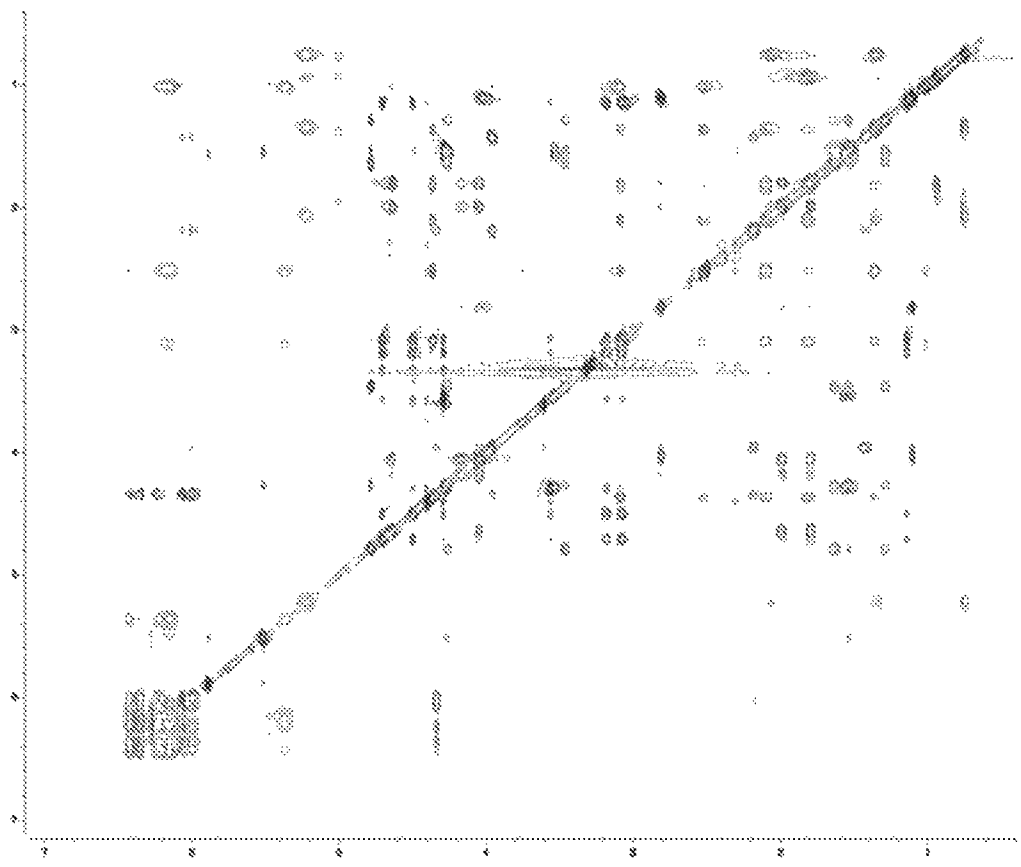


Figure 6 (Continued)

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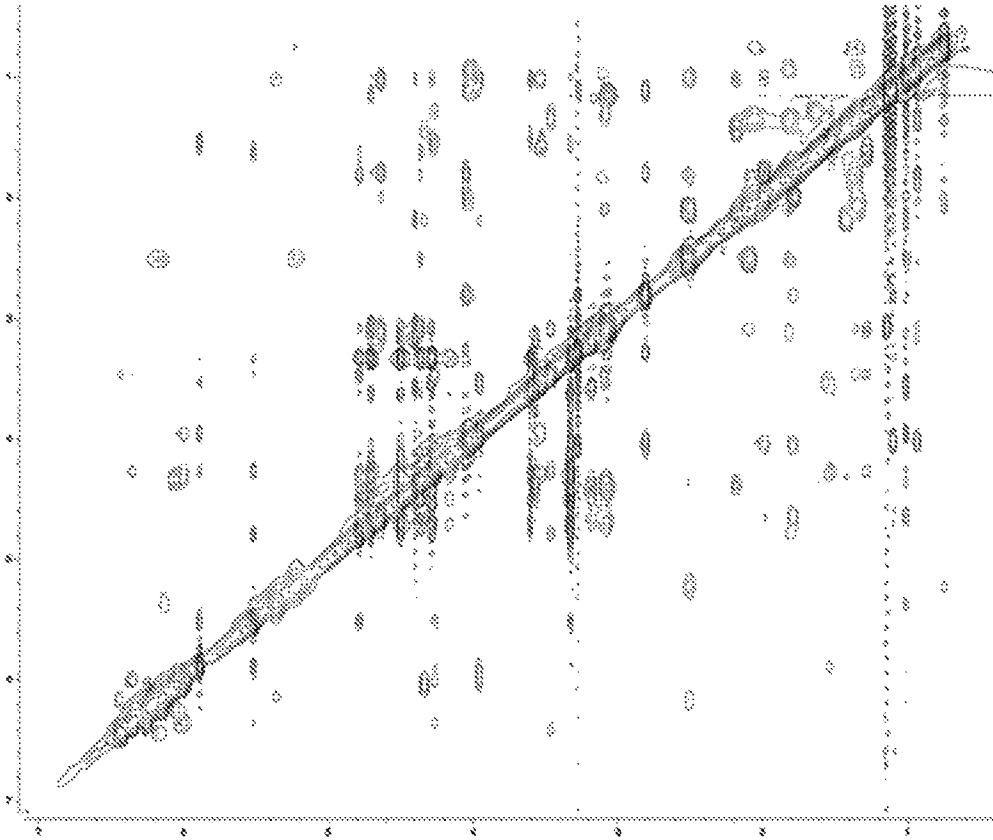


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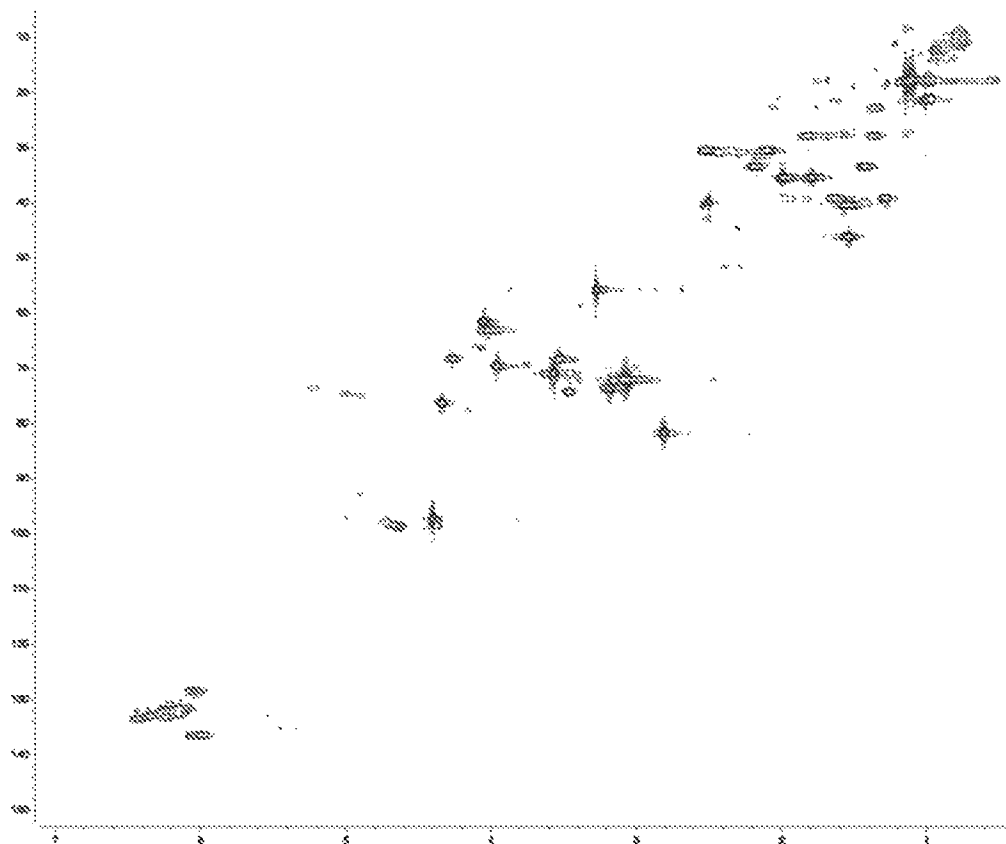


Figure 6 (Continued)

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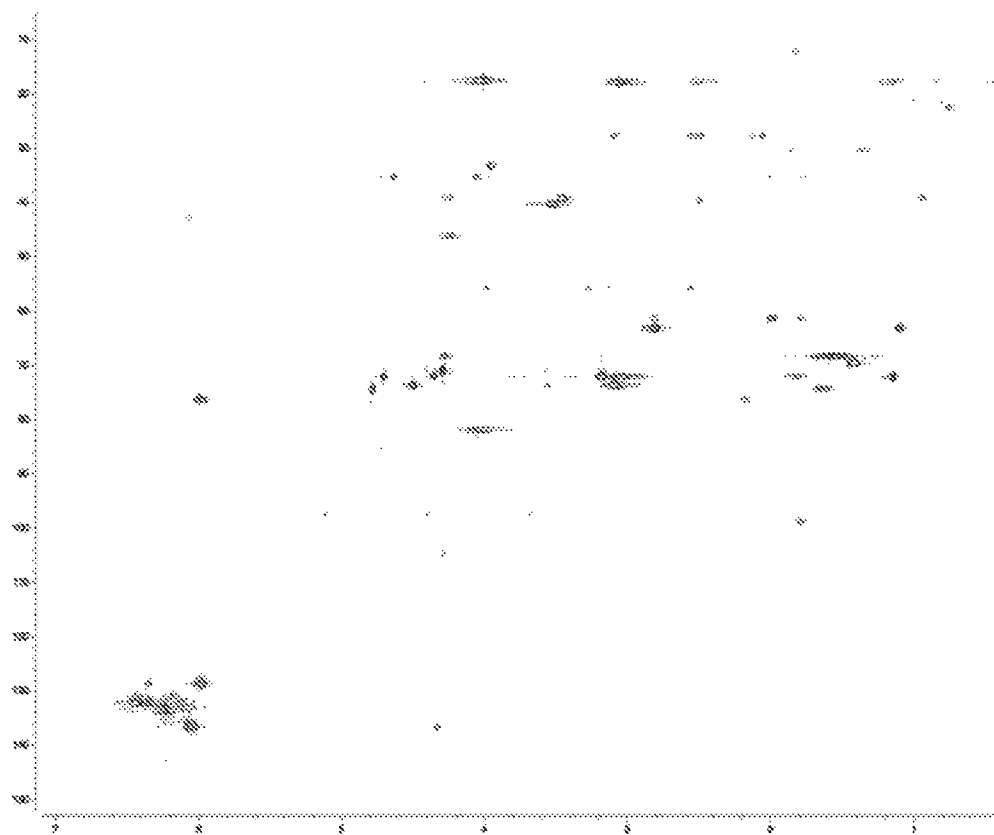


Figure 6 (Continued)

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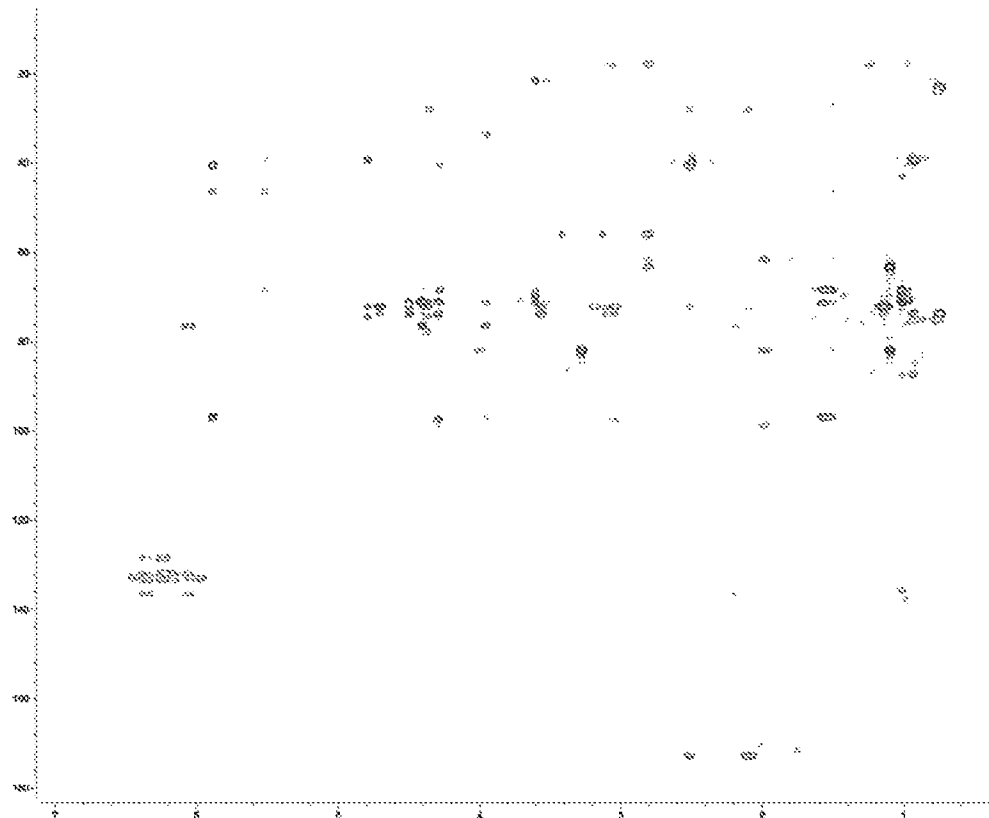


Figure 7

A

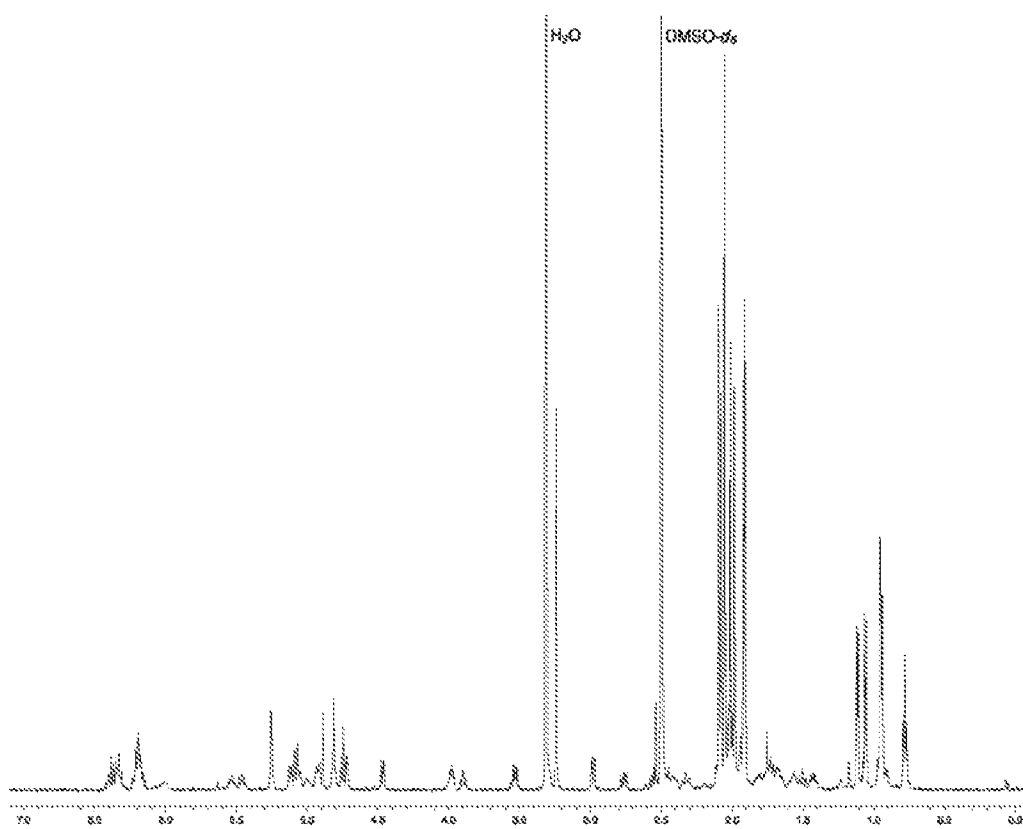


Figure 7 (Continued)

B

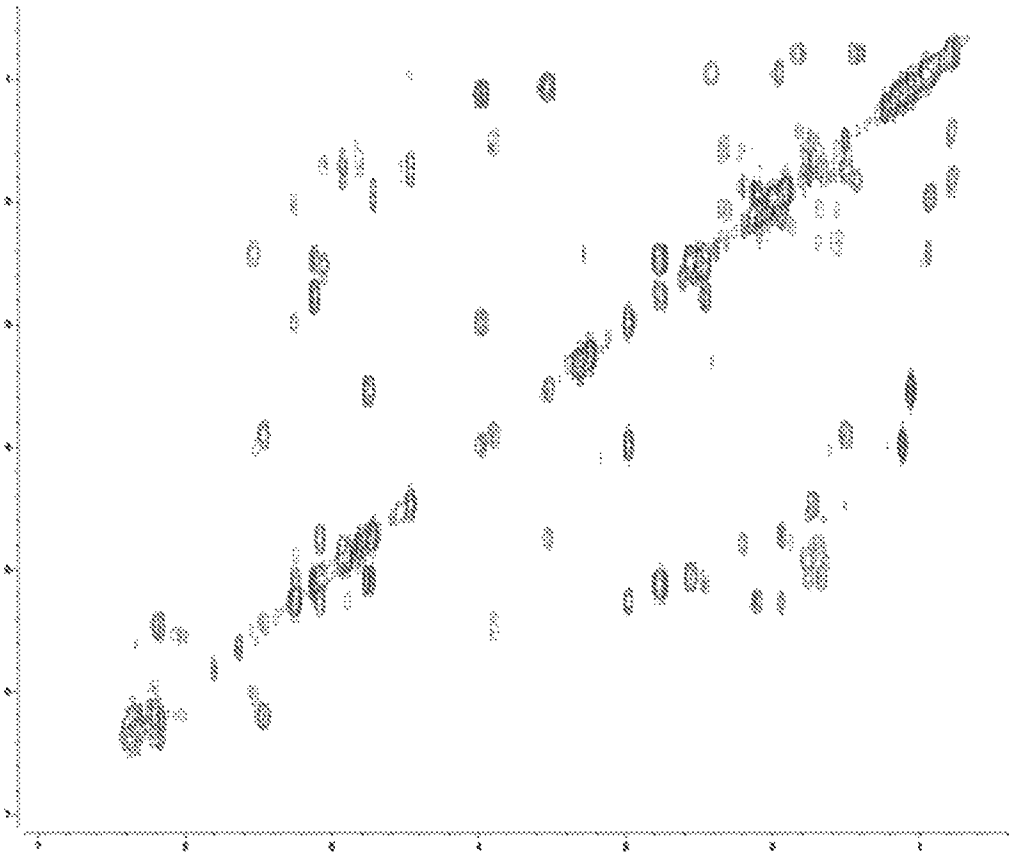




Figure 7 (Continued)

C

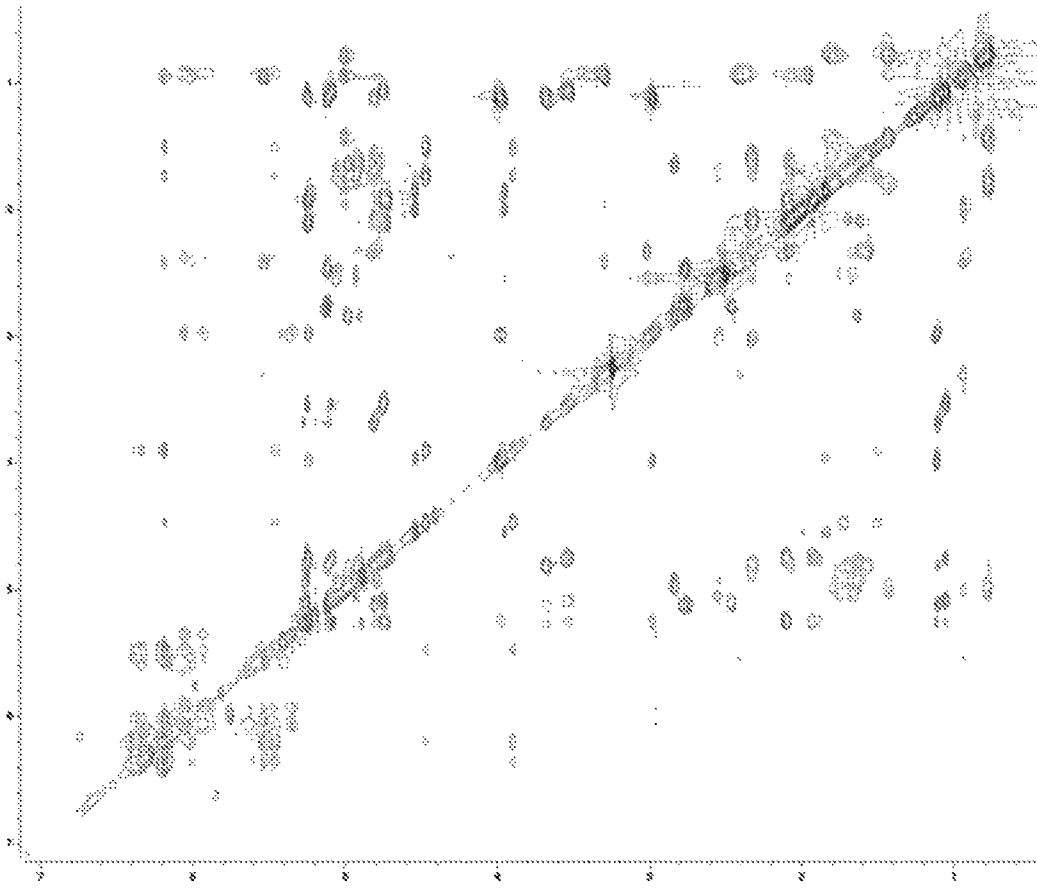


Figure 7 (Continued)

D

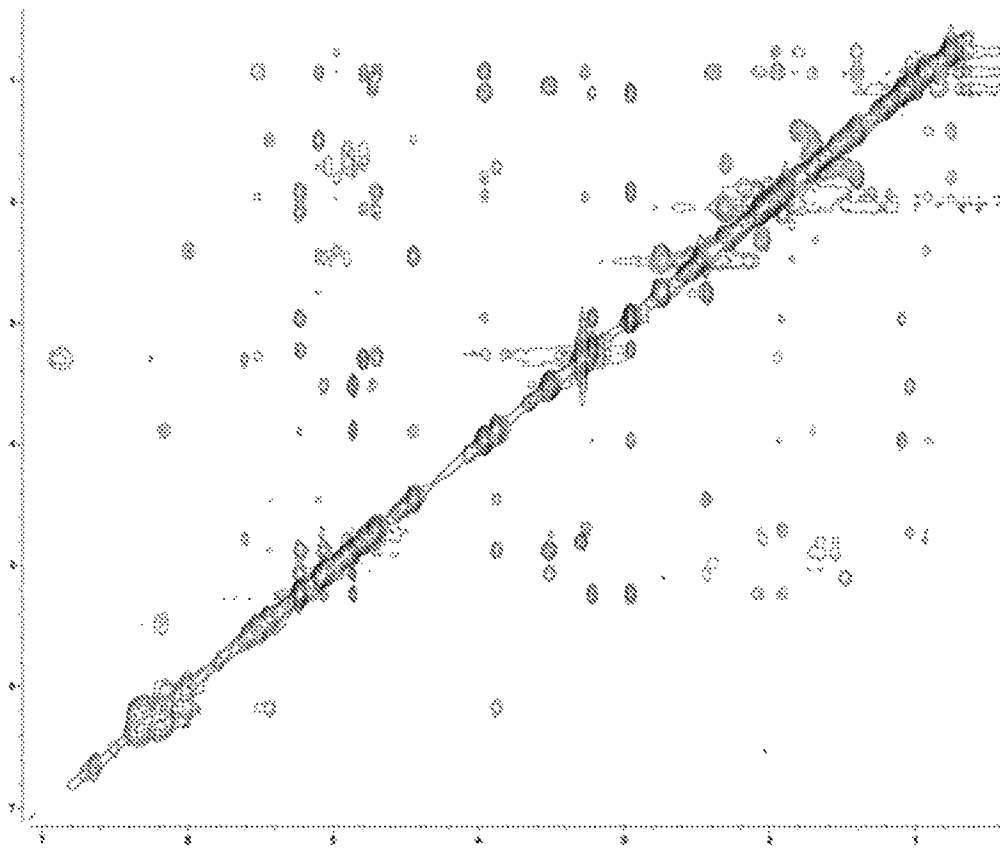


Figure 7 (Continued)

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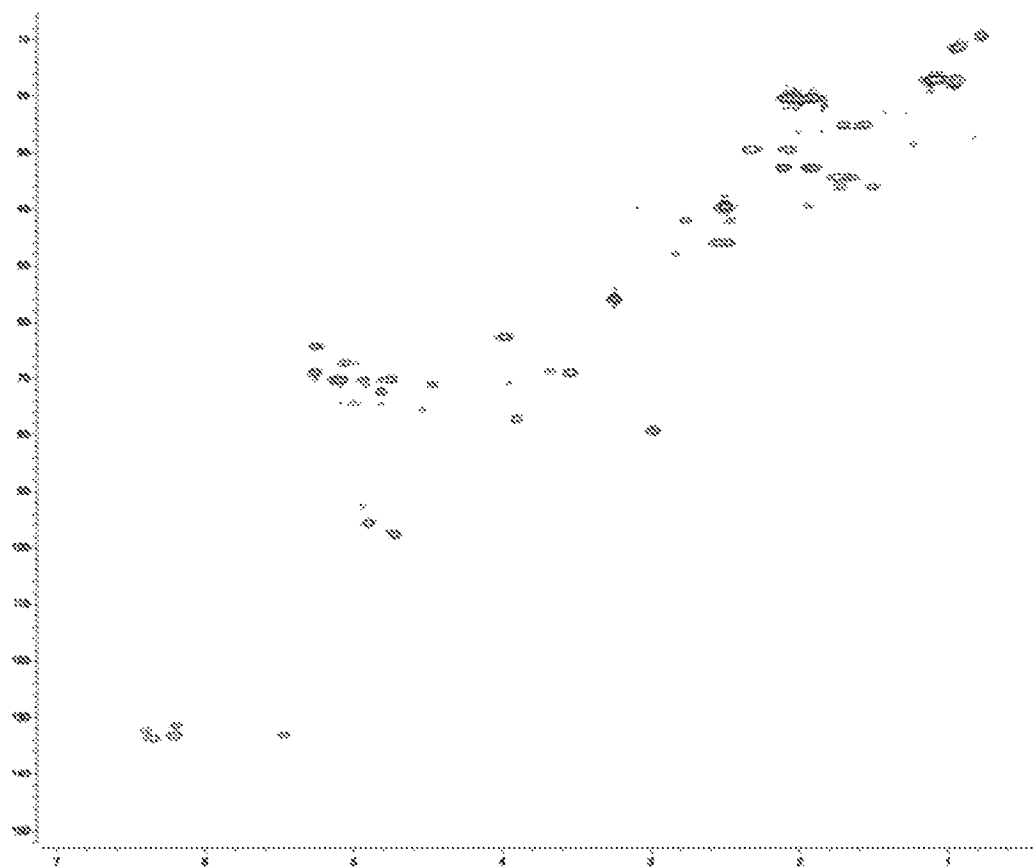


Figure 7 (Continued)

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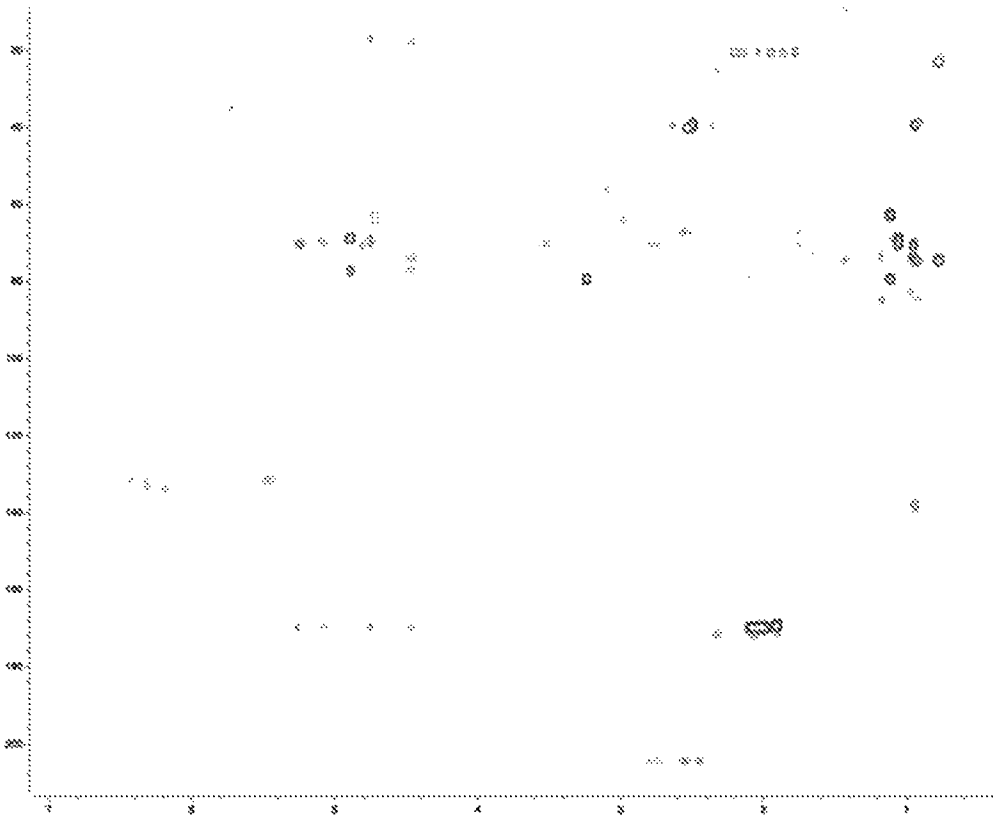


Figure 8

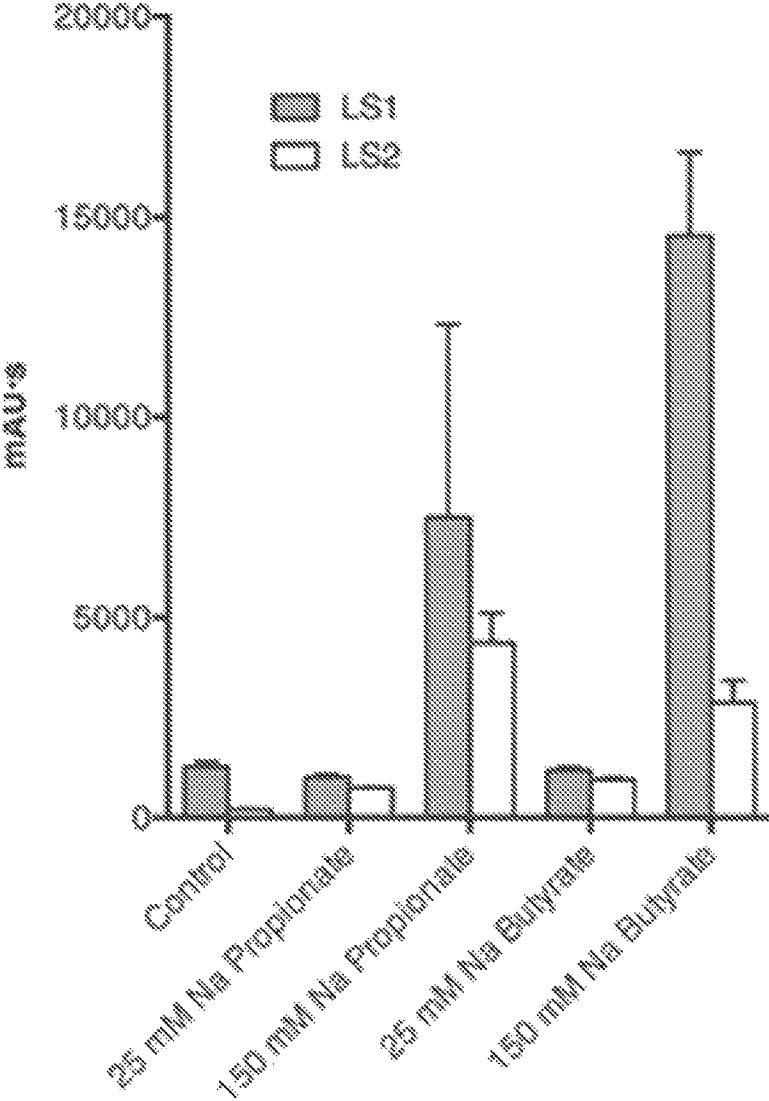


Figure 9

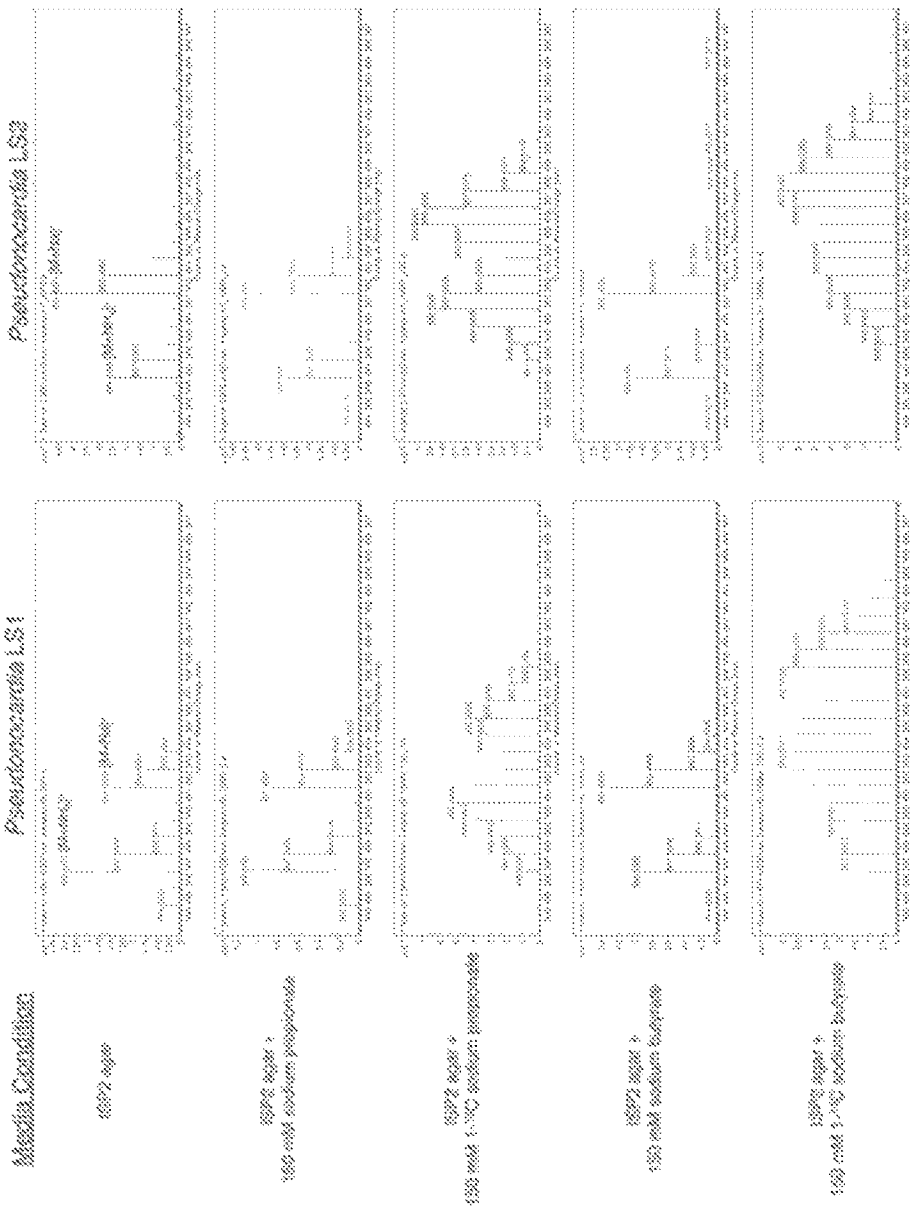


Figure 10

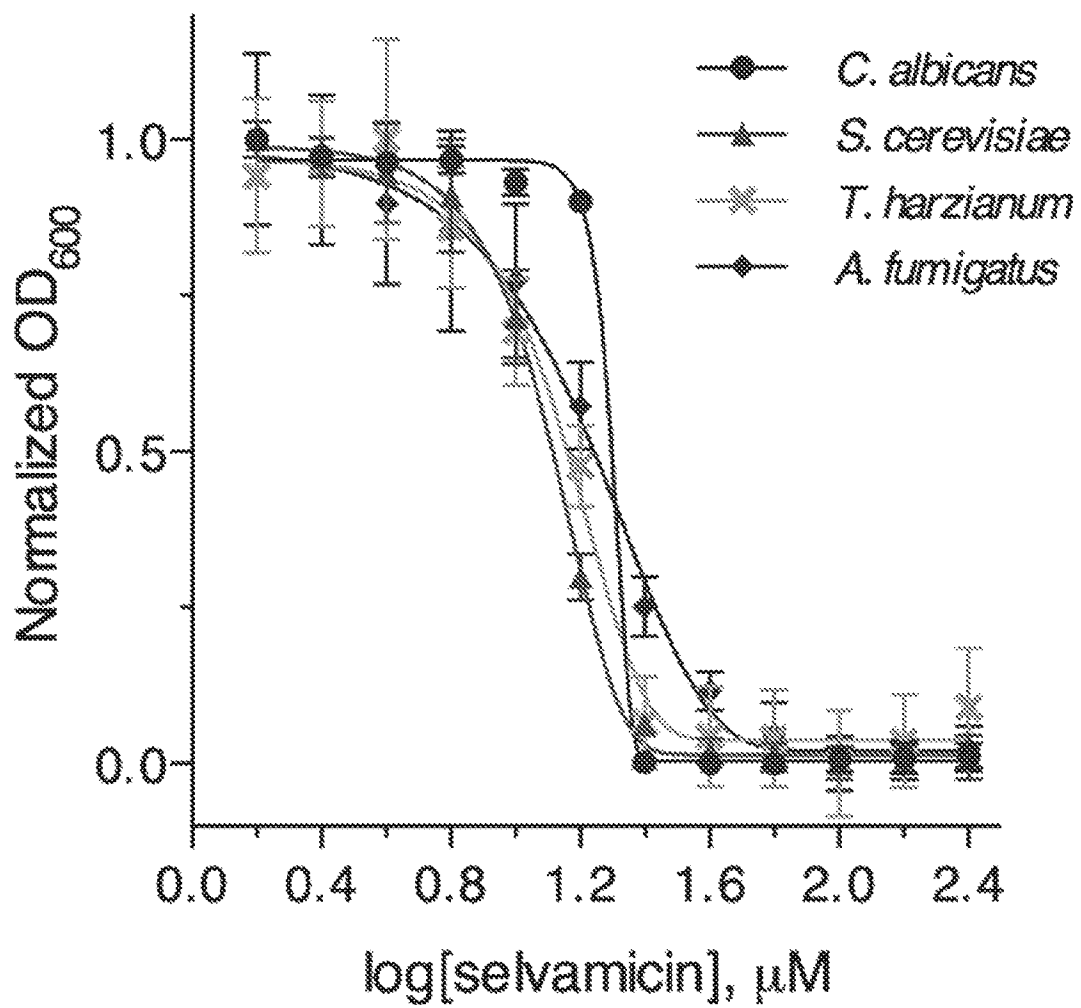
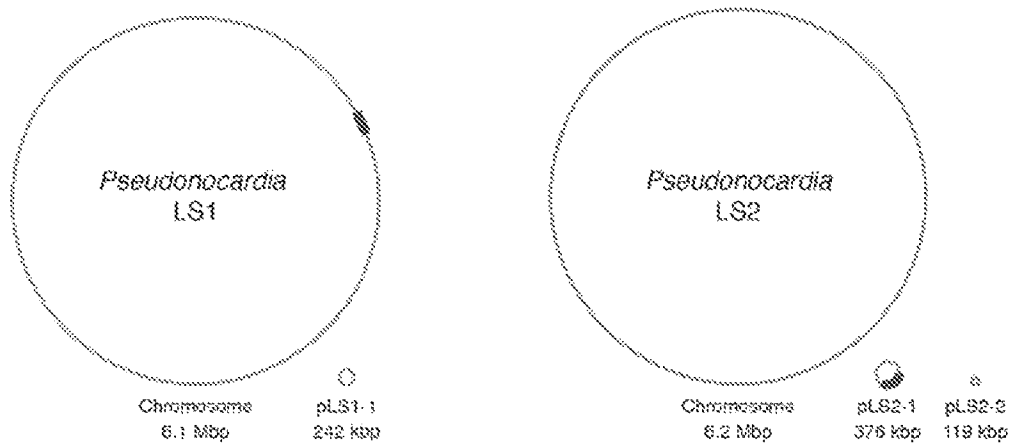


Figure 11

A



B

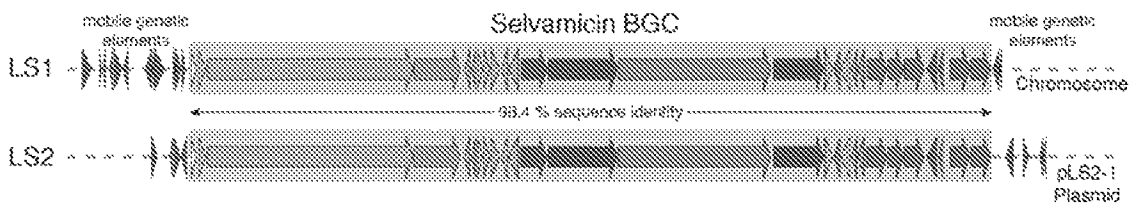
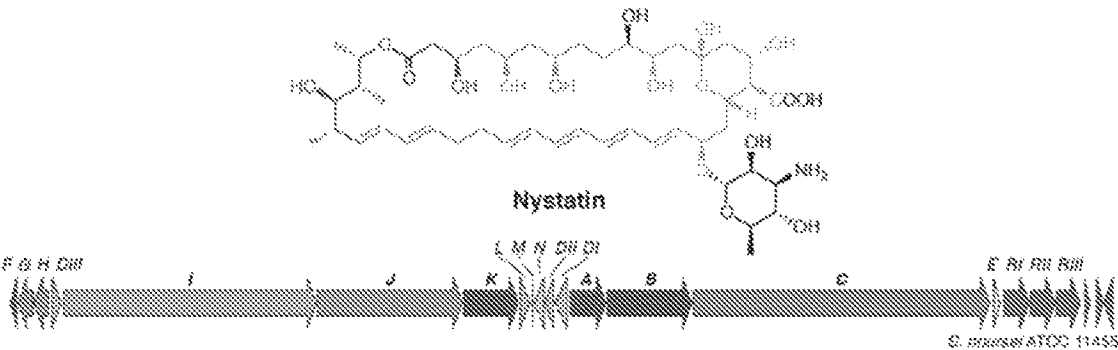




Figure 12

A



B

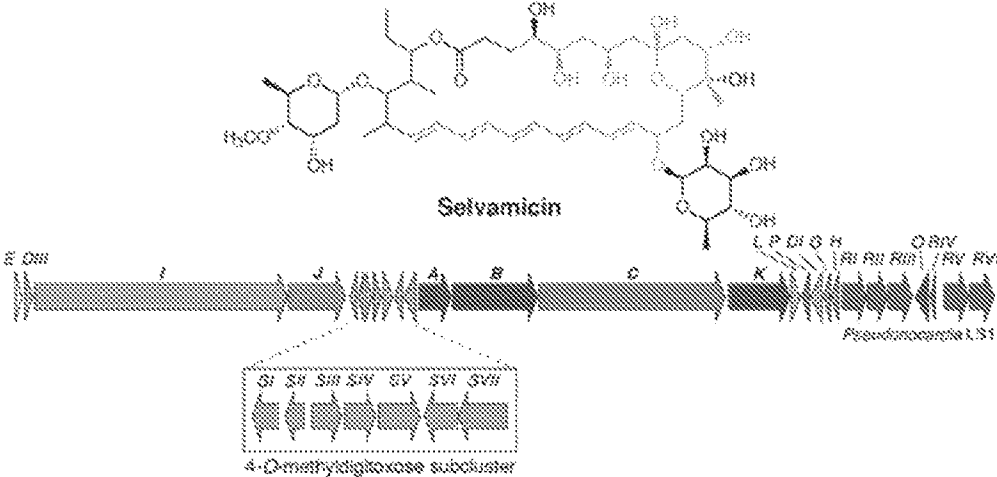


Figure 13

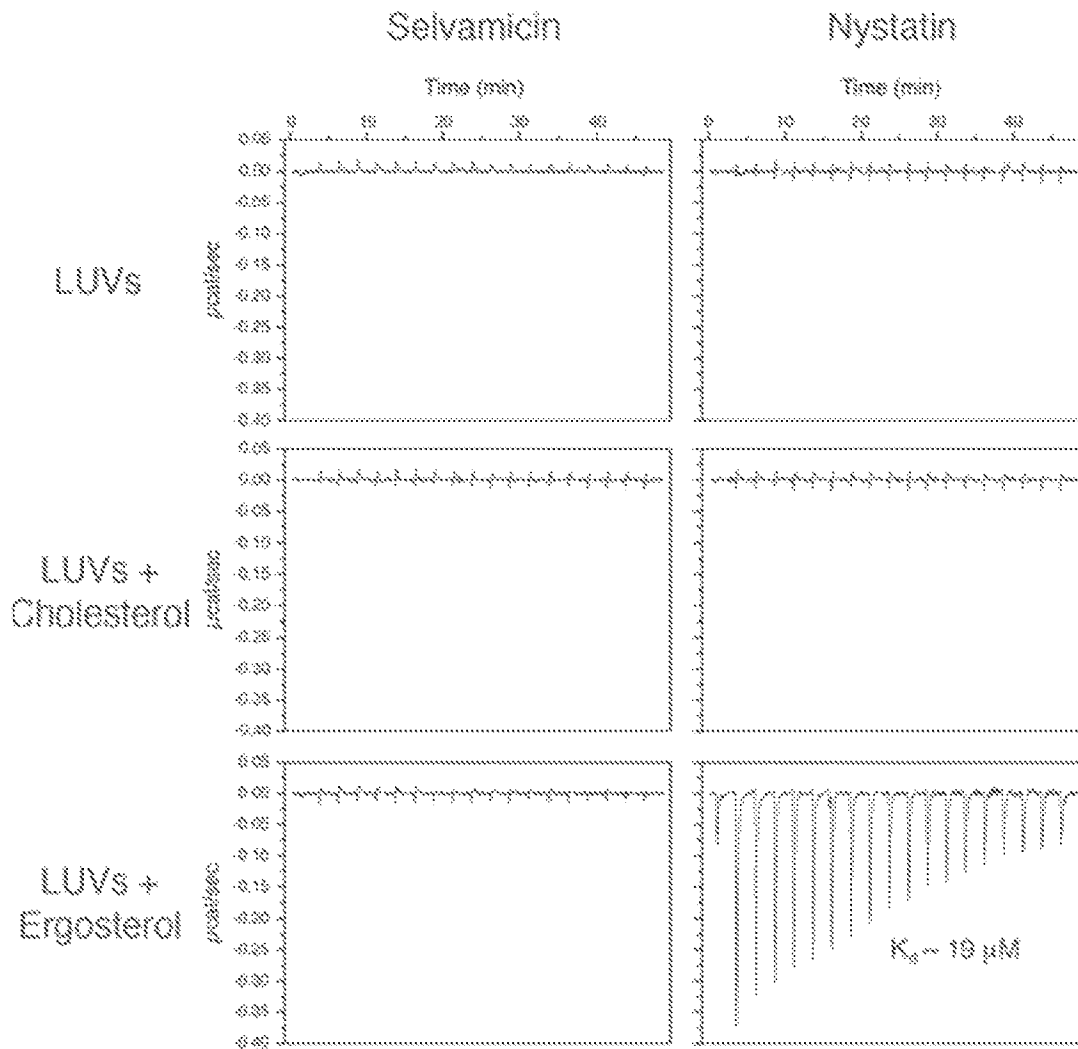


Figure 14

AT Domains:

Seq ID	Specificity motif	Action Site
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Seq1-008	RRRF	RRS Q
IM_L01	.....DDELLD	YFRRYKSLDUGVYAAASV
IM_L02	.....DFEELD	TDFYVAGLAVQGVYAAASV
M1_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M1_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M2_L01	YVYVDEAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M2_L02	YVYVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M3_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M3_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M4_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M4_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M5_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M5_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M6_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M6_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M7_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M7_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M8_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M8_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M9_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M9_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M10_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M10_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M11_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M11_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M12_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M12_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M13_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M13_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M14_L01	KLAVDRAAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV
M14_L02	KLAVDTAASAKVYVAVLISQ	RFYAVYVAGLAVQGVYAAASV

ER Domains:

	R	D
M13_L01	QVLDLQPTD---DFVDEPPTDAASGLITVY	
M13_L02	QVLDLQPTD---DFVDEPPTDAASGLITVY	
M14_L01	RFVDEKPTDVFVDFVDEPPTDAASGLITVY	
M14_L02	RFVDEKPTDVFVDFVDEPPTDAASGLITVY	

KR Domains:

	S	Y	R
M1_L01	YVYVDEAAASAKVYVAVLISQ		
M1_L02	YVYVDTAASAKVYVAVLISQ		
M2_L01	KLAVDRAAASAKVYVAVLISQ		
M2_L02	KLAVDTAASAKVYVAVLISQ		
M3_L01	KLAVDRAAASAKVYVAVLISQ		
M3_L02	KLAVDTAASAKVYVAVLISQ		
M4_L01	KLAVDRAAASAKVYVAVLISQ		
M4_L02	KLAVDTAASAKVYVAVLISQ		
M5_L01	KLAVDRAAASAKVYVAVLISQ		
M5_L02	KLAVDTAASAKVYVAVLISQ		
M6_L01	KLAVDRAAASAKVYVAVLISQ		
M6_L02	KLAVDTAASAKVYVAVLISQ		
M7_L01	KLAVDRAAASAKVYVAVLISQ		
M7_L02	KLAVDTAASAKVYVAVLISQ		
M8_L01	KLAVDRAAASAKVYVAVLISQ		
M8_L02	KLAVDTAASAKVYVAVLISQ		
M9_L01	KLAVDRAAASAKVYVAVLISQ		
M9_L02	KLAVDTAASAKVYVAVLISQ		
M10_L01	KLAVDRAAASAKVYVAVLISQ		
M10_L02	KLAVDTAASAKVYVAVLISQ		
M11_L01	KLAVDRAAASAKVYVAVLISQ		
M11_L02	KLAVDTAASAKVYVAVLISQ		
M12_L01	KLAVDRAAASAKVYVAVLISQ		
M12_L02	KLAVDTAASAKVYVAVLISQ		
M13_L01	KLAVDRAAASAKVYVAVLISQ		
M13_L02	KLAVDTAASAKVYVAVLISQ		
M14_L01	KLAVDRAAASAKVYVAVLISQ		
M14_L02	KLAVDTAASAKVYVAVLISQ		

DH Domains:

	K	Q	R	T
IM_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
IM_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M1_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M1_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M2_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M2_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M3_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M3_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M4_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M4_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M5_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M5_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M6_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M6_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M7_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M7_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M8_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M8_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M9_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M9_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M10_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M10_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M11_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M11_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M12_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M12_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M13_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M13_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M14_L01	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY
M14_L02	WLAARRVYVQD-SVLLPQTA			QVLDLQPTD---DFVDEPPTDAASGLITVY

Figure 15

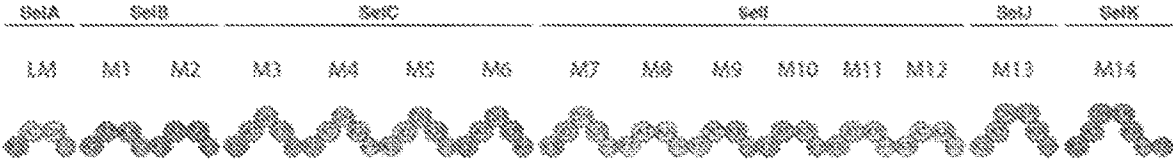
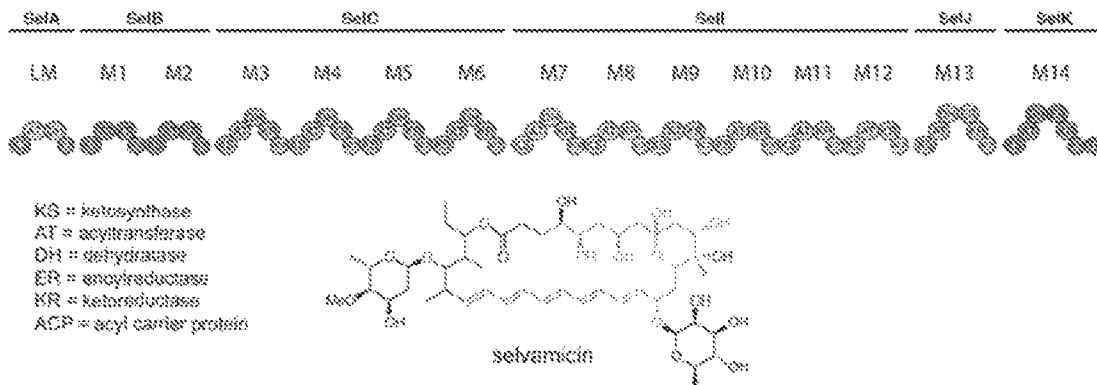
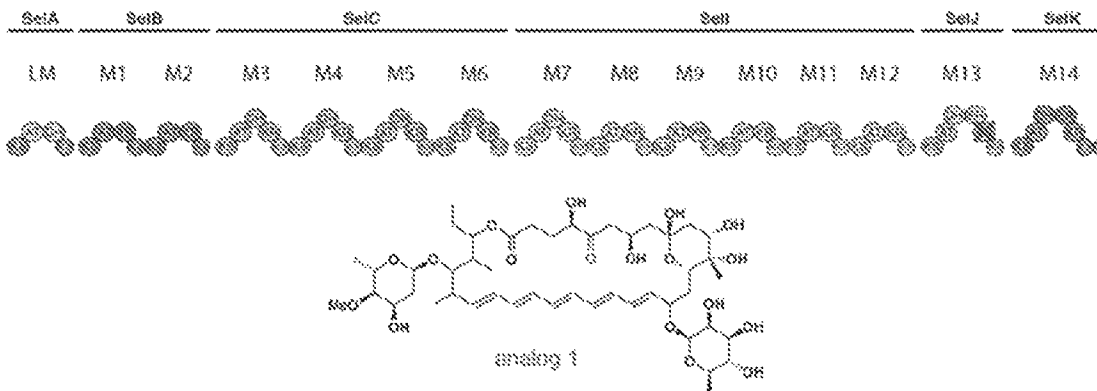


Figure 16

A



B



C

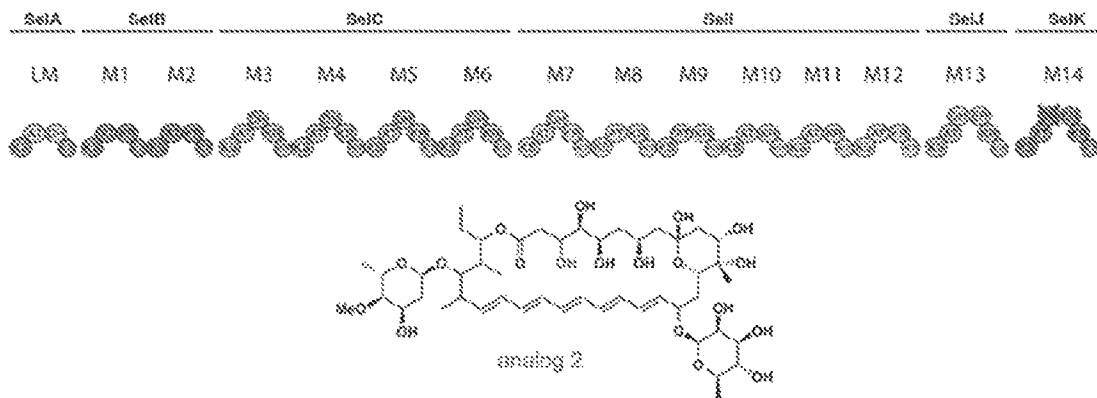


Figure 17

	Putative Protein	Putative Function	LSI top blastp hit v. nr proteins (% identity)	Nys BGC <sup>a</sup> homolog (% identity)
SelE	Thioesterase	Proofreading thioesterase	oleoyl-ACP hydrolase [Streptomyces sp. NRRL S-1568] (69%)	NysE (48%)
SelDIII	GDP-mannose-4,6-dehydratase	6-deoxymannose biosynthesis	GDP-mannose 4,6-dehydratase [Streptomyces natalensis] (79%)	NysDIII (78%)
SelF	Type I PKS	PKS module 7-12	beta-ketoacyl synthase [Streptomyces sp. NRRL B-24891] (61%)	NysI (60%)
SelJ	Type I PKS	PKS module 13	hypothetical protein VK61_12610 [Streptomyces sp. NRRL B-1568] (61%)	NysJ (58%)
SelXI	O-methyltransferase	4-O-methylglucosone biosynthesis	mannan O-methyltransferase [Streptomyces sp. 769] (58%)	...
SelSII	dTDP-4-dehydrochalcone 3,5-epimerase	4-O-methylglucosone biosynthesis	dTDP-4-dehydrochalcone 3,5-epimerase [Actinobacteria bacterium OR606] (76%)	...
SelSHI	glucose-1-phosphate thymidyltransferase	4-O-methylglucosone biosynthesis	glucose-1-phosphate thymidyltransferase [Streptomyces moolenaarii] (73%)	...
SelSIV	dTDP-glucose 4,6-dehydratase	4-O-methylglucosone biosynthesis	dTDP-glucose 4,6-dehydratase [Schizothraustera m. muenzii] (78%)	...
SelSV	Glycosyltransferase	4-O-methylglucosone glycosyltransferase	protein TrdI [Streptomyces sp. NRRL F-5126] (49%)	...
SelSVI	dTDP-hexose 3-hydroxylase	4-O-methylglucosone biosynthesis	maltoosylase [Streptomyces stelliscabiei] (55%)	...
SelSVII	dTDP-hexose 2,3-dehydratase	4-O-methylglucosone biosynthesis	NDP-hexose 2,3-dehydratase [Sciocionella sp. NE31] (88%)	...
SelA	Type I PKS	PKS loading module	module polyketide synthase [Streptomyces himantimonis] (47%)	NysA (46%)
SelB	Type I PKS	PKS module 1-2	polyketide synthase [Streptomyces wuyuanensis] (62%)	NysB (61%)
SelC	Type I PKS	PKS module 3-6	type I polyketide synthase [Streptomyces sp. NRRL B-24891] (58%)	NysC (56%)
SelK	Type I PKS	PKS module 14--thioesterase	type I polyketide synthase [Streptomyces sp. TAA 20-1] (87%)	NysK (51%)
SelL	P450 monooxygenase	hydroxylation	cytochrome P450 [Streptomyces amarae/citricellus] (54%)	NysL (53%)
SelP	2-oxoglutarate and Fe(II)-dependent oxygenase	hydroxylation	phytyl-CoA dioxygenase [Streptomyces himantimonis] (68%)	...
SelDI	Glycosyltransferase	6-deoxymannose glycosyltransferase	MET family glycosyltransferase [Streptomyces sp. Ash 205] (65%)	NysDI (63%)
SelG	ABC transporter	Efflux	ABC transporter permease [Saccharothrix zingare] (51%)	...
SelH	ABC transporter	Efflux	ABC transporter [Saccharothrix sp. NRRL B-16348] (67%)	NysH (28%)
SelRI	Transcriptional regulator	Regulation	CypRI [Pseudomonas autotrophica] (73%)	NysRI (46%)
SelRII	Transcriptional regulator	Regulation	CypRII [Pseudomonas autotrophica] (57%)	NysRII (32%)
SelRIII	Transcriptional regulator	Regulation	hypothetical protein WY02_00420 [Pseudomonas sp. AL641005.1.0] (50%)	NysRIII (33%)
SelP	Deacetylase	Unknown	CypO [Pseudomonas autotrophica] (90%)	...
SelRIV	Transcriptional regulator	Regulation	CypRIV [Pseudomonas autotrophica] (74%)	GRF4 (62%)
SelRV	Transcriptional regulator	Regulation	CypRV [Pseudomonas autotrophica] (54%)	...
SelRVI	Transcriptional regulator	Regulation	hypothetical protein [Pseudomonas sp. BC080825.64]	...

<sup>a</sup>Predicted genes/proteins and the gene products derived from sequences < 250 bp are omitted from the table.

<sup>b</sup>Nystatin BGC from *S. noursei* ATCC 1455 (accession no. AF563912).

Figure 18

SEQ ID NO.	Accession ID	Protein name	Sequence
2	ALE82578.1	SeIE	<p>1 mrrfhspgrd earlvcfpha ggsatffhpv sarfapaaev lavqypgrqd rhrepcltsv                      61 aeladrlaie laalparptv ffghsmgalv gfeaarrler dapgsaprsl vvsgrrapst                      121 rrpervheld dagllaevra ldgpdmsald ddfllalvlp lrndyravet yraddgavvg                      181 cpvlaltgrd dprttqeead awrrhtdggf elevmpghhf flvdqaravc drldeqlala                      241 hggsarpprg</p>
3	ALE82579.1	SeIDIII	<p>1 makralitgi tgqdgysylae hllslgygvw gltrgqanph kmrvgklase lsfvdgdldm                      61 ggslysvavdr vqpdevynlg aisfvamswg gaelvtevna vgvlrmlai rmvsglittsr                      121 qaadgqirfy qasssemfkg vtespgneqt vlhprspygk skayghlmtr nyresygmfg                      181 vsqilfnhes prrgpefvtr kislavaqik lglqkelrig nldavrdwgf agdyvramrl                      241 mlaqdepvdh vvgtgrrhsv rdavriaefc vglwedhvv vdpalvrpae vellcadstr                      301 arenlgweps idfpelmqmm vesdlrragr erdyaevlsa gsw</p>
4	ALE82580.1	SeII	<p>1 mdnegklrdy lkrasadlgr trqrvgelee asrepiaivg mscrypggva gpddlwgmva                      61 tgsdgisglp tdrgwldlge laaaatsggf lhdaaefdad ffgispreal amdpqgrill                      121 evaweafera gvdpasvrgs rtgmfigama qdyrvgpddg vegfvltgss ssvvsgrlay                      181 sfgtvgpavt vdtacssslv slhlaahlr agecsmalag gitvmstpat flfarqgg1                      241 atdgrcrsfa dsaagtgwae gvgvlvlerl sdaqrnghev lavvrgsavn qdgasnglta                      301 pngpsqgrvi sealtrsgls adqvdvveah gtgttlgdpv eaqallatyg qrrerplwlg                      361 svksnishtq aaagvagvik mveairngvl patlhvdtps tkvdwdsgqv riltesmpwp                      421 atgaprraav ssfgisgtna htileqapdt pdapvvvpah dadgagpap1 llsgrtaeal                      481 saqaerlldr ldaadapdlr dvafslatgr aslehravlp addaeqtrag lralaegtia                      541 pgavrgtsrr rpstafifag qgsqrlgmgr elyrrfpvfa eafdavcehl dpsvreivwg                      601 tdadalndtg vaqpalfale valhrlvssy gvrptqligh sigeiaaahv agvfslpdac                      661 alvtargrlm rslpaggamv aiaaseeva phitdgvsla avngpssvvv sgteaevhdv                      721 vehfadrtr rlrvshafhs plmepmlaef ravvagldac aptlpivstl tgrpataeel</p>

Figure 18 (Continued)

781	gsaeywaaha	rgtvrfadav	atartlgvtd	llelpgdatl	cgaarsclda	agaedaatlp
841	vlradrdeaa	tlteamaglh	virgvavdrnt	lvdgtgahr	dlptyafrrr	rffwpgkpaaa
901	ggdvraaglg	aahhp11aaa	valadsdgv	ltgrlsiaag	pwladhavhg	rvllpgtafl
961	elairagdev	gadhveeltl	aaplvlpesg	gvvgvqvlgs	pdasgrrvvt	vysrpdadd
1021	epwtrhatgv	lgrggpaadt	apattpgpewp	pagaealdvt	gayds1aaag	leygttffggl
1081	raawrrddev	faevalpqs	gtegfgvhpa	lldaalhala	iagsgedtgt	slpfswegar
1141	lhaggasavr	vritgagtdt	vslvvsdpag	dpvatvasla	lrplpaggva	gdtagrtp1f
1201	aveptpvrlg	eapasfalld	pagllgstfa	paplydslae	ladagvpevv	aapvpavegd
1261	vpgavravta	waldllqrwl	aderfagsrl	vlltrgadld	pvhasvvgla	rtaqaegpgr
1321	vavldlpgdg	saadtppspat	vvaalgtade	pelalrgeda	vaprltrllp	pgaagtpapf
1381	dadstvlitg	gtgglgavia	rhlvaghgvr	slvlagrrgp	eapgaaelaa	eiteagaeva
1441	vvacdaadrd	qlaallaehp	vtavvhsagv	lddatitsit	paafetvlap	kvdaaqnlhe
1501	lagdltafvl	fssvagtaga	agqgnyaan	aaldslaarr	raaglpatsl	awgpwsatgg
1561	mtgeltadadl	arlaragtpa	lepeqgrelf	daalaadrat	vvpvrldlav	lrangevpaf
1621	lrglvrgpar	rtaaadtagp	gsgvaglwrg	ldaadrdaav	lalvrdevaa	vlghgsgaei
1681	dpdraftdlg	fdsltavelr	nriasttglr	lpttlvfdyp	ttsalaghli	satvvgdgp
1741	rpvtpvlatg	ddpvv1vgma	crypggvssp	edlwrlvtdg	gdaisgfptd	rgwdletlhd
1801	pdpdrrgtty	asgggflhsa	pefdpgffgm	sprealatda	qqrlllessw	eaferagidp
1861	rtlrgsatgv	faglmnydyg	silargdfeg	lqsggtapsv	asgrvayalg	legpavtidt
1921	acssslvamh	waagalrsge	cs1alaggvt	vmstpaai1e	fsrqrglspd	grcrafsdda
1981	dgvwsegvy	mlvlerrsd	lrnghgilav	lrgsavnsdg	asn1gtapng	psqgrviraa
2041	lagag1gtad	vdvveahgtg	ttl1gdpieaq	allaayqgdr	etplylgsvk	snightqaaa
2101	gvagvikmve	amrhgvlpat	lhastpsshv	dwdagevell	teplpwwidg	rarragvssf
2161	gisgtnahli	leapepaqlp	apgtalpgta	lpdtalpaap	lpivvsgrtp	aalrdqaarl
2221	srhldahpdt	dlgdvaasll	gtrtafeh1ra	avaaedhdgl	rraldalatg	aatglvegt
2281	ptggrtaflf	agggsg1rpgm	grelyarfqa	yaaafdavaa	h1paev1daa	lgddadaltr
2341	tghaqpgifa	levalyrlve	swg1vpdria	ghsigeiaaa	hvagi1slpd	acalvsarar
2401	lmgalpagga	mvavaasede	vvphlidgva	1aavngpssv	vvsgaeaeve	avvarfadrr
2461	tkrlrtshaf	hsplmapnld	efrtvvegls	faapripvvs	tvargadltd	pgywvehvra
2521	tvrfadaaaa	laddgvttal	elgpdgvlca	lvesaapdri	aaapvlrpdg	petrtvvaal
2581	ghlwvhgvd1	patpggaagp	arrvdlptya	fqhehfwpdv	paagaatdgd	gsadqalwga
2641	verqddteva	allgltddrh	aalsallpal	sswrqgrnek	arldrwrprt	gwtsrrvtag
2701	arldgtwllv	raddpaqgar	atevadalra	agaevadl1v	daactdsact	aarl1sarpae



Figure 18 (Continued)

2761	ltgivslip	aerpaahrpq	vplglaltga	lvqalaaies	atplwlttag	avrtgpadpa
2821	dpaphtdqa	vwlgrvaal	ehprlwgglv	dipaephna	ldrlaavltg	pagedqvalr
2881	agtawgrrly	rhpvdalppe	taftvsgsvl	vtggtgalgg	evarllarsg	arhlvltgrr
2941	gpdapgaadl	aaeleglgas	vhvaacdvt	adavadllaa	vpaehpltgv	vhvagigqas
3001	tledtgpaef	drvyaakvtg	arvldnllgd	reidlfvlfs	siagvwgsrg	qaayaagnaa
3061	ldalaeerra	rglvatsvaw	gpwadagmat	ddavaadlar	aglralppap	avtelrralv
3121	qddtcvtvad	vdwqryapvf	taarasalfd	piddvaaldr	apddaaggel	arlrldldga
3181	aqqrllldlv	raaaaavlgh	gtadavaatr	sfrdagldsl	tavelrkrlv	gltglalpat
3241	lafdhsspsa	laehltreql	gltdaggpva	attavddepi	aiigmglrfp	ggvatpeqfw
3301	dliisggvdat	gefptdrgwd	adglhcdpdp	rpgrtyttrg	gflhdaaefd	paffgispre
3361	alsmdpgqrl	llqtgweafe	ragidpatlr	gstrgtfvgs	sfqdygagaa	agngaseghm
3421	vtgtipsvls	grlsylfgle	gpavtvdtac	sssmvalhla	cqslrsgest	lalvggatvm
3481	atpapfvafs	rqralaadgr	ckafgsgadg	mslgegavvl	lveklsdara	nghevlavvr
3541	gsavngdgas	ngltapngps	qqrvirgala	nagvepgevt	aleahgtgtp	lqdpieaqal
3601	matyglrdp	qrplllgsvk	snightqsa	gvagvikmvl	amrygllppt	lhagepsagi
3661	dwsppgvalv	deptewpegs	rragvssfgi	sgtnahvile	egdrvpara	qvtvdagdas
3721	adalepdapa	patpaalpfl	isargaeplr	draaaiall	gaadapapad	vafslattra
3781	qmvdravvvg	tgtdepaera	ralaagepaa	givtgtadvd	grtvfvfpgg	gaqwagmgae
3841	laaaspvfaa	rldecaaals	phvdwvlrdv	ltgaegtptl	ervdvvgpas	favnvslaav
3901	waahgvtpda	vlghsqgeia	aavvsгалsl	ddgarvvair	sraiaehlsq	agammsvalp
3961	adevrallae	hpgelsvaav	ngprsvvvcg	epdavtalge	qlgarevrar	riavdyashs
4021	ayveaveepv	raalapitpv	assvpflstv	tgdwldttm	dagywyenlr	revrfapavr
4081	alleqghrrf	leisphpvlt	igisetveel	gadlggpalv	sgtlrdegg	pdrvltalaq
4141	awvrgvdvdw	apaveggrrv	alptypfrre	hlwaiaepva	tlresdaaev	afwdavdaqd
4201	ldtlssdlld	dagtdgvsia	avlptheadwr	rrhrerdtld	awryrtvwkp	lpntapgtle
4261	gtwllvgtgd	tgstgadgav	vrtlrehgae	vryveldptg	tdraeiaarl	gsgpvagvls
4321	llaaderpla	egtadeqpsl	trgvaltval	iqalgdagvt	aplwcvttg	astgradpvt
4381	aplqalvqgv	vtaalehpe	rvgtvdlpa	elderaaarl	agvlagytge	dqlalrdsgv
4441	farrvvraap	gdaagpgwt	prgttlltgg	tgtlaphiar	wlarrgaehl	vltstrrgpda
4501	paaqllael	aelgteaemv	acdldrds	agileglrae	grtvrtvlht	avsitlatid
4561	etgpeqvadv	lrakvdgarh	ldelldddql	dafvlfssta	gmwsgahaa	yvagnaylaa
4621	laeqrrargv	pataiswgiw	addrdlgrvd	adqilrsglv	fmdpatalag	laralderdt
4681	vlavadidwe	ryhpfvtavr	estlfselpe	mrrpaaapep	aaaaaggala	trlaglspad

Figure 18 (Continued)

4741	tdrvlvdivr	aeaatalgls	gpselgerta	frdvgfdslt	avelrnrllaa	atgltlpttt
4801	vfdhpnvval	aaflrsmvtg	dtatpptgpv	paaavddepv	aivamscryp	ggvgspeqlw
4861	dlvtggvdav	sgfpadrgwd	aeaifdpdpd	hpgttystqg	gflhdvadfd	adffgispre
4921	alsmdpqqri	lletaweafe	ragvdpatlr	gsttgtfvga	syqdsagag	eggseghmvt
4981	galssilsgr	vayllglegp	aitldtacss	slvalhiacr	svrsgessla	laggvsvmst
5041	pdafigfsrq	ramavdgrck	aysdsadgmt	laegvglviv	erlsearrlg	hplvavirgs
5101	ainsdgasng	ltapngpaqg	rvigaalada	gltpaeidvv	eghgtgtalg	dpieaqalla
5161	tygqdrehpl	llgsvksnig	htqmasgiag	viktvlamrh	gvvprtlhvd	rpsthvdwsa
5221	geitlardef	swprtgrpr	aavssfllsg	tnahtvleqa	pdeaedvtep	aqvcvpvivs
5281	grsrealkaq	aaalrerlae	gvhptdlays	latsrgifsh	raavvtggpd	sdpdaldral
5341	saiaddrpdp	alirndtaga	gpargglavv	ftgggsqrpg	agrellyrafp	afadaldeil
5401	arfdtelrdr	lrevmfaedg	spdaalldrt	gytqpaifai	evalfrives	wgvhpdqvag
5461	hsigelaaah	vagvlsldda	ctlvaargrl	mealppsgtm	iaveasedev	tplltdgvai
5521	aavngpravv	vsgdadgtra	vaaqlaaggr	rtreltvsha	fhsplmdpml	aeftaiasrl
5581	rfhapriplv	sdltgepvda	eavttaqywa	dhvrgavrfa	dvvrglvlaag	agavlelpgd
5641	avltamardt	ldadglgadv	alvpslrrdr	peaaaltaal	aglvvhgaqt	elgaffagtg
5701	arrvdlptya	frrrrfwpep	taagatptgt	tdpvdaefwa	aiehadldtl	ateleldgtt
5761	lgtvvpals	wrrrrterna	vdgwrhrvtw	aplqssrdav	vdgtwllvgt	pdtapladal
5821	agvlgrtvvr	fetttaersd	laagltarla	aaaapvtgvv	sllatttpev	ttaagvpvag
5881	lvatttliqa	lgdagitapl	waltrgavst	grsdplrspe	qaavwglgrv	aalehpdrwg
5941	gladlpgdas	asdpsvlrri	agalaatpgs	gedqiavrts	gvlgrllsta	pdtraadgv
6001	dladlagstv	lvtgggtggig	arlarqlaga	gvahlllvsv	rgpdapgadp	lraeltalga
6061	gvtlvaadva	drdamaqvla	gapadaplr	vfhtagvdd	gvldgltper	lgtvlrakag
6121	avavldelta	dhdlaafvlf	ssvagtigaa	gggnyaaana	vldaaavvrr	aagrpatsva
6181	wgpwdetgm	adgdgvarrv	argglhmap	eralgalwta	lahgdtvsv	advdwsrfap
6241	vlsasrpapl	vadlpqvral	aptaveagpa	apdlvrtlaa	rpdaeragvv	aelvtatvag
6301	vlghgdpsai	tadraftdlg	mdsittveir	nalgaatgit	lpttvvfdhp	tpgalaahl
6361	selrlgepaa	avpahraasa	gtghdppdpv	vivgicryp	ggvtspeelw	dlvdagrda
6421	tgfpadrgwd	leslaaggsd	tghggflhdv	adfdagffgi	sprealamdp	qqrllletaw
6481	eaceragidp	rsrlrgadagv	fvgtngqdyp	qmlrrraradv	aghvatgnta	svlsgrlsyv
6541	lglegpavtv	dtacsaslva	lqwgaalrs	gecslvfagg	vsvmagpdsf	refstqsgla
6601	pdgrckafgd	gadgtawseg	agvlvlerls	darrhghpvw	avvrggainq	dgasngltap
6661	sgpaqgrvir	taladaglgp	advdaveahg	tgttlqdpie	agalmatyga	drteplruga

Figure 18 (Continued)

6721	lksnighsqa	aagvggvikm	vmamrhatlp	rtlhaetpss	hvdwaagavs	llveatpwpe
6781	rdprrragvs	afgvsgrnah	viveqapaea	eaeapaaepv	ghvpwvvsqa	graalddqla
6841	rlldghpgspv	dvgwslatgr	tafrhravll	tdgdtttvea	rgtattggrl	aalftgqgsq
6901	rpgmgrelya	rfpvfadafd	avcahldtel	dirplrdvwwg	eepgelthtg	yaqpalfaie
6961	valhrilesw	gvvpdvlagh	svgeiaaahv	agvfsladac	tlvaargrlm	qalptggamv
7021	algasedevt	phltggvaia	avnqptsvvv	sgteaeevav	varfadrrtt	rlrvshafhs
7081	plmdpmlddf	rrvvqglela	eptrpvital	agttgadmag	pdywvrhvre	pvrfadavag
7141	lvaagatgyl	eigpdgpls	maapmiddpd	vvcvpalrrd	rdevatlitta	varlhvtgvp
7201	vdwarwfdgt	garrvdlpty	afqrsrfwpe	papadaagtd	pvdaafwdav	ergdleslag
7261	tlhvgddtls	amvpalsawr	rdrreertaad	gllyattwrq	itdreitdra	tpeqaprull
7321	lvpsgtgshd	hlehlairv	evgpdgdltg	aetdvdvvis	lldtapaeil	aaldragvda
7381	plwcatrgav	avdhteapt	ldaaarwga	rttartaper	wggmidldlt	pdlldatdaaa
7441	laealtghhg	deiavrgrv	larlrvradg	ttrpwtptgt	vlvtgpadgl	ggriarrvaa
7501	rgaervllld	pagpdtpaav	tlheeigvtv	vatraadysa	drapafdgdt	ptavvhaepa
7561	grsavdgala	ldaalpvdva	fvltttiaat	wgvrgqdada	etgaaytaia	erraargasg
7621	talafaawsg	lvensmaahl	rlnglptldp	dralsalgaa	vaagtsvtva	dvdwatfaps
7681	fapgriaali	delpearrai	tdtstapagd	aelsarlagl	taeqgaeavl	dlvraeaahv
7741	lghdgpaaave	pdlpftdlgf	dsltavdlrn	rltaatgltl	patlvfdhpt	pdalaeqlrs
7801	eltgqrsava	dtsvtvadad	dpvvivgmsc	rypggvrspe	dlwrliteet	davgglpvdr
7861	gwldrlaag	rgvsraggfl	hdvadfdpgf	fgispreamv	mdpqqrivie	aaqeaferag
7921	idpstlrgsd	tgvfvgggtg	dyrppsggeg	hsataqsasl	isgrlsytfq	lqgpavtvdt
7981	acssslvalh	laagavrage	csialaggvt	vmstpvglve	fgemgalspd	grckafsdsa
8041	dgtgwsegvg	llvverlsqa	rlrghevlav	lrgsatnqdg	asnltapng	gaqqrvirrg
8101	lavaglspace	vdaveahgtg	ttlgdpieaq	allatyggdr	teplllgsvk	snightqsas
8161	gvagvikmvl	amqhgtilpat	lhvdrpsshv	dwsagsvsil	trarpwpetg	rprraavssf
8221	gasgrnahai	legapaveap	asprtsrtvv	pvvsvgrsaa	alraqagrlr	ehvartgdgv
8281	adlafsaatt	raafehrgav	vaathdelid	glaalaegrr	pggvvddrav	rrgrtaflfa
8341	gggsqrlmg	qqlherlpaf	aaafdevcdr	laghtdvdr	avvhgtdada	ldrtgnagpa
8401	lfalevalyr	lleswgvtpa	fvaghsvgei	aaahvagvis	lddacalvaa	rgrlmqalpt
8461	ggamvavsat	eeevtpllta	gvaiaavnqp	tsivvsgdad	qveavvaplr	eqgrtrrls
8521	vshafhsplm	dpitedfrac	casltfhaps	ipvvstltgr	iaedgelgdp	eywvrharha
8581	vrfadavttl	agrgvtvfge	lqpdstlaal	areslpgdgt	atvagllrrd	rdeettlitg
8641	latlaaggag	vdwpaffagt	garrvalpty	afgharfwpe	pvapataapa	gaagddsafw

Figure 18 (Continued)

			<p>8701 dvvergdilag lagtlgvehg elsavlpalg ewrrrhrrs vtdgwrqrit wtpltdlpra  8761 rpsgtwlvavi paglagdawv ratldalgtg vvplevgagt praelaaqis phvgavsgvl  8821 slaladpep davvpagtta tatlvqalgd aglpapiwav trgavsvaat eaparpeqag  8881 wvglgrvaal ehpdwrglv dlpeaagdid davaarlaai laghehedqv airasaafgr  8941 rlvaagdsdd dtaweptgtv litggtagalg aqvarhiatt rsddgraphl llagrrgpda  9001 pgaddlvael tglgaqvtva acdvadrtql talldgvgde rpltavvhta gvlddgvl dg  9061 ltperfaavf rskvtsalll deltgldaf vlfasasaav gnagganyaa anavldalae  9121 rrratgraat siswgawga gmaagadaee vsrrtgvtpm dpdravatlr rlagghqata  9181 vvsdvdlarf vrtftaarps pllrelpgya dlaattpepa gtdsgpslre klaglsparr  9241 rrtllelvcg rtadilgygg adeigpdraf rdigfdslas velrnqlgaa tglslsatlv  9301 fdhatpgela dhigtelgsg sgsppdsgsd pppdaqeae agirallasv plellresgl  9361 ldpvlalags pthghaggng haaadghtag ngnghaaang ngnghaggng haaahgppgd  9421 dgaidmaid gmaidlvra aldnehdedr sar</p>
<p>5</p>	<p>ANG09098. 1</p>	<p>SeJ</p>	<p>1 mttsqdkliad alrasmkege rlrrenrrla gaasepiavi gmgcrypggv nspedladlv  61 esgrdavgtf ptdrgwlsa lqdggvderg tsvsqgggfl dgvadfdpgf fgispreart  121 mdpqqrllle vsweaierag idptslrgtp tgvytgtnqg dyaylvvrsl adadgdvgtg  181 iaasatsgrl sytfglegpa vtvdacsss lvalhlaaha lragcslal aggvnmstp  241 gslllefsrqq glaadgrcka fsddadgtgw aegvgvile rlsearrgh pvlavvrgsa  301 vnsdgasngf tapsgragqr viraalaaag lraadvdve ahgtgtplgd piearallat  361 ygdrdpaqpl rlgsvksnig htgaaagvag vikmvqamrr gtvpatihad tpsshvdwns  421 gavrlitdae pwpetgrarr aavssfgvsg tushvvlega paldpagdpa vdpadgpart  481 vpwllsapta sglragagrl hraldgaaaa asdvgylat srtrfphrla vvgddtsala  541 galsgwldga paaaggtarr daqlgvlfag qgsqrlgmgr elharfpvfa rafdevcahl  601 dpavgevmwg ddagalndtg vaqlalfale valfrlvesw gvvpdhlvgh sigeiaaahv  661 agvfsladaa tlvsararlm galpaggvmv avaateeevt plltggvsia avngpssvvv  721 sgaesevdal vgrfadrrtk rlatshafhs plmapmmeef ravvaglefa apqipiistv  781 agrtgddvtd paywvehvra tvrfadaltt lteegvhtll eigpdtlsa laagagadia  841 vpalhpdqge etsvvtalar ldtagatvdw arfftgatpv dlptyafehe rfwarngsaa  901 tdaaglgitp aghp1lgatv pvagtgdvvl taalstathp wladhvvgga valpgtgfle  961 lairaadevg cerveeltla aplv1hgaaa thlqlrvgap addgrrdigi hsraggtdew  1021 vrhatgtliag gapaggaahp dlsgtwppeg atavdidhly atdtgvqygp vfrglraawr  1081 rgedvfadva lpdevddaga fglhpallda alhairsahd dedtal1pss wsgvtlaasg</p>

Figure 18 (Continued)

			<p>1141 asalrvrigr rdgdevtlda adpdggpvis veslalrhad patatarrnd lsglfrldwv          1201 tgaavpgrap trvtvlgpdp idlvpaltga ghhvahrdds adagpadaae tadtgpvlvp          1261 laggpagsgd tralvaaalr rlqdlvsgdg agrvvlvtrg avatdpgddv tdpaaaavwg          1321 larsaqae hp drvllvldls apesaarlpe ivaaldpeep qvavragvpr pariaplts          1381 talvppagtp wrldatgggn adglalvpcs evtepltgrd vrvrvhaagl gprdvrtalg          1441 ahrgdarrlg seaagvtdv gllvtdlrpg drvagmlsgg fgpvgvnder liaripdrws          1501 feeaaaavpsa fltayyalvd lagvqagqkv lvhngagav maaiealahh gaevyatagp          1561 gtqdilrglg vaddhiaspr dttfaeslag agidvvlhap tdgfadasrg lpvpgggvld          1621 lgptddpvvg pgttdaasal dtvdpdriht mletvlglla dgtldplprv awdvrrapea          1681 frfvtragha gavvlrvpre qdpggtvllit ggiggglgae arhlsvrgas rillagrrgp          1741 dtpgaleiaa elaahgt dar vvacdlaepg aaadivagvd pdhpltavvh aagvlddgv          1801 eamtpkrltd vlapkvdaaw elhratehld laafvlysst agvigspgqs nyaaanagld          1861 alaahrratg lpavslawgp weggagmtat lgerqtrrig aagmpplpve rglalfdaal          1921 gsdealilpl gtppsgggap sgpvppvlrn lvrggrrsaa agsaasapdl aarladlpet          1981 drraaltdlv rtaaaavlgh aspdavdadr efrllgvds l tavelnrvg aatglrlptt          2041 lvfdqptpva vaehlaellp tgpgspdggg svldrlanfe aamgaaapda deradvtarl          2101 rmlarweta padgvgdrls gasttdlfsf idnelgrsag a</p>
6	ALE82581. 1	SelSI	<p>1 mtispgvdvv dvadgrvtgt dryldlmkkv ltnviypdga yahirqiddp dstempipve          61 glgerllef d adardggrdw ptvahtmvgr rrlndvhecl eriladdvpg dvi etgvwrg          121 gvcifmrafl vahgctdrtv wvadsfaglp pagdrdpdpv aamghdvatv nermlavdla          181 qvgenfdryg llldqvrlfp gwfsdtlpta pierlsilrl dgdwystmd alvnlprls          241 sggfviiddy cvpgcadavt dyraghgida eiididrmgv ywrkp</p>
7	ALE82582. 1	SelSII	<p>1 meitetavpg afritptqip drrglfyeaw risdveaalg rpfrvaqtnf svshrntlrg          61 ihgttlppgq aklvtcvrga aldvvvdlrv gsptfgavdt tlqeagsvgv vylgdglgha          121 flaltddtdcm nylcdteyvp gtmidigald pdlaipwnlt edpirsckda aaptlseave          181 lglltayrep agt</p>
8	ALE82583. 1	SelSIII	<p>1 mkgivlaggs gsrlhplta vskqimpvyn kpmiyyplsv lmlagirdil iittprdvpa          61 fqallgdgsh lglsitygeq pepnglaeaf ligadhigdd pvalilgdni fhgpgfapll          121 qrtvdevkga vlfgyvpadv hrygigeida dgvlvsieek pasprnqav tglylydndv          181 veiaagsvrps argeleitdv nrsvlergra rminigrdfa wldtgytysl ldaggfvrtl</p>

Figure 18 (Continued)

			241 eerggthiac leelialrmgf idveqcrvlg erlersgygr yvletveavr s
9	ALE82584. 1	SeISIV	1 maltgalpgl epdelvldk ltyagnranl apvsdddrilx lvigdvcdpe lvaretagtd 61 lvvhfaaesh vdrsiagsad fvttnvvgtq vllqaavaar vervvhvstd evygsvgega 121 aaedhpllpn spyaaskass dllarafhrt hglsvsttrc snnygpyqfp ekviplfvtn 181 liegrtvply gdglhvrdwl hvddhbcrgia lvanggrdge vynigggtel snrdltdrll 241 aatgrdssav rrvtdrlghd rrycvditri sdelgyrpqv gfdgdlaatv dwyrtrrdw 301 eplrtsvsga a
10	ALE82585. 1	SeISV	1 mrvlfaissw tghyfpmvpl awamraaghd vrvlcrrpsdq advtaaglip vpaldgldll 61 rgarllnvmv llqgtwypq ppphpdtea mdpagfdiaa whaenmpamv assragtdaa 121 vafgrswapd lvvhdqslsle gplvsavtga psvlhlwgpa gtadafapvg gegaglpqdl 181 sadaftrygag tishdladhv ldpcppplr avagrdaqir yvpyngpgaa pldipepdgr 241 rprvcviwgr svtrtfgpvv nrlpqavraa adlgaevlll arpedardag plpdgvrpvh 301 evplslvlpq cdavvhyaga gsvmtaltag vpglsvpcgf dqpmvaerls atgaglhvhn 361 ldadaatigq alekliggps yadaardlaq rcaampspae vvadlealaa r
11	ALE82586. 1	SeISVI	1 madrkalpaa tsigeielva vasrtrqraa efaerhggrp tgyqelidap dvdavyvstp 61 aalhhwrtaa alragkhvlc ekpltdnlpd teelaelaea rdldlrenfa flhhpqhtv 121 adllragqlg slrtfaatfg ipelpaddir hspelgggal ldvgvypvra aqqilegplt 181 vvaatsqvdd rfgvdsghv llhsadgvva ddfdgfrhry rnryrlwtst asleidrfft 241 pppdhrsllr ieeqhttdtv vvepcdqfre slrsfahaat agpdhrdeqa wtaaretar 301 llqeirrvav rlpdptrstv g
12	ALE82587. 1	SeISVII	1 mspappalrt adrtlprrla rsalwdaaga ararewiaer naahrhdvrr ipfdelrswa 61 fdpatgnlrh dtgrffsveg lqvhtdhgqv rswsqpiinq peigilgilm aeidgvlhcl 121 lqaktepgnv ngvqlsptvq atrsnytgvh agnavpyley frnpgagrvi sdvlqseggs 181 wfykrnrnm vveveepfea hedfrwiplg qvhelcavdn ivnmdtrtv agmptgfgem 241 agtgsgglad alarscvass gglhtdaevl switdrgsgh eirteliplh dvahwrtpd 301 rirhdpesff sviavavat srevgswtqp llephgvgrv allvarfggv lhalmarve 361 pgyleavela ptvqfapety rglglaapaf ldvveeagpg ervlfdaels eeggrfhar 421 nryqiievdp vlddrttpdh rwltvaqlng llhnnynv qarслиaclr gla

Figure 18 (Continued)

<p>13</p>	<p>ALE82588. 1</p>	<p>SeIA</p>	<p>1 mtqtatpvd dqvaivgmac rapggvrspq dlrelttsrg eafsafptdr gwdsalsgd          61 qpvangrggf lddaagfdag ffgispreav amdpqqrqll evswealera aidprtllrgt          121 dagvfvghi qdyavaahgs rddlvghamt gmsgavasgr layvlgcggp avtldtasss          181 slvalhyavr slrsgecsla laggasvmst esgflgygrq gglspsgrpv pfsddadgtv          241 wgegvgllvl erladarrhg hpvlavvrgt avnqdgasdg ltvpsgaaqe rvvaraldda          301 glrpadvdv eahgtgtrvg dpvevtalra aygagrerp1 llgsvkshvg hlqaaagvis          361 viatvlairt gvlpglrrlg tpttradwsg elleplartt dwpdtgrpr agvssfgvsg          421 tnahvvlega agppvvdgaq apddrlvpw avsartatal qtaveqlrga aagrsvrdvg          481 htlavgratf dhramllagp qgtvevargr vgdgetallf gggraapagag relaerfpvv          541 ataldgvhah rhdsggdeta tfalqvalyr lweswgvtpr rvagsavgev aaahvagvls          601 ladatallea rallgerpad raagpdpeld rfratfaglr fappripvvc gaagraatad          661 eladpdrwvp rpgpvadpva aarvihadgv etfleigpda tasaavrtal gervttvptl          721 rgggdevtsv ltalgrlhva gtpvdltaav gdgrrvelpg ypfehrtywp apgdggrtga          781 tghpllgard dlagagllf sgrvparahp wiadhrpggg gatlpvpalv elvlraadev          841 gcdriddlra gdplpvdehg tvelqtwlga anagrrvvtv hsrtagtqqp gaegsgwelr          901 aratvsrgap aaggdgsdlp dgavpltpaa lgerldgagf gpdlaglvga gweldddtwv          961 evtlppdvdr agfghlpall taalgavgrr gdgsevparw rdvalhaega savrvritrt          1021 dgstlrleav dvagapvltv gaielgrgrt vpvpsavpda pdrparpvrr aaalpgasga          1081 gatgvdvval tgphrrrglr mlvraeaadv lglsppdevl grarfkeggf esltgaelvn          1141 rmaartglal qpplvfdhpt pdllaghlad eldarddgpa pdavpdpapg pgpepgspdd          1201 pldseiadas ldrlmdiida eigva</p>
<p>14</p>	<p>ALE82589. 1</p>	<p>SeIB</p>	<p>1 mtdaeagnagt qqhdgaatap qdkvvdylrk vttdlrrtr rldeietren epmavvgmac          61 rypggvrspq qlwdlvasga daitgfpdr gwdrqalagg gagssatadg gfldgvgdgd          121 aefferispre alamdpqqrll levsweale ragiaptslr dsatgvfvgs yhwghsqqpa          181 dpevdlgght ltgtaasvas grisytllgr gpaltvdtac ssslvalhla arslragess          241 lalvggvvm sdpslfvefs rggglspdgr crafgegadg tgwaegagvl vlerlsdarr          301 hghevliavvr gsavnqdgas ngltapngps qraligaals aaglrgdvd vveahgtgts          361 lgdpieagal latygrdreql plwlglksn ightqaaagv ggvikvmmal qrgmlpatlh          421 aetpssrvdw sagavrlite pvawepgerp rragvssfgv sgtnahaiie eppaadgedt          481 sdrpdalttc awsfsargpe slgagaagla arltdsdpyd vayslartra sledravvig</p>

Figure 18 (Continued)

541	sdreellaga	ravaagepsa	avvtgradld	ggtvfvfpgq	gaqwagmgae	lldtspvfae
601	afdaaaaaalr	phvgfsphdv	vrqvpgapgl	davdvvqpl	favmvalaav	wrhgghvhpda
661	vlghsqgeia	aavvagalsl	ddgarvvalr	araigehlag	aggmlsvpls	rdevvtrigs
721	rstlsvaaien	gpravvvsqs	aetvqglhae	lvadgvrarm	iavdyashsa	hveaieqrll
781	ddlagitpgp	aavpmlstvt	gewldggeld	agywyrnlr	tvfgfpavet	llegghrafi
841	evgphpvlsg	avadsareng	tdvlvtgtlr	rgrggpaqil	tsfaeahvrg	idvdwaslfp
901	grrvalpty	pfrrrrfwag	patpesaaad	pagvdpgeqa	fwaavedgdv	aaltsslhad
961	adslaavlp	lsdwrrtnre	ratldswsyr	vewrpvpaag	tptlsgdwl	vttdddtgt
1021	ddvvaalaa	gaavhpvld	gacdgraaaa	ellaaatgva	saagvsvlla	aderadpdp
1081	gstvglrtil	alvqalqdl	vhaplwfltr	daartgpsdr	lthpiqalvh	glawtaaleh
1141	pdriggtvdl	ppgaldahg	prlavalsga	ppedqlavrp	aglytrrivr	tvpgaastgg
1201	perewaphgt	tlvtgaggal	apdlarwlsr	qgaedlvlg	rrgpdapgta	elveelarlg
1261	tavrveacd	gdrdavaall	aglaeaghvv	rhvvhavavm	elesvdatda	aevanvlrgk
1321	vdgarhldei	ldggsldtfv	lytstagmwg	sgrhaayaag	naylsalaeh	rrarglpata
1381	vhwgkwpdav	gsteeatdph	rvrrtgleli	dpdtamaglr	rvldhdehvi	glmavnwpry
1441	hdvftgrpt	tlfdeipevr	lrntaadaga	pavsehgdgr	llgrlrplpa	aeqerllem
1501	vraevaavlg	hgsgaevpel	rafrdigfds	vtavdlrnr	aaatganppa	tmvfdhptpi
1561	alarhlrtel	lggestapaa	papgaaasdd	piavvamscr	lpggvasped	lwclvadgld
1621	visdfpddrg	wdadalrdpd	pdapgrtyst	vggflhdate	fdagffgisp	realsmdpqq
1681	rillettwev	feragidpaa	lrgsatgafv	gagagpypha	vgdagethmm	tgtaasvlsq
1741	risylfgleg	psvtvdtacs	ssivalhlac	rslrsgessl	alaagatvmp	tpepfvgfsr
1801	qralatdgrc	kafadgadgm	slaegvgvvl	lerlsdarrh	ghrvlalvrg	sainsdgasn
1861	gltapngpsq	qrviraalad	agitpdgvda	veahgtgtal	gdpieaqail	gtygrdrdpd
1921	rp1llgslks	nightqaaag	iagviktvla	fqhdelprtl	hagtpssrvd	wsagavrllid
1981	epspwpqaer	prraavsafg	isgtnahavl	eqappepvaa	gpeatvvapg	gdapvhdtpt
2041	iwplsarsae	alcaqaarl	asfdghrpdg	pgraeptgdp	arrpddvgs	larlragfeh
2101	ravvlqgdld	tllaglesva	agetapgvqr	gtaaegdrp	vfvfpgqgsq	wqmggrella
2161	sspvfratia	dceralsphv	dwsltevlag	dadpalsarv	dvvgpalfat	mvalaalwra
2221	ygvepaavvg	hsqgeiaaah	vagaltldda	amivalrsra	lltisagggm	tsvaagpdrv
2281	aeliapwsda	itvaavngps	stvsqdaaaa	ldelaahcaa	egvrsrrvdv	dyashgthve
2341	avrdelaavi	agvrpvsspi	pfystvdgav	vdtagldagy	wytnlrepvr	meaatralld
2401	dgrrvlleis	phpvlgtale	etveahgadt	avalgtlrrd	dggpdrvlt	vaeahthgva
2461	vdfaavfagr	darpvdlpty	afrrrrywpe	eiapaapapt	dgvgrfwel	vasgdgesla



Figure 18 (Continued)

			<p>2521 aelgvgsngt rsslдавlpa lsawwdraar rdtadgwryr igwtrirpqs agrpagrvll  2581 vrppgmpdle pvreafgpgt ttveldpiva adraraaaaal adaavgadlv vflaaagtps  2641 ddgevptala atlglvqalg digaaaplwc vtrgavrtgp gdttvvdppa gsvwglgrvv  2701 alenparwgg lidlpaepdr rsaealaafll aapagedgva vrsagisarr lihatpaadr  2761 pwttsgaalv tgggtggvgal varwlvdrga rhivltsrrg pdapgaaelv adlrergatv  2821 tvvacdaadr aalaqvlqgi dtpgglrsvf haagvsdgdа pvadltgeql rallhpkapa  2881 aghldelvgd reldafvlfs sgasawsggg qpgyaaanaw ldalaerrqa qgrvatsvaw  2941 gawaqagmat dpvaharler qgvtamdpld alqaldttla hapavaaita mdwtrfadgf  3001 tsvrpspila elaeagevvd tvpdaaadgv apllgrlagl ppaerdraml eavrteasat  3061 lghddpaavp agrafrdvgf dsvtavelrn rlrqatglrl paslvfdfpn prdlarhlgt  3121 lafggdaapd gppdpdaptr ellasipldr lrraglldel lrlagapedd pheqsdehgt  3181 slddmdgesi lrlvseasn</p>
<p>15</p>	<p>ALE82590. 1</p>	<p>SelC</p>	<p>1 mtttdsnqyve alrsslkene rllrqnealt aaaaepiavl gigcrfpggv aspedllwell  61 drggdavsgf ptdrgwdlet laagsaggdg gegrslateg gflddvsgfd agffgispre  121 avamdppqri llevtweale ragidpsrlr gsdagvfigt tggdygevla gsaddaevya  181 ttghaasvis grlsytlgie gpavtvdtgc ssslvamhqa mgalrarecs laltggaaam  241 atplaftaft aqnglaangr ckpfadaadg tgwgegagvl vlarvsdarr lghpvlavl  301 gsainqdgas ngltapngps qqrviraaalr nadleptdvd vveghgtgtt lqdpieaqal  361 iatygrnrrq plwlgslksn ightqaaagv agvikmvlam rhgtvpatih veapssnvdw  421 dgggvelpvt acpwpetgrv rraavssfgi sqtnahvile qapaeapsqa qtpardaepa  481 wvpwvpvgar dddalsdrvr alcdpagsag savdvgsia tgraafehra vilpgptgha  541 evargvtdeg llatvfaggg sgrlqmgrtl herfpvfaqa fdevcahldp svrevmwgtd  601 agalndtgta qpalfavqva sfrlleswgv apdylvghsi geiaaahvag vlsvadaaql  661 vsararlmsa lpaggvmvav eatedevtph ltpgvsiaav ngpssvvvsg aesevdavvg  721 rfadrtrkrl atshafhspl mapmieefra vvagltfaap ripiistvag rtgddvtdpg  781 ywvehvsatv rfadavaelg rrdvgttlel gadgtlsalv gqvlptatvv pilhrdhded  841 rsaitalarv wttgadvdwt allpggrrvd lptypfqrer ywpaparaad agaagldave  901 hpllrsavtl adaagvlag rlslatqpwl adhevagrал lpgtafvela vragdevgce  961 rveeltlaap lmvpptgavq iqvhvgaaeg tsagpvrrpf tvssraagav elpwtrhaag  1021 tltggdpdag etapfdaeaw pppgaepvdl dgcyerltdl gfrygptfrg lraawlrdge  1081 vyaevtlpgd dpdtarfglh pavldaaqha avyadlgpls egglpfityeg vtilhaagatt  1141 vrvrltrgsd dsvsiaiadt aggavatvgs lvsrrtgags pagaagagrđ plfaidwhpq</p>

Figure 18 (Continued)

1201	aptaatpept	avavagplpa	gfdgahvavh	pdlldtlldp	agpsgtvlfp	vvpsgadlps
1261	avreatatvl	talqrlade	rgdgarlvvv	tcggaavadg	ddvdpagaav	rglvrsaqa
1321	npgrfglidi	erdadapata	aaaalaglhg	gepdlavrgg	svlvprlvra	lpgtadpgap
1381	gwrpdgtvli	tggtggigal	tarhlaaerg	vtrllllsrr	gpdapgaael	vaeltglgae
1441	atavavdvgd	rdalarvlda	vprehpvrav	vhtagvvdg	vigs1tpdrl	dtv1rpklda
1501	awhlheltgd	ldafvlfssv	aavvgsppgg	nyaagnaald	alaahrraag	lpalslawgp
1561	wtrtvgmtaa	lsdadaarva	rsgmpeidvd	aglalldaal	dqprpavapv	rdlvalrag
1621	gdvphvlral	vrlprrraaa	rgevadglar	rlgtlgaper	dealfdlvre	evarvlghte
1681	agevpatrpf	telgidslsa	velnrnrlsgv	tglrlsatlv	fdhptprala	ghlrdelfgg
1741	gteapvpvpm	lpataedpvv	ivgmacrypg	gvsspedlwr	lvtddgdais	gfptdrgwdl
1801	eglydppdpr	pehthavggg	flhgaggfda	effgmsprea	lgtdaqqril	lecsweafer
1861	agldpvs1rg	satgvfagvm	yndystllpg	geheafrng	sapsvasgrv	aynlglegpa
1921	vtidtacsss	lvambhwaaga	lrsgecslal	aggvtvmstp	stfvdfsrg	glspdgrcra
1981	fsddadgvgw	segvgmvvle	rlsdarrngh	evlavlrsga	vngdgasngl	tapngpsqqr
2041	vimaalasag	lrssdvdvve	ahgtgttlgd	pieaqallaa	ygqdretply	lgsvksnigh
2101	tqaaagvagv	ikmveamrhg	vlpatlhast	psshvdwdag	evellteplp	wdidgrarra
2161	gvssfgisgt	nahlileapd	papvaeaadq	esgvvpwpls	ghtpdalcaq	aarladaalr
2221	erpvdigfsl	attratfah	avvlahdhsd	aeqalralad	gtadervvtg	ragtgtgvtf
2281	lfagqgaqri	gmgrelydrf	rvfadafdaa	cahlapavre	vmwaddaeal	rdtaiagpal
2341	falevalsri	leswgtper	vvghsigeia	aahvagvlsi	pdagtlvsar	arimgalpag
2401	gamvavaate	devtplitag	vsiaavngps	svvsvgvese	vdavvarfad	rtrkrlatsh
2461	afhspmapm	ldefrtvveg	lsfaapripv	vstvagtga	emaepgyvvd	hvaatvrfad
2521	altglgdtvt	veigpdatlt	alaagvapag	atavpalhpe	rdetgtvnaa	varcwsagad
2581	vdwaavltgg	rrvdlptyaf	qheyfwpepv	praadagtv	lrpaghgll	gviettdgvl
2641	ltgrisrth	pwlvdhavsg	tvllpgsall	dlaarageet	gydrveelml	taplalpegg
2701	gialrvtvga	atpdgprtvv	vhsrpdaht	wtsptwteha	sgllgkhtpp	lspfaqqwpp
2761	agavpvdvdg	cyqrfaddgf	dygpvfrglr	aawrrgdeif	veaalpdgtd	pepfglhpal
2821	ldavlhpiae	iqpddergav	pfawrgvtry	adgatsarar	lrrvpggavs	idladaagap
2881	laavhqlelr	altasrtaap	drdalfrpgw	ervpatvpsg	ltvhaetvdg	gpvpgdlaal
2941	lersgvrgad	taevllldar	sggtaatpdg	aaharttav	arlqteasgt	rtrvvltrga
3001	tdgadpaaaa	vaglvrsaat	ehpgrftald	taldtgadal	daaafaaalg	rtdepqlavh
3061	dtelrvlrlt	rlepdpas	aerpavpwrp	dmtvlvtggt	gglgaqvarh	lvtahgvgs1
3121	llagrrgpsa	pgaaeltael	taagagvevv	acdaadrda	aallarrpvd	avvhaagvvd

Figure 18 (Continued)

3181	dgvlegltpd	rlaavlrpkv	daaqlhela	gdveafvlfs	slagtlgsag	qanyaaanaf
3241	ldglavhrha	aglpatsltw	gpwsgaggmv	gdlddaarer	maragmpgve	pgralalfds
3301	avatgepvva	pvpldpaalr	arggdvpaal	rgivgavrra	aatavipsgl	reqlaarpva
3361	errarigglv	rdeiahvlgh	aegsridpdr	aflldigfddl	tavelnrria	astgiglpst
3421	lvfdhptaaa	lavvhhdelf	gadtapepvt	atatgpadgd	dpvvvvgmac	rypggvsspe
3481	dlwrlvtdgg	daiseftpdr	gwdlanlydp	dphdpgtstt	rhggflhgag	rfaeffgms
3541	prealttdag	qrlllecswe	aferagidpv	slrgsatgvf	agvmyhdygd	lhapehegy
3601	qghgsagsia	sgrvsytfgl	egpavtvdta	cssslvgmhl	aaqalrgec	slalaggvtv
3661	matpatfvef	srqrglspdg	rcrafsddad	gvwsegvgm	vvlerlsdar	rnghevlavl
3721	rgsavngdga	sngltapngp	sqqrvimaal	asaglrssdv	dvveahgtgt	tlgdpieaga
3781	llaayggdre	tplylgsvks	nightqaaag	vagvikmvea	mrhgvlpatl	hastpsshvd
3841	wsagaveilt	anrvwnadrp	rragvssfgi	sgtnahvle	apepaeavar	pdtagplpww
3901	lsartgpala	aqaarlagsl	ehrtdvdald	vgwslatgra	rfghravvia	edtaaarral
3961	aafaageqhp	avvegtvaag	gtafilfaggg	sqrllgmrel	harfpvfara	fdevcahldp
4021	avgevmwgdd	agalndtgva	qlalfaleva	lfrlveswgv	vpdhlvghsi	geiaaahvag
4081	vflsadaatl	vsararlmga	lpaggvmvav	aateeevtpl	ltggvsiaav	ngpssvuvsg
4141	aesevdalvg	rfadrtrkrl	atshafhspl	mapmmeefra	vvaglefaap	qipiistvag
4201	rtgddvtdpa	ywvehvratv	rfadavaald	edgtliveigp	datlsgmagq	ltdartvptl
4261	rtsgpdgdrd	evtalfaala	rlgtagadir	wetaldggrt	vdlptypfqh	dtywpapapa
4321	nrgdagsigl	sgpghpllga	vvaradtdgv	lltgrlstvt	gpwladhvvg	grvllpgtal
4381	lemavragde	agcdvvrelt	laappleipgg	gvtvqvwlda	pddagdravs	ihsragetap
4441	wtvhatgllg	tggtaapetl	twpppggaep	fdvtdrydrl	aetglaygpa	frglraawrr
4501	ggdvfaeivl	gegagpadgf	ghpalldaa	lhaagtvggt	asvpfgwgdv	tihatgatal
4561	rvrlrtdapd	tlsvlvadga	gdpvatvgal	tlrplpegap	graerdiyrr	vwipatdtpd
4621	tgettigvla	edtavlvdpg	gtrhadlaea	ldaapdvllv	pvatgdgdla	arthdatsrv
4681	ldlltrwtad	ersagsrlvv	ltrgavaaqd	gdgvvdpaaa	avsglvraaq	aeypgrigll
4741	dldldfdadp	asaaaipval	agdepqrair	agrvidprlq	rhdvtatdgt	dgtgdtdgta
4801	tdgtdatggt	aggtgwrrdg	tvlltgggtg	lgaltarhla	arhdvrhlil	lsrrgpdapg
4861	aadltaelee	lgarvtvva	daadraaltr	vldaipaehp	ltavvhtagv	lddgvlaslt
4921	pqrllrtvlrp	kvdaawnlhe	laadiegvfl	fssvagtllga	agganyaaan	aflldalatvr
4981	raagrpalst	awgpwepvgg	mtgtltdadr	armsrsglpp	mpvarglell	daalgeaapv
5041	etapvllpvp	fdldalrgrp	eipamlrglv	rapsarrsaa	agssgasgtl	gdrlaalgea
5101	drhdhvlqlv	rdevaavlgv	asaasvdpdr	aftdlgfdsl	tavelnrllt	vtvgtlrlpst

Figure 18 (Continued)

5161	lvfdhpsaga	lathllgelv	ghvaatpvgs	ptavdrddpv	vivgmacryp	ggvsspedlw
5221	rlvtdggdai	sgfptdrgwd	leglydppdp	rpekthavgg	gflhgaggfd	aeffgmspre
5281	algtdaqqri	llecswaefe	ragidpvslr	gsatgvfagv	myndystllp	ggeheafrgn
5341	gsapsvasgr	vaynlglegp	avtidtacss	slvamhwaag	alrsgecsia	laggvvmst
5401	pstfvdfsrg	rglspdgrr	afsdadagvg	wsegvgmvvl	erlsdarrng	hevlavlrgs
5461	avnqdgasng	ltapngpsqq	rvimaalasa	glrssdvdiv	eahgtgttig	dpieaqalla
5521	ayqcdretpi	ylgsvksnig	htqaaagvag	vikmveamrh	gvlpatlhas	tpsshvwdwa
5581	gevelltepi	pwdidgrarr	agvssfgisg	tnahlvieap	epsaapvapa	gaaqddpgdl
5641	vpwvlsgrtr	ealqagaal	rtaapdgpra	dvqfslattr	safehravvl	atsrdealaa
5701	lealargdrd	ervvdgrtaa	ggtafllfagq	gsqrlgmgre	lharfpvfae	afdaacaqld
5761	pavrevmwad	daaalrdtai	aqpal falev	alfriveswg	vvpdhlvghs	igeiaaahva
5821	gvfsladaat	lvsararlmg	alpaggvmlva	vaateeevtp	lltggvsiaa	vngpssvvvs
5881	gaesevdavv	arfadrtrkr	lrtshafhsp	lmammeefr	avvvglefaa	peipvvstva
5941	grtgaemtdp	sywvehvsat	vrfadavtal	dedgvttlve	igpdtltal	taqaltgeqi
6001	svptlragea	epatllrava	tvhvgrtvd	waaqlpgarr	velptyafrh	trfwptasaa
6061	rsgdatslgl	arpghpllga	vmdradagdv	vltgrlspat	qpwladhtvg	grvllpgtal
6121	lemvvrage	vgcdlvhdlt	laapveiphd	ravqlqvvg	epdgdgrtv	dvhsrgegdr
6181	twtrhatgvl	aggasagwsp	dvwppagavp	lgldgcydrf	aeagfgygpa	frglraawsd
6241	gtttfaeval	pegtgadrfg	lhpalldaal	haamltdgdd	daaglpfswq	gaalyasgas
6301	alrvclgrda	gggltidatd	pagapvvsvg	slqvravpaq	ahtgavprda	lfrptwaplp
6361	dapahtgsvt	vleagldelg	agldagsaap	etvllpvhgt	gdvptsahel	satvlaavqt
6421	wladerlars	rlvlltrgav	atgigtdgd	vtdpaaaaar	glvrsaraeh	pvrfglldld
6481	patdtgvpdg	lpfdtepdla	vrsgtvyaalr	larvpdtard	daatgwddp	tvltvggtgg
6541	lgravarhly	tdrgarhlll	asrrgpaadg	vdalveelta	hgarvgvvac	dladpaaata
6601	lvdgvdpehp	lvavvhtagv	lddgvvdalt	pqrvervlrp	kvdaawalhe	atrgtdlqgf
6661	vlfssvagta	gsagqanyaa	gnafldalag	yrrasgiagq	slawgawdgd	ggmaaaldda
6721	nrarmaragm	pplstaegla	lfdaaldadd	alltpvrldl	avlreraevp	silrglvrap
6781	argaaasapd	vadlagrlag	ldedgrrqvl	ldvvathvag	tlghtdlsqi	gpddefgelg
6841	fdsltavefr	nrlgaatgla	lpatlvfdhp	tpgalaghlq	tlvtpagadg	adalldelae
6901	lerrfgavev	deaahervga	rlealrsrwa	girpttdeaa	padsgtaefd	fdtasdddmf
6961	alldsqlgtt					

Figure 18 (Continued)

16	CP011868. 1	SelK	<pre> mtdeeklvdy lkwtadlhe arrrlaevea grqepvaivg macrfpggig spedlwelvs tggdaisgfp adrgwdmdal rdgrsatdgg gflegagdfd pgffdispre avamdpgqrl llevsweale ragvdprglr gsrtgvfvgt sgqdyihlal aadvdmegha stglaasvms grlsfalglq gpaltvdtac ssslvalhla arslrdgecs lalaggvvm stsanfssfs rqgglapdgr cktfadaadg tawsegvgvl lverladaer ighpvlavvr gsavnqdgas ngltapngps qqrvi rdala agglgpadvd vveahgtgtr lgdpieaqav latygaerer pallgsvksn lghtqaaagv aglikmvgai rhgtvpatlh vdrpsshvdw tqgavelate sqpwpetgre rraavssfigi sgtnahvive qapqtpdpe adtgtvpvpl vpwvvsartp deldaqivri galaapggps atdvgfalat grtlfdhrav laptadvre largsaahat gsvgvlfsgq gsqqlmgre laarfpvfae afdavcaeld pllgrplrev vwqddesvlq qtgwaqpalf avevalyrlv eswgvrpgmi aghsvgeiaa ahvagvlsip daarlvraag rlmqalpagg vmvsrated evtpllegvv svaalntpga vvlsgaedav davlaglgr rstrlsvsha fhspmdpml edfraalspi vfgeptipvi sdtvgepatd lgadywvrhv retvrfadgv ramsaagvtt fvevgpggvl aaaaagslpa satvvpplr drseesava alagmshsvg avdwpalfag tgarwvdlpt ypfrherywp rpattghp11 gppvpvagtg etvltghlsv rshpwladhv vggvhimpga atvelvnrav davgrhried ltlvapvvlp drdavrvtqr vgepdghdrc eitvharpdg gewmvhavgs lagdpvdlgf dggvwppaga tevslegfye ryaetglqyg pafrglrsvy trgdevfaev vapesaatan gyglhpalld avlhanvfig rgdgalpfa wngvslhrsg asvlrarlrp gtgdgveiaav tdaegdpvls vaslvraas gagagtagql sgirwvpgta aepatgtrwa vvggdeldlg yaihrageav tayadtlgga vgedgslpdv flvplgtaga geddadvpat ahtlthrvla llqewqstpa laatr1vfvfvt cgavsvdaep lrdpaaaavw glvraaqvei lgakllladl ddafasav1 pallgadeqq vavrdaavrv arlaplsagp dlvpvpgvwr lhpargsis gl1elvecpev tepltgrqvr igvraagmnf rdalttlgmy pgeagllgge aagevtgtgp evtglrtgdr vtglvfggfg pigvtder11 vrvpepwsa qaasvplvfl tawyalvdl1a glragekvlv hagagvgms a1q1ahh1ga evyatasdak qdvlrdlgva ddhiassrtt d1fasawagag idvvl1nalsg efvdaslgl1 gdqgrfvemg ktdvrdpdal pgvayrafdl meagpdriaa mwqtll1elfe sgvlaplvr twdvr1saraa fthmsaarhv gklvltvppa rdpdgtvlit gg1tgg1gael arhlvsehgv rhllltgrrg pdapgalelr aeltahgadv tvlaadvaer devaallsti pdehpltavv haagvlddgm lds1n1pdrmd avlrpkvdga wh1heltaea dlsafv1fss isgl1gg1gq gnysaantfl dalaehrrgl grvgtslvwg pwdseagmvq gltdadarm sgsmp1pvv ergla1fdaa l1taepvvvp vrpdvrgpav agavpsv1rg sgaatrtte ttdr1rgld adareel1re lvisraasvl ghtdttaidp rgef1slgfd </pre>
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Figure 18 (Continued)

			<p>slvavelrnk lageldtlp asvdfdnetp drlaswlhee laghlvaada ptegggpaav            avdtdseetl vglflaavrr dksveamqmi davaalrptf srtseleerpa spvvladgpt            tpklifvsap gatggvqhya rlaahfrgrr rvlalplvgf epgetlpatg eaaiesvaes            vlraadgapf vlvghstggs layeaaglme erwgvgpeav imldtmslry aegegadyeg            vgryyladid spavaltstr ltamvhwynr aaalrpvget taptllvras iplpggkqpq            eappldtdav ltidadhltn akehsgvtae ameewltslg aatr</p>
17	ALE82591. 1	SelL	<p>1 mttndiptva tgpqqrllrps pamarlqega pvhrvrtpag deawlvtrya elkqllmdkr            61 vgrshkdpas aprymdnrfm dmliiegdge tgmrehtdmr stlspmfslr rinalrpmvd            121 asanelvdam eaagppadh rdfsmpfaln vlygligvap dkrgrmfell gamavlt dpq            181 sardaglams aflndlvaqk rsdpgddvis rlieaglsdq viatrcagll fagldsvvsh            241 idvgvvliae ypeqraaaqa dptvlkhave evlrtasagd sslpryanad ieiggvtire            301 gdlvllldftl tnfdprefdr peefdverhp nphmtfghgi whcvgaplar velqsafvtl            361 fgrrlpglrpt tpllldads vslsggfnhl pvtw</p>
18	ALE82592. 1	SelP	<p>1 mspqlsrtpa dasvdeasei ldrdggllae nlidrdtlka lwadlrpala gneygtnsfa            61 ggktkrlssl farsrgmekl alnplflgva raqigrasae qfgsqrveit pnigvsttga            121 iqiwpgesqq vahreddvahl lpcpgpnrsv qimlamsefs aenggtvvyp gshrweadrs            181 ptpeeavate mspgscliwv gglyhrggpn rspgprrgtlt msyvrgnlrq eenqylavpr            241 eilreypeel qrllgydicp pnlgwvnded phrvlredat vs</p>
19	ALE82593. 1	SelDI	<p>1 mqptrqipivf vshpesglfn pmlvlaeels rrgvadlyfa adsyrradve aagrtptitf            61 vplgdsvpew taatwddety ravtqrsrfr ahraliehtf hpeasiekyr lleaaverig            121 palmviesmc aygvelaitk kiryalnspf mpsnlltshv plmrstprp fpvphsglpy            181 dmtlagritn etfkwrvtgm slqktmrell rrdkvtael giapeakgfl srvdhaalil            241 sytvaeleyp msypdtmrlv gtmvpplpqa pddgglgawl dsdsvvymg fgtvtrltre            301 hvesllever rlgeqghhvl wkllppdqtm lppaemrpdv vrieswvpsq ldvlahekvr            361 vilthaggng fhglyfgvp lvvrplwidc ddqavrgsdf gvsitldrpe tvdvadvmdk            421 ldrvlrdpaf rdraahyqrl lrqaggrta adellgltp tatptqpa</p>
20	ALE82594. 1	SelG	<p>1 mstpalarpap taerwhgapf vrqvtiltrr qlyamvhdpq lvvfgliqpc vilflftqif            61 sniiqtsvlp agtsyldflm pavlvnhvvq sstqsgvglv edldngivsr lrsllpirpvs            121 mlarsladi vrnvvqivll llialalmgy apggglsgil vscaltlflc wslswiflai            181 aastrsaetm nsisvlavlp imflssgfvv lqalspwlaa iagvnpityv ieasrslaig</p>

Figure 18 (Continued)

			241 sdpgnlvtia lftclvlaav giagavrgfr epvlt
21	ALE82595. 1	SeIH	<p>1 mtrarsdepi ieaigigmf gstpalagvd ltvgrgtvmg llghngagkt tlvniltamv          61 pptshtarva gfdvsrepge vrkrigltgq yasvdeklsa idnlvllarl lgasktrara          121 radellieafg lthaasrkar tysggmrrrl dlaaclvgnp evivldeptt gldpssrram          181 wdivtqlvde gtsvllttqy ldeadtladr itvlssgrvv asgtsaelks qvgqrtvtvt          241 lapgsatgta rsalvsagta pavrdcgtiv vpiasarreta tviraldevg idvaelafge          301 ptliddvylal ahgtpefaa</p>
22	ALE82596. 1	SeRI	<p>1 msdhsppgrrr lvgrdvesaw laealvaaaa gepavrllvg ragigksall dqlcdtrppg          61 advrllrarg reqtadvfsa vvrldifgplg lgsgagspel leggarwsms alaedfagad          121 pdnvypvlhg lywltvnltt qapllvvvdd lqwddgsia flafllrrca glplavvlat          181 rtdetgtlpa rlagiggqig vdvkqvrplg radiarlava rgpldaepih adlldalaea          241 sggspilver lvaelgpvtr eqatgrvhel grevlrlve rhvvapdvaa vasavavvga          301 eatdvlasls gvpagsvkda vdilvrtdivf apgrtdfrhd llrsavlrll pedrlitelrr          361 rgarvisdag rpaesvaavi lalpeisepw madvllaat aaghragaqa varylapvlq          421 arphdvgvrm rlaaalggta pdeavrqlre aldlapdlpt rarvavqlam tslavqqape          481 garilqdvld aldaadtds gpeatelrth veaallvagl dekstvaeti arlrmsvpa          541 grtpaerqkl ammtvakame gdgadaavem arrvllvdea tlggwavlas slvlrladev          601 eestavldrj vtqsrrqasa wtyslaigtr sanqilvgdl agaeddaqaa ldvaeqeawr          661 gntvvptial asvrhlqgsp eealalldgl srprledfaw eyhlylmtra gasadtgdve          721 valalyrrcg qslaaagian pmlapwwaha avlladtgra aaargmvelg eqsaarwgta          781 rsrqlalial gvitppggpp elideavavl ensparmeli laylrlgrav lelgypeaar          841 ehlrhaatla aragalraat aarellvrag gmmrrptgsp ldpltgaerr vvalavdgar          901 nreiaeaafi tlrtvevhl t safrklgvad raglaeivsg arvrrg</p>
23	ALE82597. 1	SeRII	<p>1 mseptirvrg ggtaalgral dslaagtstv vvtgpepgtg rsrllhtaaa garargvrvl          61 taravvaese yplgvvhgll rpldgsaelr rapgapadta llhrwcrllvl daahrpvl1          121 vvdldhwadt esqrwlqml1 rhrhgapvgv lvaangthea aewagapair anvtlirtgpl          181 plaavraavt aaygaapdra fsvvarratg gnpavlaatl arldrsvtpt spavpelrrc          241 aalaraeqvr avldgipadi vtalraaavc gpdlwpvvdv igggpbstga dvtrlaatg          301 lvrgpgcill cdevvtdvvl agidpdrrog lfaraaaalav raglpddgva rallaaptlg          361 epwgaellyr vacghrggrn haaaaacaer allepvppgl sgplmvelat arswtepvaa          421 rmlalvvqe adptdghga qaadilladg dvgaarrala itvrrcagdt tahrdllsls</p>

Figure 18 (Continued)

			<p>481 rltdegydd llaapscape pagpgtdppp aastaaasgs lawseavrgr draaatrlar  541 ealaapdagw tpvmprvmaa mtlevagcph ealralepvl ldlagdrsvp pailamtalv  601 alragddlga rrdlraaraa sagrarpggg dplvaavqil lhlaegdlae atvvasarhg  661 vggdrpgial layalgrvha arggaragfe lfmrcgrlll drgrvnpalv pwsaaaaal  721 aacdehaaa1 riardehrla vrwgappia vagaavaalg relshvagg</p>
24	ALE82598. 1	SeiRIII	<p>1 mlrdrepelr vlrdavlraa dgrggaillg ggigtgrtal ldaaadiava aglrvlrata  61 dvveqdfdhg varqlfdpll ataargdrer wlagrdvpqa layvpadadd ptvahrwiqe  121 lqdlleavaa ggpvavcvdd lqwadgpsqr winhiavrvt glpvvlvata ldgdpcsqrp  181 pvrarfarsaa vlrarrippe avdaviaerf wpaaapefvl achetcagnp lildtvlgel  241 vaagvrpdaa qagavraarp valrerlarc vrggdpsarr ylravavlga gpdpevlrri  301 geldradlrt vpaslveqgl ltgggvrvv hplveevate paeredlhr aarylhefgh  361 palevaghll avtaplatwa ievlraaaqq aatpvpdar hsgvdpdav dtairclrra  421 lldsgatsre rgvllvelas verfvephta vrhvaqalpl ldsardraaa ltlidpamcr  481 dapdsvgeai rradtgdadg tvalrirara rmaeerpeg laeschilre vlrapdamls  541 tsagrelvgv llhaamtgh vpariahlg erllritpar qlppppgvpp gdgprgllvl  601 alvaadrpap veawlagggd rdpavasade lalvqlaggr vaaaalpgvl raagpptaafh  661 aallaaalds rvlvpgravt drppgvglla hvthgmraa racaheepdl alecfldggr  721 hldhlgwrnp alfpwrgwaa rlygrrgeyd aavayadeql tlaeawgapa algralring  781 slaegadgta qlraavdvla gsgdlrelgr seialggria ragdpagdel vrrgrqtae  841 lgadaaatvd papapaaggt ppaepateaa agptgpeppd plteaerrvv rlavggatnq  901 aiaddigis ravekrltsv yrklgvsgra alpgag</p>
25	ALE82600. 1	SeiO	<p>1 mtatsdidaa tqdlrsrvae lhatrrearl gpsrqateqg hargkltvhe ridlildpgs  61 freieqfrrh ratgfgledr rphtdgvvtg wgridgrtvf vyahdfrihg gslgeahatk  121 ihkvmklaes agaplislsd gagariqegv talagyggif rrvrasgvv pqisvmlgpc  181 aggatyspal tdyvfmvrdd sqmyitgpdv vsavtgesit heelggahvh atetgaaafa  241 yddeetcfad vrhlvsllps nnreippvva tddprdrmtg alldivpadt sraydmhdvi  301 aevvddgdlf evhatwatni icglarldgh tvgivangps smagvldiha sekaarfvst  361 cdafsipivt lvdvpgflpg gdqehggiir hgakllyayc aatvprvqvi lrkayggayi  421 vmdsrsgad islawptnei avmgaeaaan vvfrrreiaaa pdpeearsqr ikqyrqelmh  481 pyyaaeaglv ddvidpaetr aalvealavl rakrtelpqr khgnppt</p>



Figure 18 (Continued)

26	ALE82601. 1	SelRIV	<p>1 mrvstsegmt gerlssdsts acmvslldrs1 rivaanqemf rrfhrtdtas icgssfctlv          61 hpsirtrign qlerlldgqq prvyersval lgpdstvwgd lmatatarda grvegvmavl          121 rpvegdagpm agrgaprkil sdmdarileg vasgastvql astlflsrgg veyhvtallr          181 knkvknrpal iskaysmgff elgswppqvv pdhvk</p>
27	ALE82603. 1	SelRV	<p>1 mhadaapmsp vpgpavlher dddiaavegi vdrsfgggtg lvvvtgplga grtallaeca          61 rraaerdvly rrargaaaer rygfgvvrql lggdapdlfp apehpgsgpa gssdavseal          121 levlrldtla rpglllvddv tradpaslrw lahlgrrsag lratvvlavp dgdvvpvgdta          181 vgellaradv vrplrpltp egiagvararl gtraddavvt algevsegnp lfildavveel          241 raapsdgrrv sghqvractp arlrdmaaa vrllpeptrr ylaalaviqd vaddvllarl          301 aeldhadada arrvageagl irpgrprlr hrvvadalat tgsaeerrgt hlraatllhn          361 dgirpdrvas hllyvtssyp rwaigalrea avlatrrgep wtairylrha lladapeadr          421 aqvlvelasl ersvdaglal rrvvaavpll apltaradal crampitleg aassvlamlr          481 gvaeeldgvt dpdpatrela lrlrarvlya drhrpagvta avarldeler qpgglpldtp          541 gerelacvlt haaalsgrrt aaavaavgrt ilarepsagh vhtiglvvg slcmadapee          601 ltawlgvald haraegatat eavvraeaa vlvcsgripe aeeqvrlsfe lfgeadedal          661 lpglilaavi pglqdrapae hilarygaaa evpegfgacl qmlrarvald agdpdaaley          721 cldagrrfer agwdgaavaw rpwaieirrg lqqlsearal aeeelvrtra wgaplqlgra          781 lrvlgelcgr draepiltea vevlrsandd relahairsl halpdrvghp ppdgscpttv          841 qtagftpsvl vdlspagrrg ghsgatwalt rsegrvalma aggrtnqeis dvlgvsvrav          901 ekhltgyvrk lrvsgrsalg rmwedgsdls a</p>
28	ALE82604. 1	SelRVI	<p>1 mdgapllerr aevdalreav ahacagrtrv vvtgpagsg rtrlldvadg laaahdalvl          61 ragggrhpg rspfalardl lrrsaagptt daaallrdaa rrtartegaag tdvaailglv          121 rsvagltaes pvvlladdld radpesvrwl ahlahhadgl pllvvgsvhs tpgagptara          181 ldelasapgv ghlapaplsr davrswlhaa avvpahpevl dacvgatggn palvarvvqr          241 lahpapvtda adrihgigaa laveqvsavl rdlspeelial ahavaviged tapravaiva          301 elddvavdra aarlalgil drdgrfrha aartavigt1 sddrrcrlra wagr vleseg          361 appervavqf ldagppadrg vvelmhgaac rarqrgapel aasflvhalr gnvpdtraa          421 lllldgiter hsapgrahrh ltralslsgc arerarvitl lvafhtgpa eglvgllerg          481 lrdlaavpe sgpeppgdrd lrlglealll yasaedsaqa aavrwdgdr dtphltgpcgag          541 asalrsahvf ystlllrtda aesavlarga ldgaldesea lqpirmgalg vlawteaddt          601 laplherala darrqqrpel haslrgvrsm lhircgrvpe aladarasid vitgelsget</p>

Figure 18 (Continued)

			661 rlmilhcavl alielgevne aaalvhpanl egtsdrsrw swlldaraav laargprea
			721 laqageagr lrnvgivnpa algwqgrtal lhheigehaa aravalehig larrwgthgh
			781 vgaalrvlgv vqgvsgglrs lqdaavelgr sprvldsarc avdlgvmvre igdeaqarvl
			841 lregvdlaeg cgarvlsrra rteltaaggr grrrsggvs1 tpaelevarl aaagasnrsv
			901 aaslgvsrvt velhltrcyr kldipgrael aralrrrvlp qpgesg

Figure 19

Position	$\delta_H$	mult (J in Hz)	$\delta_C$	
1			172.68	C
2	H <sub>a</sub> 2.53 H <sub>b</sub> 2.10	obs ddd (17.4, 11.6, 5.7)	39.40	CH <sub>2</sub>
3	1.81 1.36	obs obs	27.79	CH <sub>2</sub>
4	3.10	obs	71.00	CH
4-OH	4.26	d (7.0)		
5	3.46	m	74.17	CH
5-OH	4.78	d (5.3)		
6	H <sub>a</sub> 1.63 H <sub>b</sub> 1.28	dt (14.6, 10.4, 10.4) d (13.8)	39.17*	CH <sub>2</sub>
7	4.26	m	68.27	CH
7-OH	5.51	s		
8	H <sub>a</sub> 1.53 H <sub>b</sub> 1.33	obs obs	46.16	CH <sub>2</sub>
9			97.32	C
9-OH	5.89	s		
10	H <sub>a</sub> 1.56 H <sub>b</sub> 1.52	obs obs	40.39	CH <sub>2</sub>
11	3.53	ddd (12, 7.2, 4.8)	68.27	CH
11-OH	4.28	d (7.2)		
12			71.18	C
12-OH	3.61	s		
13	3.96	d (9.1)	69.57	CH
14	H <sub>a</sub> 1.42 H <sub>b</sub> 2.10	dd (14.6, 9.3) dd (15.1, 3.8)	33.38	CH <sub>2</sub>
15	4.34	d (7.6)	76.29	CH
16	5.08	dd (15.3, 9.1)	136.38	CH
17	6.06	dd (15.2, 10.4)	128.35	CH
18	6.36	dd (14.8, 10.5)	152.88	CH
19 - 24	6.88 - 6.46		131.5 - 133.5	6 CH
25	5.35	br s	155.57*	CH
26	2.50	obs	42.85*	CH
27	3.10	obs	73.50*	CH
28	1.82	obs	39.39*	CH
29	3.22	br s	73.53	CH
30	H <sub>a</sub> 1.35 H <sub>b</sub> 2.06	obs obs	22.68	CH <sub>2</sub>
31	0.75	s (7.3, 7.3)	10.78*	CH <sub>2</sub>
32	1.01	s	21.44	CH <sub>2</sub>
33	1.01	obs	17.87*	CH <sub>2</sub>
34	0.93	d (7.1)	12.17	CH <sub>2</sub>
1'	4.40	s	96.80	CH
2'	3.57	dd (5.2, 3.4)	70.89	CH
2'-OH	4.29	d (5.2)		
3'	3.18	ddd (9.1, 6.0, 3.3)	73.65	CH
3'-OH	4.50	d (6.2)		
4'	3.08	obs	72.00	CH
4'-OH	4.71	d (4.9)		
5'	3.06	obs	72.13	CH
6'	1.14	d (5.6)	17.93	CH <sub>2</sub>
1''	4.64	br s	98.66	CH
2''	H <sub>a</sub> 1.79 H <sub>b</sub> 1.99	obs dd (12.9, 4.7)	35.38	CH <sub>2</sub>
3''	4.05	d (7.9, 4.1, 4.1)	61.41	CH
3''-OH	4.17	br s		
4''-OMe	3.28	s	55.79	CH <sub>2</sub>
4''	2.81	dd (6.6, 2.9)	81.80	CH
5''	4.07	obs	63.10	CH
6''	1.16	d (6.4)	17.61	CH <sub>2</sub>

\*Chemical shift extracted from HMQC spectrum

Figure 20

Position	$\delta_H$	mult (J in Hz)	$\delta_C^*$	
1			171.48 <sup>†</sup>	C
2	H <sub>a</sub> 2.33 H <sub>b</sub> 2.08	ddd (17.4, 11.5, 4.6) obs	29.38	CH <sub>2</sub>
3	H <sub>a</sub> 1.70 H <sub>b</sub> 1.57	obs obs	25.14	CH <sub>2</sub>
4	4.81	obs	73.34	CH
5	4.92	dt (9.8, 2.2, 2.2)	70.38	CH
6	H <sub>a</sub> 1.75 H <sub>b</sub> 1.67	obs obs	34.33	CH <sub>2</sub>
7	3.95	obs	67.26	CH
8	3.56 2.47	dt (15.9, 9.9) obs	45.93	CH <sub>2</sub>
9			204.20 <sup>†</sup>	C
10	H <sub>a</sub> 2.47 H <sub>b</sub> 2.77	obs dd (18.3, 9.4)	41.98	CH <sub>2</sub>
11	5.11	dd (9.4, 2.5)	70.28	CH
12-CH	4.81	s		
12			73.98 <sup>†</sup>	C
13	4.47	d (9.7)	71.68	CH
14	H <sub>a</sub> 1.50 H <sub>b</sub> 1.73	t (12.7, 12.7) obs	36.01	CH <sub>2</sub>
15	3.96	t (9.8, 9.8)	77.10	CH
16	5.46	dd (14.2, 8.9)	133.01	CH
17-23	6.14-6.40		131.0 - 134.0	7 CH
24	6.01	m	130.17	CH
25	5.54	dd (14.8, 9.8)	132.95	CH
26	2.41	m	*	CH
27	3.36	obs	*	CH
28	1.98	obs	39.25	CH
29	5.80	br s	74.48	CH
30	H <sub>a</sub> 1.40 H <sub>b</sub> 1.82	dt (15.3, 7.9, 7.9) obs	22.93	CH <sub>2</sub>
31	0.78	t (7.3, 7.3)	9.41	CH <sub>2</sub>
32	0.95	s	17.77	CH <sub>2</sub>
33	0.95	obs	17.0	CH <sub>2</sub>
34	0.95	obs	11.45	CH <sub>2</sub>
1'	4.89	d (1)	95.51	CH
2'	5.25	obs	68.88	CH
3'	5.08	dd (10.2, 3.6)	70.72	CH
4'	4.75	t (9.9, 9.9)	70.19	CH
5'	3.93	dq (9.5, 6.4, 6.4, 6.4)	68.95	CH
6'	1.66	d (8.1)	17.05	CH <sub>2</sub>
1''	4.72	d (4.66)	97.64	CH
2''	H <sub>a</sub> 1.93 H <sub>b</sub> 2.10	obs obs	32.58	CH <sub>2</sub>
3''	5.25	obs	64.28	CH
4''	2.98	dd (9.4, 3.0)	79.33	CH
4'-OMe	3.24	s	55.96	CH <sub>2</sub>
5''	3.98	dq (9.4, 6.4, 6.4, 6.4)	62.63	CH
6''	1.11	d (6.3)	17.28	CH <sub>2</sub>
Ac	1.91-2.09		20.3 - 20.7	9 CH <sub>2</sub>
Ac			168.5 - 170.5 <sup>†</sup>	9 C

\* Chemical shifts extracted from H<sup>13</sup>C spectrum, except where noted

† Chemical shift extracted from HMBC spectrum

\* not observed

Figure 21

	selvamycin	nystatin
<i>Candida albicans</i> SC5314	29	1.0
<i>Saccharomyces cerevisiae</i>	21	1.1
<i>Trichoderma harzianum</i> T22	26	2.1
<i>Aspergillus fumigatus</i> ATCC 1026	40	1.2

Figure 22

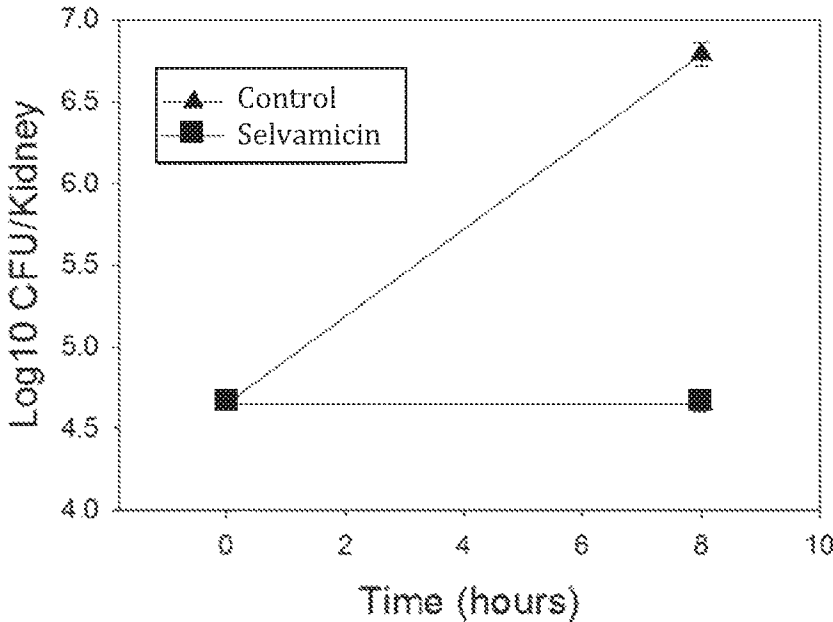
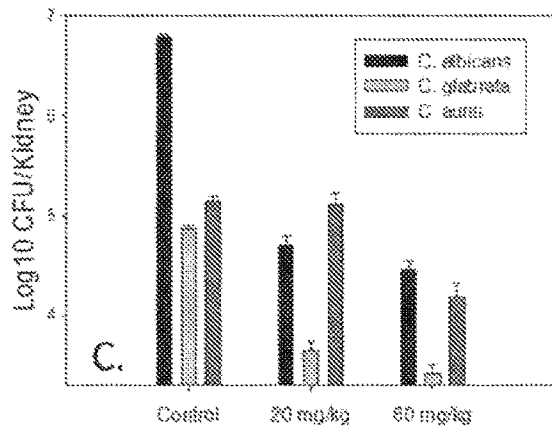
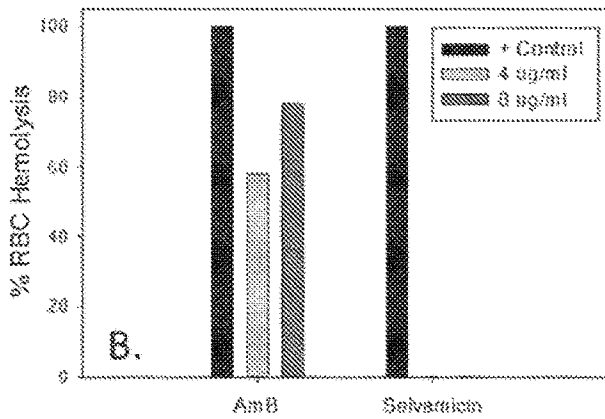
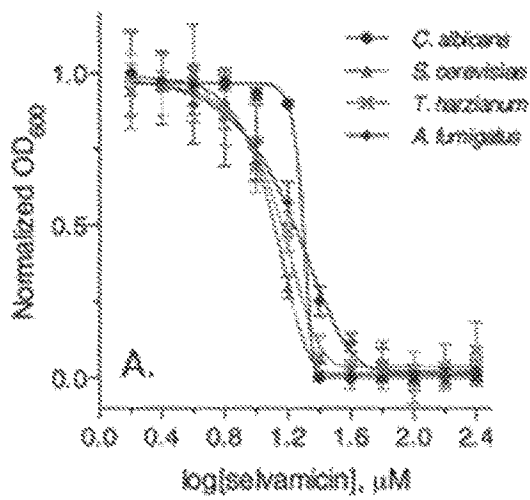


Figure 23



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## ANTIFUNGAL COMPOUNDS

## RELATED APPLICATIONS

This application is a § 371 national-stage application based on PCT/US17/35697, filed Jun. 2, 2017 which claims the benefit of priority to U.S. Provisional Application No. 62/345,516, filed Jun. 3, 2016, and U.S. Provisional Application No. 62/397,079, filed Sep. 20, 2016, each of which is hereby incorporated in its entirety.

## GOVERNMENT INTEREST

This invention was made with Government support under Grant No. AI109673 and Grant No. GM086258, awarded by the National Institutes of Health. The Government has certain rights in the invention.

## BACKGROUND

Fungal diseases are often caused by fungi that are common in the environment. Most fungi are not dangerous, but some types can be harmful to health, particularly in immunocompromised individuals. Over the past several decades, there has been a significant rise in the number of recorded

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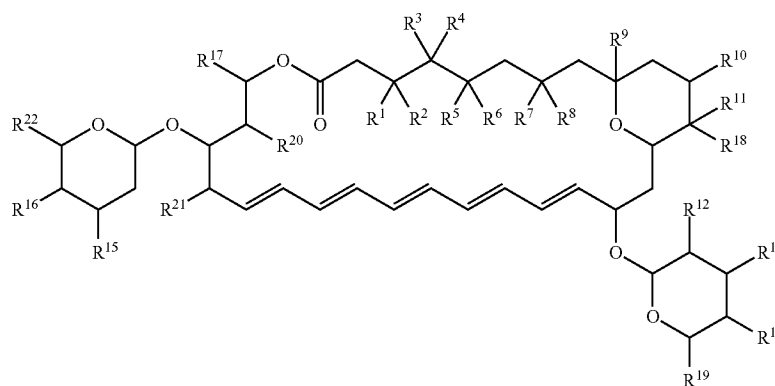
instances of fungal infection. In part this is due to increased awareness and improved diagnosis of fungal infection. However, the primary cause of this increased incidence is the rise in the number of susceptible individuals. This is attributed to a number of factors, including new and aggressive immunosuppressive therapies, increased survival in intensive care, increased numbers of transplant procedures and the greater use of antibiotics worldwide.

Clinically indispensable antifungal natural products include amphotericin B and nystatin A<sub>1</sub> both members of the World Health Organization's *List of Essential Medicines*, along with the food preservative and topical antifungal natamycin. However, the existing suite of clinically useful antifungals is limited. Although amphotericin B and nystatin A<sub>1</sub> have been used widely over the past 50 years, they suffer from major liabilities, most notably high toxicity and negligible oral bioavailability.

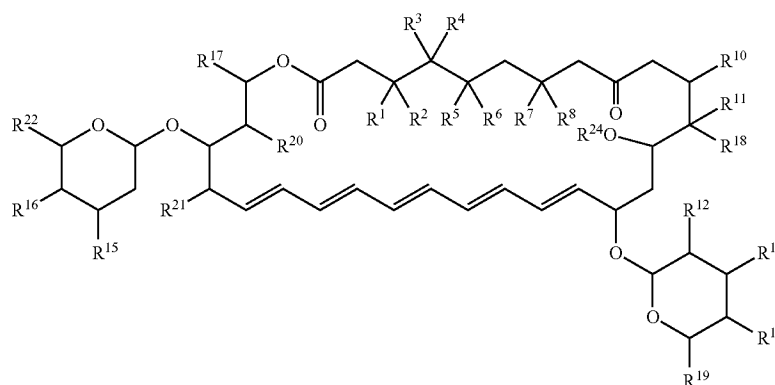
Hence, there is a need for effective antifungal agents and methods of producing such agents.

## SUMMARY

In certain aspects, provided herein are compounds (e.g., antifungal compounds) having the structure of Formula I or Formula II:



Formula I



Formula II



and pharmaceutically acceptable salts thereof, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup> and R<sup>24</sup> are as defined herein.

In certain aspects, provided herein is a pharmaceutical composition comprising any one of the aforementioned compounds and a pharmaceutically acceptable carrier.

In some aspects, provided herein is a method of inhibiting the growth of a fungus, the method comprising contacting a fungus with a compound of any one of the aforementioned compounds or compositions.

In some aspects, provided herein is a method of treating or lessening the severity of a fungal infection in a subject, the method comprising administering to the subject a compound of any one of the aforementioned compounds or compositions. In some embodiments the method comprises treating candidiasis in a subject comprising administering to the subject a compound of any one of the aforementioned compounds or compositions.

In some aspects, provided herein is a selvamycin biosynthetic gene cluster (BGC). In some embodiments, the selvamycin BCG comprises one or more polynucleotides encoding SelE (SEQ ID No.: 2), SelDIII (SEQ ID No.: 3), SelI (SEQ ID No.: 4), SelII (SEQ ID No.: 5), SelSI (SEQ ID No.: 6), SelSII (SEQ ID No.: 7), SelSIII (SEQ ID No.: 8), SelSIV (SEQ ID No.: 9), SelSV (SEQ ID No.: 10), SelSVI (SEQ ID No.: 11), and SelSVII (SEQ ID No.: 12), Sel A (SEQ ID No.: 13), SelB (SEQ ID No.: 14), SelC (SEQ ID No.: 15), SelK (SEQ ID No.: 16), SelL (SEQ ID No.: 17), SelP (SEQ ID No.: 18), SelDI (SEQ ID No.: 19), SelG (SEQ ID No.: 20), SelH (SEQ ID No.: 21), SelRI (SEQ ID No.: 22), SelRII (SEQ ID No.: 23), SelRIII (SEQ ID No.: 24), SelO (SEQ ID No.: 25), SelRIV (SEQ ID No.: 26), SelRV (SEQ ID No.: 27), and/or SelRVI (SEQ ID No.: 28). In some embodiments, the selvamycin BCG comprises a modified selvamycin BCG (e.g., comprising one or more inactivated or deleted genes selected from SelE, SelDIII, SelI, SelJ, SelSI, SelSII, SelSIII, SelSIV, SelSV, SelSVI, SelSVII, Sel A, SelB, SelC, SelK, SelL, SelP, SelDI, SelG, SelH, SelRI, SelRII, SelRII, SelO, SelRIV, SelRV, and SelRVI).

In some aspects, provided herein is a polynucleotide or expression vector (e.g., an isolated polynucleotide or expression vector) comprising a selvamycin BGC described herein (e.g., a modified selvamycin BCG).

In some aspects, provided herein is an engineered microorganism (e.g., an engineered bacterium) comprising one or more nucleic acids encoding a selvamycin BGC (e.g., a modified selvamycin BCG described herein). In some embodiments, the engineered microorganism is not *Pseudocardia*.

In some aspects, provided herein is a method for producing an antifungal agent a polyene macrolide, including, for example, a compound of Formula I), the method comprising: culturing a microorganism (e.g., an engineered microorganism such as an engineered bacterium) comprising a selvamycin BGC described herein (e.g., a modified selvamycin BCG described herein) under conditions such that the bacterium produces the antifungal agent. In some embodiments, the engineered microorganism is not *Pseudocardia*. In some embodiments the microorganism is cultured in the presence of sodium butyrate. In certain embodiments, provided herein are the antifungal agents produced by such methods.

#### BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 includes 2 panels (Panels A and B). Panel A depicts structures of exemplary antifungal polyene natural products

currently in clinical use. Panel B depicts the structure of selvamycin and NMR correlations establishing its planar structure.

FIG. 2 shows the UV spectrum of selvamycin in methanol.

FIG. 3 includes 2 panels (Panels A and B), which show the Selvamycin NMR correlations. Panel A depicts H2BC correlations supporting the planar structure of selvamycin. Panel B depicts ROESY correlations supporting the relative stereochemistry of selvamycin from C4-C13.

FIG. 4 depicts Ac<sub>9</sub>-selvamycin NMR correlations supporting its planar structure

FIG. 5 depicts NMR correlations and coupling constants supporting sugar stereochemistry.

FIG. 6 includes 8 panels (Panels A-H), which show Selvamycin NMR spectra in DMSO-d<sub>6</sub>. Panel A shows the 600 MHz <sup>1</sup>H NMR spectrum. Panel B shows the 100 MHz <sup>13</sup>C NMR spectrum. Panel C shows the 600 MHz COSY spectrum. Panel D shows the 600 MHz TOCSY spectrum. Panel E shows the 500 MHz ROESY NMR spectrum. Panel F shows the 600 MHz multiplicity-edited HSQC NMR spectrum of selvamycin in DMSO-d<sub>6</sub>. CH and CH<sub>3</sub> group correlations are shown in red and CH<sub>2</sub> group correlations are shown in blue. Panel G shows the 500 MHz H2BC NMR spectrum. Panel H shows the 500 MHz HMBC spectrum.

FIG. 7 includes 6 panels (Panels A-F), which show Ac<sub>9</sub>-selvamycin NMR spectra in DMSO-d<sub>6</sub>. Panel A shows the 600 MHz <sup>1</sup>H NMR spectrum. Panel B the 600 MHz COSY spectrum. Panel C shows the 600 MHz TOCSY spectrum. Panel D shows the 600 MHz ROESY NMR spectrum. Panel E shows the 600 MHz multiplicity-edited HSQC NMR spectrum of Ac<sub>9</sub>-selvamycin in DMSO-d<sub>6</sub>. CH and CH<sub>3</sub> group correlations are shown in red and CH<sub>2</sub> group correlations are shown in blue. Panel F shows the 500 MHz HMBC spectrum.

FIG. 8 is a bar graph showing the induction of selvamycin production by sodium propionate and sodium butyrate.

FIG. 9 is the Selvamycin mass spectra from HPLC-ESI-HRMS of *Pseudocardia* culture extracts.

FIG. 10 is a plot showing the growth inhibition of *Candida albicans*, *Saccharomyces cerevisiae*, *Trichoderma harzianum*, and *Aspergillus fumigatus* by selvamycin.

FIG. 11 includes 2 panels (Panels A and B). Panel A shows the genomes of *Pseudocardia* isolates LS1 and LS2. The selvamycin BGC in each is marked with a box. B) Selvamycin BGCs from LS1 and LS2. Mobile genetic element genes flanking the selvamycin clusters are shown.

FIG. 12 includes 2 panels (Panels A and B) showing Nystatin (Panel A) and selvamycin (Panel B) BGCs. Polyketide synthase genes are labeled with bold font.

FIG. 13 shows isothermal calorimetry traces assaying polyene-sterol interactions.

FIG. 14 shows the extractions from PKS domain alignments. Active site residues and AT specificity motifs are in bold.

FIG. 15 is a schematic of selvamycin PKS domain architecture. Putative inactive domains are shaded gray.

FIG. 16 includes 3 panels (Panels A-C). Panel A is a schematic of selvamycin PKS domain architecture. Panel B is a schematic of a modified selvamycin domain structure where the ketoreductase domain of module 13 is disrupted. Panel C is a schematic of a modified selvamycin domain structure where the dehydratase domain of module 14 is disrupted.

FIG. 17 is a table of predicted proteins of the selvamycin biosynthetic gene cluster (BGC)

FIG. 18 is a table of exemplary genes of the Selvamycin biosynthetic gene cluster.

FIG. 19 is a table of NMR Spectral data for selvamycin in DMSO-d<sub>6</sub>.

FIG. 20 is a table of NMR Spectral data for Ac<sub>9</sub>-selvamycin in DMSO-d<sub>6</sub>.

FIG. 21 is a table of MIC values (μM) for selvamycin and nystatin against a pane of fungi.

FIG. 22 is a plot showing the in vivo antifungal activity of selvamycin.

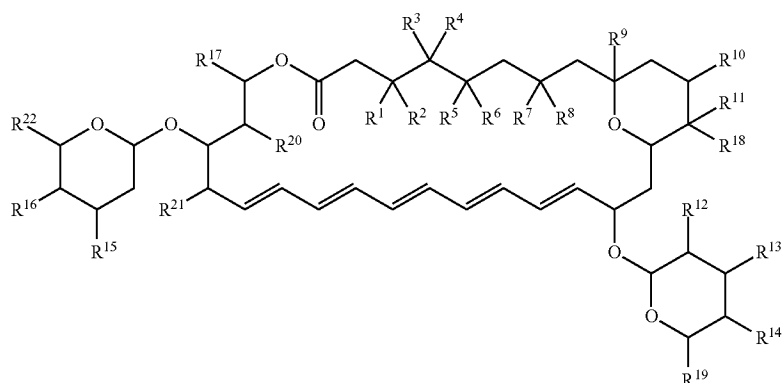
FIG. 23 shows in vitro and in vivo efficacy (Panels A and C, respectively) and safety (Panel B AmB is amphotericin). Single intraperitoneal doses of selvamycin in the neutropenic murine disseminated candidiasis model against strains of *C. albicans*, *C. glabrata*, and *C. auris* are shown.

#### DETAILED DESCRIPTION

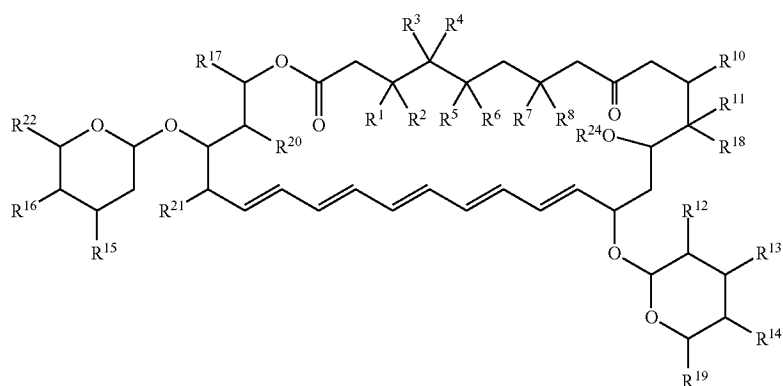
In certain aspects, provided herein are methods and compositions related to novel polyene macrolide compounds. In certain embodiments, the polyene macrolide compounds are related to selvamycin, a novel polyene macrolide isolated from *Pseudonocardia*. As disclosed herein, selvamycin elicits antifungal activity.

#### I. Compounds

In certain aspects, provided herein are compounds having the structure of Formula I or Formula II, or a pharmaceutically acceptable salt thereof:



Formula I



Formula II

wherein

R<sup>1</sup> and R<sup>2</sup> are, independently for each occurrence, H or OR<sup>23</sup>, or R<sup>1</sup> and R<sup>2</sup> together with the carbon to which they are bound form a carbonyl moiety;

R<sup>3</sup> and R<sup>4</sup> are, independently for each occurrence, H or OR<sup>23</sup>, or R<sup>3</sup> and R<sup>4</sup> together with the carbon to which they are bound form a carbonyl moiety;

R<sup>5</sup> and R<sup>6</sup> are, independently for each occurrence, H or OR<sup>23</sup>, or R<sup>5</sup> and R<sup>6</sup> together with the carbon to which they are bound form a carbonyl moiety;

R<sup>7</sup> and R<sup>8</sup> are, independently for each occurrence, H or OR<sup>23</sup>, or R<sup>7</sup> and R<sup>8</sup> together with the carbon to which they are bound form a carbonyl moiety;

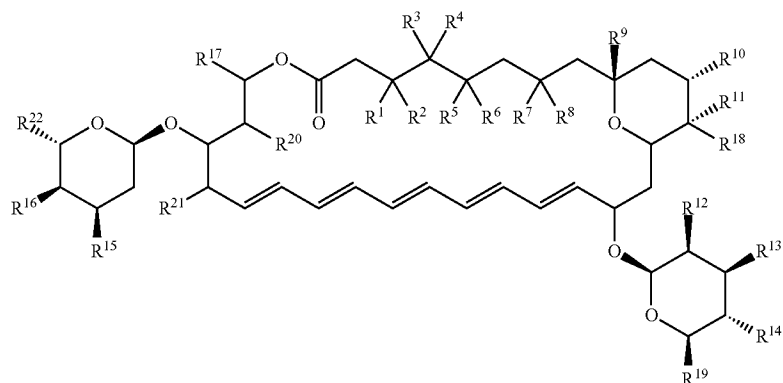
R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> are, independently for each occurrence, H or OR<sup>23</sup>;

R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup>, and R<sup>22</sup> are, independently for each occurrence, H or optionally substituted alkyl;

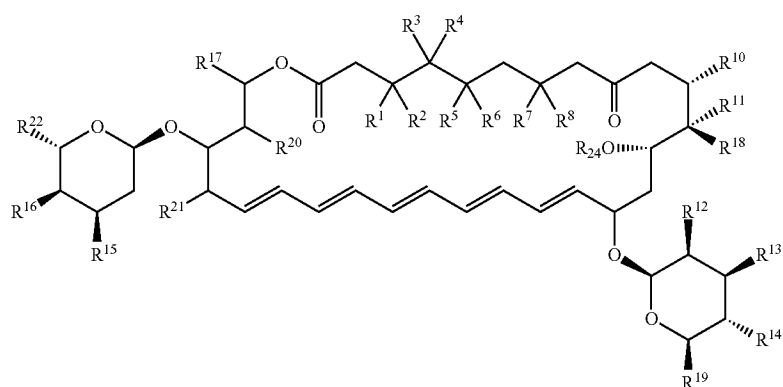
R<sup>23</sup> is, independently for each occurrence, H, optionally substituted alkyl, or optionally substituted acyl; and

R<sup>24</sup> is, independently for each occurrence, H, optionally substituted alkyl, or optionally substituted acyl.

In certain embodiments, the compound has a structure of Formula III or Formula IV or a pharmaceutically acceptable salt thereof:



Formula III



Formula IV

In certain embodiments,  $R^1$  and  $R^2$  are H.

In certain embodiments,  $R^3$  is  $OR^{23}$  and  $R^4$  is H. In certain such embodiments,  $R^3$  is OH and  $R^4$  is H. In certain embodiments,  $R^5$  is  $OR^{23}$  and  $R^6$  is H. In certain such embodiments,  $R^5$  is OH and  $R^6$  is H. In certain embodiments,  $R^7$  is  $OR^{23}$  and  $R^8$  is H. In certain such embodiments,  $R^7$  is OH and  $R^8$  is H.

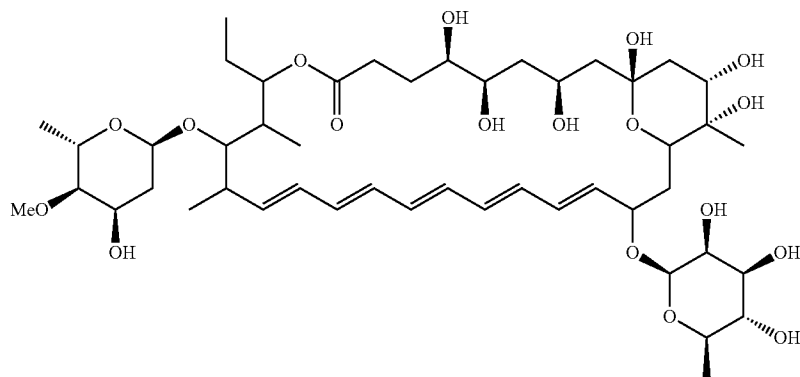
In certain embodiments,  $R^9$  is  $OR^{23}$ . In certain such embodiments,  $R^9$  is OH. In certain embodiments,  $R^{10}$  is  $OR^{23}$ . In certain such embodiments,  $R^{10}$  is OH. In certain embodiments, wherein  $R^{11}$  is  $OR^{23}$ . In certain such embodiments,  $R^{11}$  is OH. In certain such embodiments,  $R^{12}$  is  $OR^{23}$ . In certain embodiments wherein  $R^{12}$  is OH. In certain embodiments, wherein  $R^{13}$  is  $OR^{23}$ . In certain such embodi-

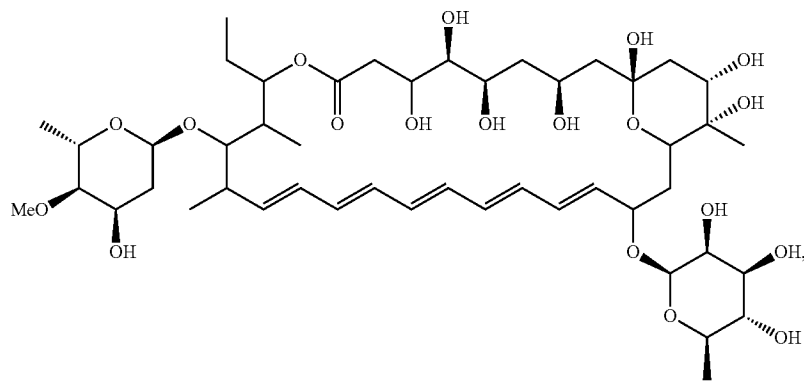
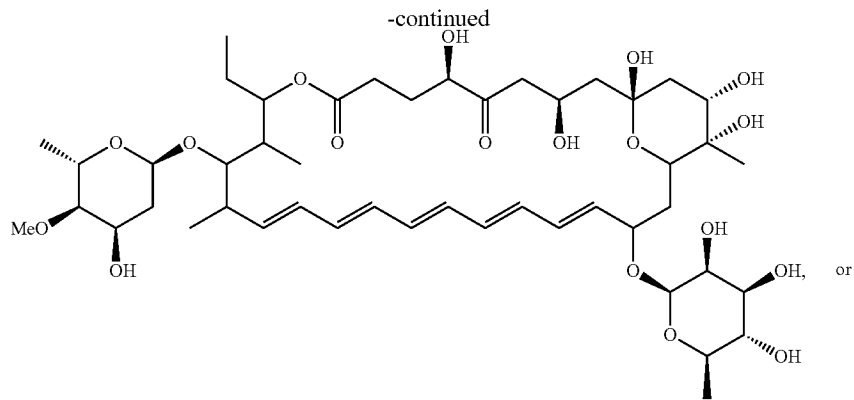
35 ments,  $R^{13}$  is OH. In certain embodiments, wherein  $R^{14}$  is  $OR^{23}$ . In certain such embodiments,  $R^{14}$  is OH. In certain embodiments, wherein  $R^{15}$  is  $OR^{23}$ . In certain such embodiments,  $R^{15}$  is OH.

In certain embodiments,  $R^{16}$  is  $OR^{23}$ . In certain such 40 embodiments,  $R^{23}$  is lower alkyl, preferably  $R^{16}$  is  $OCH_3$ .

In certain embodiments,  $R^{17}$  is lower alkyl, preferably ethyl. In certain embodiments,  $R^{18}$  is lower alkyl, preferably methyl. In certain embodiments,  $R^{19}$  is lower alkyl, preferably methyl. In certain embodiments,  $R^{20}$  is lower alkyl, preferably methyl. In certain embodiments,  $R^{21}$  is lower 45 alkyl, preferably methyl. In certain embodiments,  $R^{22}$  is lower alkyl, preferably methyl.

In certain embodiments, the compound has the structure

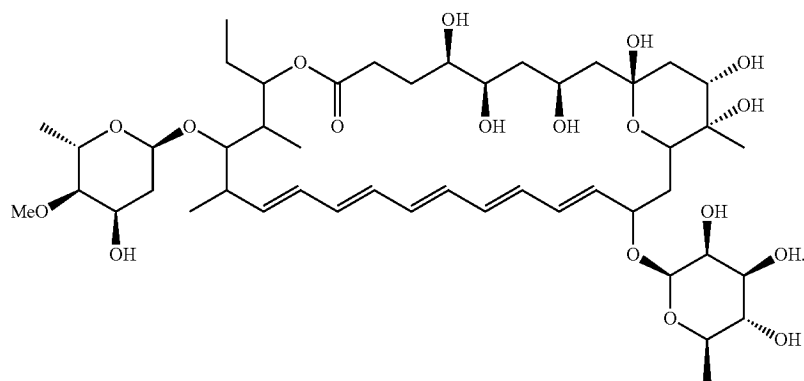




or a pharmaceutically acceptable salt thereof.

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In certain embodiments, the compound does not have the following structure:

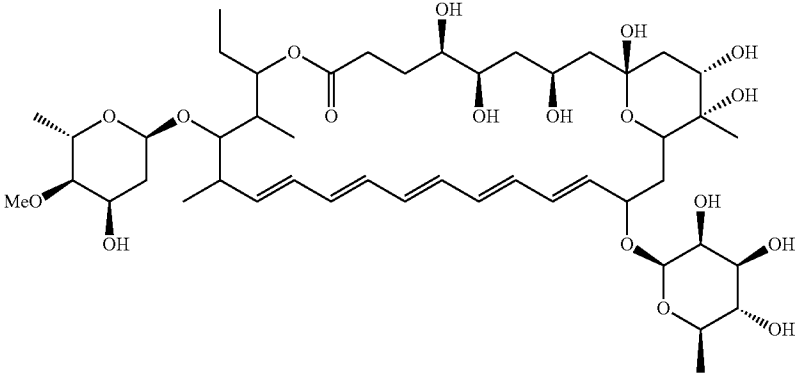
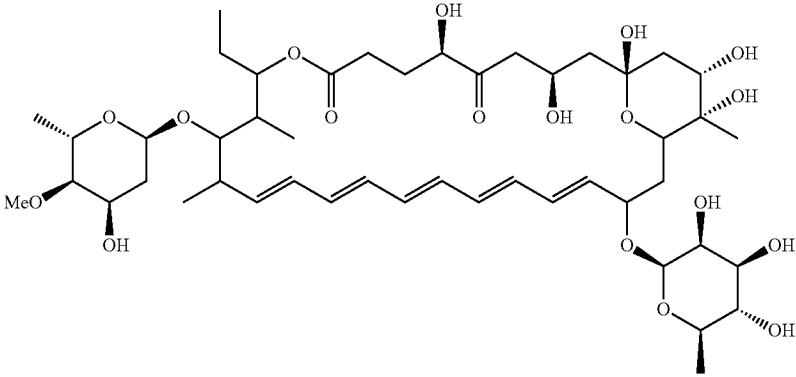
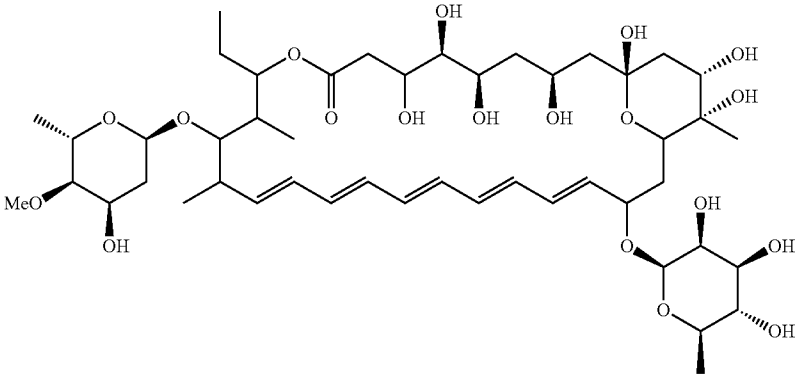
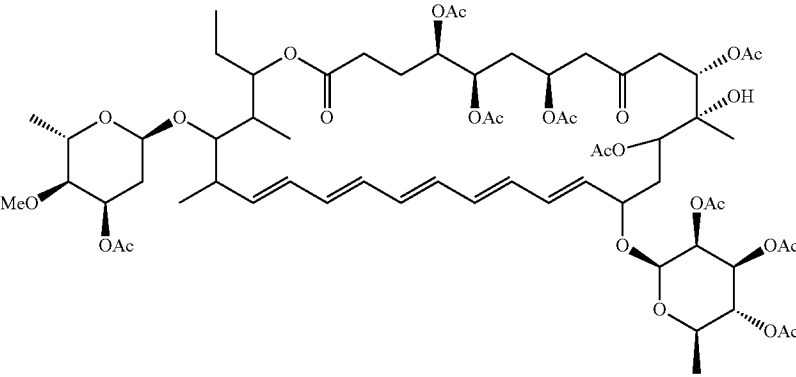


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Exemplary compounds of Formula I and Formula II are depicted in Table 1. The compounds of Table 1 may be depicted as the free base or the conjugate acid. Compounds may be isolated in either the free base form, as a salt (e.g., a hydrochloride salt) or in both forms. In the chemical structures shown below, standard chemical abbreviations are sometimes used.

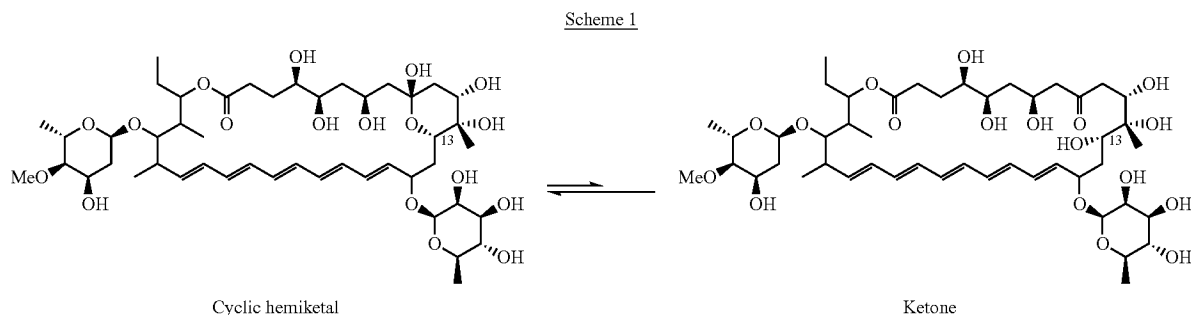
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TABLE 1

Ex.	Structure	Name
1	 <p>The structure of Selvamycin is a complex polyketide. It features a central polyene chain with seven conjugated double bonds. This chain is substituted with a methyl group at C1, a methyl ester group at C2, and a methyl group at C3. The chain is terminated at C14 by a methyl group and a methyl ester group. The polyene chain is linked via ether bonds to two pyranose rings. The left pyranose ring is substituted with a methyl group at C2, a methoxy group at C3, and a hydroxyl group at C4. The right pyranose ring is substituted with a methyl group at C2, a hydroxyl group at C3, and a hydroxyl group at C4. The polyene chain also has several hydroxyl groups: one at C5, two at C6, and one at C7.</p>	Selvamycin
2	 <p>Analog 1 is a derivative of Selvamycin. It has the same polyene chain and pyranose rings as Selvamycin. However, the hydroxyl group at C6 of the polyene chain is replaced by a carbonyl group (C=O). The methyl ester group at C2 is also present.</p>	Analog 1
3	 <p>Analog 2 is another derivative of Selvamycin. It has the same polyene chain and pyranose rings as Selvamycin. The hydroxyl group at C6 of the polyene chain is replaced by a hydroxyl group (OH). The methyl ester group at C2 is also present.</p>	Analog 2
4	 <p>Ac<sub>γ</sub>-Selvamycin is a derivative of Selvamycin where all hydroxyl groups are acetylated. The polyene chain has an acetyl group (OAc) at C5, two acetyl groups at C6, and one acetyl group at C7. The methyl ester group at C2 is also present. The pyranose rings have acetyl groups at C3 and C4.</p>	Ac <sub>γ</sub> -Selvamycin

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Selvamicin includes a hemiketal. Under the appropriate conditions, the molecule may adopt a ketone form (Scheme 1).



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compound such as a compound described herein. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxi-

In certain embodiments, compounds of the invention may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example, a compound of the invention may have greater than 30% ee, 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee, or even 95% or greater ee. The compounds of the invention have more than one stereocenter. Consequently, compounds of the invention may be enriched in one or more diastereomer. For example, a compound of the invention may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de, or even 95% or greater de.

## II. Pharmaceutical Compositions

In certain embodiments, the provided herein are pharmaceutical compositions comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

The compositions and methods described herein may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound described herein and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a

dants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a selfemulsifying drug delivery system or a selfmicroemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound described herein. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example,

drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound described herein, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound described herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations provided herein suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophilic, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound described herein as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as

quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophilic for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan

esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound described herein to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated herein. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Pat. No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. A preferred route of administration is local administration (e.g., topical administration, such as eye drops, or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperito-

neal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrastemal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some embodiments, the pharmaceutical composition may further comprise an adjuvant that can augment the immune response by increasing delivery of antigen, stimulating cytokine production, and/or stimulating antigen presenting cells. In some embodiments, the adjuvant can be administered concurrently with the pharmaceutical composition and/or vaccine composition disclosed herein, e.g., in the same composition or in separate compositions. For example, an adjuvant can be administered prior or subsequent to the pharmaceutical composition disclosed herein. Such adjuvants include, but are not limited to: aluminum salts, non-toxic bacterial fragments, cholera toxin (and detoxified fractions thereof), chitosan, homologous heat-labile of *E. coli* (and detoxified fractions thereof), lactide/glycolide homo and copolymers (PLA/GA), polyanhydride e.g. trimellitylimido-L-tyrosine, DEAF-dextran, saponins complexed to membrane protein antigens (immune stimulating complexes—ISCOMS), bacterial products such as lipopolysaccharide (LPS) and mummyl dipeptide, (MDP), liposomes, cochelates, proteinoids, cytokines (interleukins, interferons), genetically engineered live microbial vectors, non-infectious pertussis mutant toxin, neurimidasegalactose oxidase, and attenuated bacterial and viral toxins derived from mutant strains.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.



Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods provided herein, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested in vivo in recent years for the controlled delivery of drugs, including proteinacious biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments described herein, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

In some embodiments, provided herein is the use of pharmaceutically acceptable salts of compounds described herein in the compositions and methods described herein. The term "pharmaceutically acceptable salt" as used herein includes salts derived from inorganic or organic acids including, for example, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, phosphoric, formic, acetic, lactic, maleic, fumaric, succinic, tartaric, glycolic, salicylic, citric, methanesulfonic, benzenesulfonic, benzoic, malonic, trifluoroacetic, trichloroacetic, naphthalene-2-sulfonic, and other acids. Pharmaceutically acceptable salt forms can include forms wherein the ratio of molecules comprising the salt is not 1:1. For example, the salt may comprise more than one inorganic or organic acid molecule per molecule of base, such as two hydrochloric acid molecules per molecule of compound of Formula I or Formula II. As another example, the salt may comprise less than one inorganic or organic acid

molecule per molecule of base, such as two molecules of compound of Formula I or Formula II per molecule of tartaric acid.

In further embodiments, contemplated salts described herein include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts described herein include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylalucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts described herein include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring, and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

In certain embodiments, the pharmaceutical preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of Formula I or II). An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1% as compared to the amount of the other enantiomer, e.g., in the composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grains of a second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

In certain embodiments, the pharmaceutical preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of Formula I or II). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

### III. Therapeutic Uses

Provided herein are novel methods of inhibiting the growth of a fungus. In some embodiments, the method

includes contacting a fungus with any compound or composition disclosed herein. In some embodiments, the method includes administering to a subject suffering from a fungal infection a compound or composition provided herein. In some embodiments, the method includes administering to a subject susceptible to fungal infection (e.g., an immunocompromised subject) a compound or composition disclosed herein. In some embodiments, the method includes treating an object (e.g., a food product or an exposed surface) with a compound or composition provided herein to prevent fungal growth on or in the object. In some embodiments, the fungus is *Aspergillus* (e.g., *Aspergillus fumigatus*, *Aspergillus flavus*), *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus* (e.g., *Cryptococcus neoformans*, *Cryptococcus gattii*), *Histoplasma* (e.g., *Histoplasma capsulatum*), *Pneumocystis* (e.g., *Pneumocystis jirovecii*), *Sporothrix*, *Stachybotrys* (e.g., *Stachybotrys chartarum*), *Tinea*, *Exserohilum* and/or *Cladosporium*. In certain embodiments, the fungus is *Candida albicans*, *Saccharomyces cerevisiae*, *Trichoderma harzianum*, and/or *Aspergillus fumigatus*. In some embodiments, the fungus is *Candida glabrata*. In certain embodiments, the fungus is *Candida auris*.

In certain embodiments, disclosed herein are methods of preventing, treating or lessening the severity of a fungal infection in a subject (e.g., a subject that has a fungal infection and/or a subject that is susceptible to fungal infections, such as an immunocompromised subject), the method comprising administering to the subject any compound or composition disclosed herein. In some embodiments, the fungal infection is an infection with *Aspergillus* (e.g., *Aspergillus fumigatus*, *Aspergillus flavus*), *Blastomyces*, *Candida* (e.g. *Candida albicans*, *Candida glabrata*, *Candida auris*), *Coccidioides*, *Cryptococcus* (e.g., *Cryptococcus neoformans*, *Cryptococcus gattii*), *Histoplasma* (e.g., *Histoplasma capsulatum*), *Pneumocystis* (e.g., *Pneumocystis jirovecii*), *Sporothrix*, *Stachybotrys* (e.g., *Stachybotrys chartarum*), *Tinea*, *Exserohilum* and/or *Cladosporium*. In some embodiments, the subject treated has aspergillosis, blastomycosis, candidiasis, coccidioidomycosis (valley fever), a *C. neoformans* infection, a *C. gattii* infection, a fungal eye infection, histoplasmosis, mucormycosis, *Pneumocystis* pneumonia, ringworm, sporotrichosis, tinea pedis and/or tinea entris.

In certain embodiments, the compound or composition provided herein is administered to the subject, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). In some embodiments, the compound or composition is applied locally, directly to the site of the fungal infection.

#### IV. Selvanticin Biosynthetic Gene Cluster

Disclosed herein are a selvamicin biosynthetic gene cluster (BGC) and the proteins encoded by the selvamicin BGC (FIG. 17).

In certain embodiments, also provided herein are modified selvamicin BGCs. In some embodiments, the modified

selvamicin BGC comprises one or more inactivated or deleted genes selected from SelE, SelDIII, SelI, SelJ, SelSI, SelSII, SelSIII, SelSIV, SelSV, SelSVI, SelSVII, Sel A, SelB, SelC, SelK, SelL, SelP, SelDI, SelG, SelH, SelRI, SelRII, SelRIII, SelO, SelRIV, SelRV, and SelRVI (FIG. 18). (Each Accession Number nucleotide sequence incorporated by reference herein).

In certain embodiments, the inactivated gene is selected from SelP and SelL. In certain embodiments, the deleted gene is selected from SelP and SelL.

In some embodiments, provided herein are one or more polynucleotides encoding a selvamicin BCG. In some embodiments, the selvamicin BCG is a modified selvamicin BCG. In some embodiments, the genes of the selvamicin BCG have a nucleic acid sequence that is at least 80 (e.g., at least 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99) % identical to the sequences disclosed herein. In some embodiments, the selvamicin BGC polynucleotide comprises a mutation or deletion in one of the polynucleotides that encode the proteins selected from SelE (SEQ ID No.: 2), SelDIII (SEQ ID No.: 3), SelI (SEQ ID No.: 4), SelJ (SEQ ID No.: 5), SelSI (SEQ ID No.: 6), SelSII (SEQ ID No.: 7), SelSIII (SEQ ID No.: 8), SelSIV (SEQ ID No.: 9), SelSV (SEQ ID No.: 10), SelSVI (SEQ ID No.: 11), and SelSVII (SEQ ID No.: 12), Sel A (SEQ ID No.: 13), SelB (SEQ ID No.: 14), SelC (SEQ ID No.: 15), SelK (SEQ ID No.: 16), SelL (SEQ ID No.: 17), SelP (SEQ ID No.: 18), SelDI (SEQ ID No.: 19), SelG (SEQ ID No.: 20), SelH (SEQ ID No.: 21), SelRI (SEQ ID No.: 22), SelRII (SEQ ID No.: 23), SelRIII (SEQ ID No.: 24), SelO (SEQ ID No.: 25), SelRIV (SEQ ID No.: 26), SelRV (SEQ ID No.: 27), and SelRVI (SEQ ID No.: 28). In certain embodiments, SelP or SelL is mutated or deleted.

In some embodiments, the method includes a cell (e.g., a microbial cell, such as a bacterial cell) comprising a selvamicin BCG described herein. In certain embodiments, the polynucleotides can be introduced into the cell using any method known in the art. For example, in some embodiments, the polynucleotides are introduced in a vector. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. In some embodiments, the plasmid is linearized before introduction into the cell. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal eukaryotic vectors). Other vectors (e.g., non-episomal eukaryotic vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome.

Certain vectors are capable of directing the expression of genes to which they are operatively linked (expression vectors). The expression vectors provided herein are able to facilitate the expression of the encoded domain in a host cell, which means that the expression vectors include one or more regulatory sequences (e.g., promoters, enhancers), selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. The design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like.

The polynucleotides can be introduced into prokaryotic or eukaryotic host cells via conventional transformation or transfection techniques. Examples of transformation and

transfection techniques include calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, electroporation, optical transfection, protoplast fusion, impalefection, hydrodynamic delivery, using a gene gun, magnetofection, and particle bombardment. Polynucleotides can also be introduced by infecting the cells with a viral vector an adenovirus vector, an adeno-associated virus vector, a lentivirus vector or a retrovirus vector). Suitable methods for transforming or transfecting host cells can be found in Sambrook et al. (Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

Also provided herein are proteins encoded by the selvamycin BGC polynucleotides disclosed herein. "Polypeptide," "peptide," and "protein" are used interchangeably and mean any peptide-linked chain of amino acids, regardless of length or post-translational modification. In some embodiments, the selvamycin BGC polynucleotides encode variant proteins. The variant proteins described herein comprise one or more amino acid substitutions, insertions, or deletions, relative to the wild-type protein from which they were derived. In some embodiments, a variant protein comprises at least one (e.g., at least two, three, four, five, six, seven, eight, nine, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, or more than 100) amino acid substitutions, deletions, or insertions, relative to the wild-type, full-length NS3 protein from which it was derived. In some embodiments, a variant protein comprises no more than 150 (e.g., no more than 145, 140, 135, 130, 125, 120, 115, 110, 105, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1) amino acid substitution (s), deletion(s), or insertion(s), relative to the wild-type, full-length protein from which it was derived.

As used herein, the term "conservative substitution" refers to the replacement of an amino acid present in the native sequence in a given polypeptide with a naturally or non-naturally occurring amino acid having similar steric properties. Where the side-chain of the native amino acid to be replaced is either polar or hydrophobic, the conservative substitution should be with a naturally occurring amino acid, a non-naturally occurring amino acid that is also polar or hydrophobic, and, optionally, with the same or similar steric properties as the side-chain of the replaced amino acid. Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine, and leucine; aspartic acid and glutamic acid; asparagine, glutamine, serine and threonine; lysine, histidine and arginine; and phenylalanine and tyrosine. One letter amino acid abbreviations are as follows: alanine (A); arginine (R); asparagine (N); aspartic acid (D); cysteine (C); glycine (G); glutamine (Q); glutamic acid (E); histidine (H); isoleucine (I); leucine (L); lysine (K); methionine (M); phenylalanine (F); proline (P); serine (S); threonine (T); tryptophan (W); tyrosine (Y); and valine (V).

The phrase "non-conservative substitutions" as used herein refers to replacement of the amino acid as present in the parent sequence by another naturally or non-naturally occurring amino acid, having different electrochemical and/or steric properties. Thus, the side chain of the substituting amino acid can be significantly larger (or smaller) than the side chain of the native amino acid being substituted and/or can have functional groups with significantly different electronic properties than the amino acid being substituted.

In some embodiments, a variant protein described herein, or a fragment thereof, has an amino acid sequence that is at least 80 (e.g., at least 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99) % identical to the sequences disclosed herein. Percent amino acid sequence identity is defined as the percentage of amino acids in a candidate sequence that are identical to the amino acids in a reference sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software, such as BLAST software or ClustalW2. Appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared can be determined by known methods.

#### V. Methods of Producing Antifungal Agents

In certain embodiments, disclosed herein are methods for producing an antifungal agent (e.g., an antifungal agent described herein), the method comprising culturing a microorganism described herein (e.g. an engineered microorganism, such as an engineered bacterium comprising a selvamycin BGC described herein) under conditions such that the microorganism produces the antifungal agent. In some embodiments, the method further comprises isolating the antifungal agent. In some embodiments, the microorganism is cultured in the presence of sodium butyrate. In certain embodiments, provided herein are the antifungal agents produced by such methods.

In embodiments the microorganism is cultured on or in a microbial medium (e.g., an agar medium or a broth medium). In some embodiments, the agar or broth may contain nutrients that provide essential elements and specific factors that enable growth. An example would be a medium composed of 20 g/L glucose, 10 g/L yeast extract, 10 g/L soy peptone, 2 g/L citric acid, 1.5 g/L sodium phosphate monobasic, 100 mg/L ferric ammonium citrate, 80 mg/L magnesium sulfate, 10 hemin chloride, 2 mg/L calcium chloride, 1 mg/L menadione. Another examples would be a medium composed of 10 g/L beef extract, 10 g/L peptone, 5 g/L sodium chloride, 5 g/L dextrose, 3 g/L yeast extract, 3 g/L sodium acetate, 1 g/L soluble starch, and 0.5 g/L L-cysteine HCl, at pH 6.8. A variety of microbiological media and variations are well known in the art (e.g., R. M. Atlas, *Handbook of Microbiological Media* (2010) CRC Press). Culture media can be added to the culture at the start, may be added during the culture, or may be intermittently/continuously flowed through the culture. The strains in the bacterial composition may be cultivated alone, as a subset of the microbial composition, or as an entire collection comprising the microbial composition. As an example, a first strain may be cultivated together with a second strain in a mixed continuous culture, at a dilution rate lower than the maximum growth rate of either cell to prevent the culture from washing out of the cultivation. In some embodiments, the microbial medium comprises sodium butyrate (e.g., between 50 and 500 mM sodium butyrate, such as about 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 350, 400, 450 or 500 mM sodium butyrate). In some embodiments, the microbial medium comprises between 100 and 200 mM sodium butyrate. In some embodiments, the microbial medium comprises about 150 mM sodium butyrate.

In certain embodiments, disclosed herein are methods for producing a modified polyene macrolide, the method comprising: culturing a host cell (e.g., a microorganism, such as a bacterium) comprising a polynucleotide encoding SelSI (SEQ ID No.: 6), SelSII (SEQ ID No.: 7), SelSIII (SEQ ID No.: 8), SelSIV (SEQ ID No.: 9), SelSV (SEQ ID No.: 10), SelSVI (SEQ ID No.: 11), and SelSVII (SEQ ID No.: 12), under conditions such that the host cell produces a modified polyene macrolide. In certain embodiments, disclosed herein are the modified polyene macrolide produced by such methods. In certain embodiments the host cell is a bacterium.

In certain aspects, provided herein are engineered microorganisms (e.g., bacteria) described herein. In some embodiments, the engineered microorganisms are modified to enhance certain desirable properties. The engineered microbe(s) may be produced using any technique known in the art, including but not limited to site-directed mutagenesis, transposon mutagenesis, knock-outs, knock-ins, polymerase chain reaction mutagenesis, chemical mutagenesis, ultraviolet light mutagenesis, transformation (chemically or by electroporation), phage transduction, directed evolution, or any combination thereof.

In certain embodiments, disclosed herein are engineered microorganisms comprising a polynucleotide of selvamicin BGC (SEQ ID No.: 1). In certain embodiments, the polynucleotide of selvamicin BGC is modified. In certain embodiments, one or more of the polynucleotides selected from SelE (SEQ ID No.: 2), SelDIII (SEQ ID No.: 3), SelI (SEQ ID No.: 4), SelII (SEQ ID No.: 5), SelSI (SEQ ID No.: 6), SelSII (SEQ ID No.: 7), SelSIII (SEQ ID No.: 8), SelSIV (SEQ ID No.: 9), SelSV (SEQ ID No.: 10), SelSVI (SEQ ID No.: 11), and SelSVII (SEQ ID No.: 12), Sel A (SEQ ID No.: 13), SelB (SEQ ID No.: 14), SelC (SEQ ID No.: 15), SelK (SEQ ID No.: 16), SelL (SEQ ID No.: 17), SelP (SEQ ID No.: 18), SelDI (SEQ ID No.: 19), SelG (SEQ ID No.: 20), SelH (SEQ ID No.: 21), SelRI (SEQ ID No.: 22), SelRII (SEQ ID No.: 23), SelRIII (SEQ ID No.: 24), SelO (SEQ ID No.: 25), SelRIV (SEQ ID No.: 26), SelRV (SEQ ID No.: 27), and SelRVI (SEQ ID No.: 28) is imitated or deleted. In certain embodiments, the engineered microorganism is a bacteria other than *Pseudonocaidia*. In some embodiments, the engineered microorganism is *Escherichia coli*. In certain embodiments, disclosed herein are methods of producing a compound of Formula I, the method comprising: culturing an engineered microorganism of any disclosed herein; and allowing the compound of Formula I to accrue.

## VI. Definitions

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “acyl” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)—, preferably alkylC(O)—.

The term “acylamino” is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH—.

The term “acyloxy” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O—, preferably alkylC(O)O—.

The term “alkoxy” refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto.

Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term “alkoxyalkyl” refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term “alkenyl”, as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both “unsubstituted alkenyls” and “substituted alkenyls”, the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

An “alkyl” group or “alkane” is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C<sub>1</sub>-C<sub>6</sub> straight chained or branched alkyl group is also referred to as a “lower alkyl” group.

Moreover, the term “alkyl” (or “lower alkyl”) as used throughout the specification, examples, and claims is intended to include both “unsubstituted alkyls” and “substituted alkyls”, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy-carbonyl a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amino, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfarnoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), —CF<sub>3</sub>, —CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxy, alkylthios, aminoalkyls, carbonyl-substituted alkyls, —CF<sub>3</sub>, —CN, and the like.

The term “C<sub>x-y</sub>” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term “C<sub>x-y</sub>alkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C<sub>0</sub> alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms “C<sub>2-y</sub>alkenyl” and “C<sub>2-y</sub>alkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in

length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "carboxy", as used herein, refers to a group represented by the formula  $-\text{CO}_2\text{H}$ .

The term "heteroalkyl", as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

As used herein, the term "oxo" refers to a carbonyl group. When an oxo substituent occurs on an otherwise saturated group, such as with an oxo-substituted cycloalkyl group (e.g., 3-oxo-cyclobutyl), the substituted group is still intended to be a saturated group. When a group is referred to as being substituted by an "oxo" group, this can mean that a carbonyl moiety (i.e.,  $-\text{C}(=\text{O})-$ ) replaces a methylene unit (i.e.,  $-\text{CH}_2-$ ).

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. In some embodiments, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamide, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

"Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3<sup>rd</sup> Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("EMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

As used herein, "administration" broadly refers to a route of administration of a composition to a subject. Examples of routes of administration include oral administration, rectal administration, topical administration, inhalation (nasal) or injection. Administration by injection includes intravenous (IV), intramuscular (IM), intratumoral (IT) and subcutaneous (SC) administration. The pharmaceutical compositions described herein can be administered in any form by any effective route, including but not limited to intratumoral, oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), intradermal, ophthalmic, (intra)nasally, local, non-oral, such as aerosol, inhalation, subcutaneous, intramuscular, buccal, sublingual, (trans)rectal, vaginal, intra-arterial, and intrathecal, trans-nucosal (e.g., sublingual, lingual, (trans)huccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), intravesical, intrapulmonary, intraduodenal, intragastrical, and intrabronchial. In preferred embodiments, the pharmaceutical compositions described herein are administered orally, rectally, intratumorally, topically, intravesically, by injection into or adjacent to a draining lymph node, intravenously, by inhalation or aerosol, or subcutaneously.

As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

The term "treating" includes prophylactic and/or therapeutic treatments. The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The terms "polynucleotide", and "nucleic acid" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribo-

nucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. A polynucleotide may be further modified, such as by conjugation with a labeling component. In all nucleic acid sequences provided herein, U nucleotides are interchangeable with T nucleotides.

The term "isolated nucleic acid" refers to a polynucleotide of natural or synthetic origin or some combination thereof, which (1) is not associated with the cell in which the "isolated nucleic acid" is found in nature, and/or (2) is operably linked to a polynucleotide to which it is not linked in nature.

The term "isolated polypeptide" refers to a polypeptide, in certain embodiments prepared from recombinant DNA or RNA, or of synthetic origin, or some combination thereof, which (1) is not associated with proteins that it is normally found with in nature, (2) is isolated from the cell in which it normally occurs, (3) is isolated free of other proteins from the same cellular source, (4) is expressed by a cell from a different species, or (5) does not occur in nature.

The term "percent identical" refers to sequence identity between two amino acid sequences or between two nucleotide sequences. Identity can each be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When an equivalent position in the compared sequences is occupied by the same base or amino acid, then the molecules are identical at that position; when the equivalent site occupied by the same or a similar amino acid residue (e.g., similar in steric and/or electronic nature), then the molecules can be referred to as homologous (similar) at that position. Expression as a percentage of homology, similarity, or identity refers to a function of the number of identical or similar amino acids at positions shared by the compared sequences. Expression as a percentage of homology, similarity, or identity refers to a function of the number of identical or similar amino acids at positions shared by the compared sequences. Various alignment algorithms and/or programs may be used, including FASTA, BLAST, or ENTREZ. FAST, A and BLAST are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.), and can be used with, e.g., default settings. ENTREZ is available through the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Md. In one embodiment, the percent identity of two sequences can be determined by the GCG program with a gap weight of 1, e.g., each amino acid gap is weighted as if it were a single amino acid or nucleotide mismatch between the two sequences.

The term "prodrug" is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents described herein (e.g., a compound of formula I). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. For

example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs described herein. In certain embodiments, some or all of the compounds of formula I in a formulation represented above can be replaced with the corresponding suitable prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid present in the parent compound is presented as an ester.

## EXAMPLES

The invention now being generally described will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

### Experimental Methods

General chemical analysis procedures: UV-visible absorbance spectra were collected on an Amersham Biosciences Ultrospec 5300 Pro spectrophotometer. High resolution mass spectrometry analysis was performed on an Agilent 6530 ESI QTOF mass spectrometer interfaced with air Agilent 1290 Infinity Binary LC. COSY, TOCSY, ROESY, HSQC, H2BC, HMBC, and 1H NMR experiments were performed on either a Varian VNMRs 600 MHz spectrometer equipped with a triple resonance HCN inverse probe or on a Varian INOVA 500 MHz spectrometer equipped with a triple resonance HCN coldprobe. 13C NMR experiments were performed on a Varian 400 MHz spectrometer equipped with a Varian OneNMR probe. Chemical shifts were referenced to the residual solvent peak in DMSO-d<sub>6</sub>. Optical rotation was measured on a Jasco P-2000 polarimeter fitted with a microcell (10 mm path length).

Selvamicin production and purification: Spores of *Pseudonocardia* LS1 were diluted into sterile double distilled water (ddH<sub>2</sub>O) and spread onto plates of ISP2 agar (BD Difco™ ISP2; 60 mL agar per 150×15 mm Petri dish) supplemented with sodium butyrate (Aldrich, 150 mM final concentration, added after autoclaving), which were incubated at 30° C. for 14 d. Agar was then cut into squares and soaked in ethyl acetate overnight to extract organic components from the solid media. This extract was decanted and the agar was soaked in an additional volume of ethyl acetate for 3 h. The combined ethyl acetate extracts were concentrated in vacuo and adsorbed onto celite for dry packing onto a 10 g C18 SepPak column (Waters) that had been conditioned with acetonitrile and pre-equilibrated with 30% acetonitrile in water. Fractions were eluted with a step gradient of 30%, 50%, 70%, and 100% acetonitrile in water and concentrated to dryness. Consecutive fractions from elution at 50% acetonitrile were most active in inhibition of *Candida albicans*. Semipure material from these fractions was purified by reversed-phase HPLC (Agilent 1200 series preparative HPLC equipped with a diode array detector; Phenomenex Luna 10 μm phenyl-hexyl preparative column, 250×21.20 mm, 10 mL/min) with a gradient of 40% to 63% acetonitrile in water over 20 min. Selvamicin eluted at 12.5 min. The overall yield of pure selvamicin (isolated as an amorphous pale yellow solid) was 100 mg/L of agar.

Selvamicin: [α]<sub>D</sub> 26+128° (MeOH); UV (MeOH) λ<sub>max</sub> (log ε) 305 (4.4), 319 (4.7), 334 (4.9), 352 (4.9) nm; NMR spectral data, see FIG. 19; HR-ESI-TOFMS m/z 951.4928 [M+Na]<sup>+</sup> (calcd for C<sub>47</sub>H<sub>76</sub>NaO<sub>18</sub>:951.4924)

Preparation of Ac<sub>9</sub>-selvamicin: Selvamicin (18 mg) was dissolved in anhydrous pyridine (0.5 mL) under nitrogen in an oven-dried vial containing a dry stir bar. This solution was cooled to 0° C. with stirring and a solution dimethyl-

aminopyridine (1 mg) in anhydrous pyridine (100  $\mu$ L) and acetic anhydride (100  $\mu$ L) was added dropwise. After 5 min the reaction solution was warmed to room temperature and was stirred at room temperature under nitrogen for 5 h, at which point the reaction was complete by TLC. The reaction solution was evaporated to dryness in vacuo and Ac<sub>9</sub>-selvamicin was purified by reversed-phase HPLC (Agilent 1200 series semipreparative HPLC equipped with a diode array detector; Phenomenex Luna 5  $\mu$ m C18 column, 250  $\times$  10 mm, 3 mL/min) with an isocratic solvent mixture of 87% acetonitrile in water. Ac<sub>9</sub>-selvamicin eluted at 8.4 min.

Ac<sub>9</sub>-selvamicin: NMR spectral data see FIG. 20; FIR-ESI-TOFMS  $m/z$  1329.5885 [M+Na]<sup>+</sup> (calcd for C<sub>65</sub>H<sub>94</sub>NaO<sub>27</sub>: 1329.5875)

Solubility determination: Solubility for selvamicin and nystatin was measured with minor modifications from a previously reported protocol. 1 Briefly, in microcentrifuge tubes, 20  $\mu$ L 5 mM HEPES (pH=7.4) was added to 2.5 mg of selvamicin and of nystatin and the resulting suspensions were vortexed vigorously for 30 min at 22° C. The tubes were centrifuged, the resulting supernatants were diluted in HEPES buffer, and concentrations were determined by UV-vis absorbance (306 nm for nystatin and 335 nm for selvamicin).

Isothermal Calorimetry Sterol Binding Assay:

Large unilamellar vesicle (LUV) preparation: In a glass vial, a 25 mg/mL solution of palmitoyl oleoyl phosphatidylcholine (POPC) in chloroform (0.96 mL, Avanti Polar Lipids) was mixed with a freshly prepared 4 mg/mL solution of the appropriate sterol (ergosterol or cholesterol. Aldrich) in chloroform (0.35 mL). The sterol solution was omitted for preparation of sterol-free POPC LUVs. The resulting solution was evaporated to dryness in vacuo to yield a lipid film, which was placed under high vacuum for at least 5 h. To this film was added 1 mL 5 mM HEPES (pH adjusted to 7.4 with KOH) and the resulting suspension was vortexed for 3 min. This lipid suspension was loaded into a syringe and passed through a 0.1  $\mu$ m filter (Whatman) 21 times using an Avanti Polar Lipids Mini-Extruder to yield an LUN suspension (32 mM POPC, 11 mol % sterol; assumed no loss during extrusion).

Isothermal calorimetry (ITC) experiments: Solutions of polyene (150  $\mu$ M selvamicin or nystatin) in 1% DMSO/5 mM HEPES (pH=7.4) were prepared by dilution from a 1.5 mM solution in DMSO. 8 mM POPC LUV suspensions in 1% DMSO/5 mM HEPES (pH=7.4) were prepared by dilution of the above LUV suspensions with HEPES buffer and DMSO. ITC experiments were performed on a MicroCal iTC200 instrument (Malvern Instruments) with the 150  $\mu$ M polyene solution in the sample cell (200  $\mu$ L) and the LUV suspension injected by pipette. Experiments were performed at 25° C. and consisted of an initial injection of 0.4  $\mu$ L followed by 18 injections of 2  $\mu$ L each at intervals of 150 s. Experiments were performed for both nystatin and selvamicin with sterol-free LUVs, cholesterol-containing LUVs, and ergosterol-containing LUNs, with a minimum of two replicates for each condition. Robust binding, as indicated by heats evolved, was observed only for nystatin with ergosterol-containing vesicles. A dissociation constant for the nystatin-ergosterol interaction was estimated with the MicroCal ITC-ORIGIN analysis software in which the integrated heat for the last injection was subtracted from all of the data and a single binding site was assumed.

Induction with propionate and butyrate: Spores of each *Pseudonocardia* isolate were diluted into sterile double distilled water (ddH<sub>2</sub>O) and spread onto ISP2 agar (BD Diko™ ISP2; 1.5 mL agar per well in 12-well plates)

supplemented with the appropriate inducer (sodium butyrate or sodium propionate, Aldrich; 1-13C-sodium butyrate or 1-13C-sodium propionate. Cambridge Isotope Labs; 0, 25, or 150 mM final concentration with all conditions in duplicate; added after autoclaving), which were incubated at 30° C. for 14 d. The agar was cut out of each well and soaked in 2 mL ethyl acetate for 48 h. The ethyl acetate extract was evaporated to dryness in vacuo, redissolved in 0.1 mL methanol, and analyzed by HPLC (Agilent 1200 series, equipped with a diode array detector). The selvamicin peak in the 375 nm absorbance chromatogram was integrated for each sample. Samples were also analyzed by HPLC-high resolution

Determination of minimum inhibitory concentration: Fresh DMSO solutions of selvamicin and nystatin were prepared as serial dilutions and dispensed into clear flat-bottom 96-well plates in four replicates. A starting inoculum of the appropriate test strain in media was added to each well to yield a final concentration of 1% DMSO by volume. The plates were incubated at 30° C. with shaking at 200 rpm. Growth was assayed by OD600 readings taken on a M5 plate reader (Molecular Devices). For *E. coli*, *B. subtilis*, and *M. luteus*, the starting inoculum consisted of an overnight culture in LB diluted into LB media at 10  $\mu$ L/mL and final OD readings were taken at 22 h. For *C. albicans* and *S. cerevisiae*, the starting inoculum consisted of an overnight culture in YPD media diluted to an OD600 of 0.05 in YPD media and final OD readings were taken at 14 h. For *T. harzianum* and *A. fumigatus*, the starting inoculum consisted of a stock of concentrated conidia diluted into potato dextrose broth at 2 uL/mL and final OD readings were taken at 22 h. Using Prism (GraphPad), the OD data were normalized and fit to a Gompertz function, from which MIC values were extracted.

Genome sequencing and data deposition: DNA isolation and genome sequencing was performed. The complete genome for *Pseudonocardia* LS2 (HH130630-07) has been deposited in the GenBank database (accession nos. CP013854, CP013855, and CP013856) and raw sequence data has been deposited in the Sequence Read Archive. The *Pseudonocardia*. LS1 (HH130629-09) genome can be accessed using Genbank accession nos. CP011868 and CP011869.

Sequence comparison and analysis: Conserved replicons in the two chromosomes were compared using an average nucleotide identity (ANI) calculator, which provided a two-way ANI value of 83.3% from 8071 genomic fragments. The selvamicin gene cluster annotations were performed using antiSMASH24 and blastp (nonredundant proteins db). The Geneious aligner was used for pairwise alignment with proteins from the nystatin biosynthetic gene cluster from *S. noursei* ATCC 11455 (accession no. AF263912). Polyketide synthase domains were detected by antiSMASH2.4 and the translated protein sequences were aligned using Clustal W. Extractions from these domain alignments are displayed in FIG. 14.

#### Example 1

##### Discovery and Structure Elucidation of Selvamicin

Two *Pseudonocardia* isolates from ants in the genus *Apterostigma* collected at La Selva Biological Station, Costa Rica, HH130629-09 and Hh-1130630-07 (hereafter LS1 and LS2, respectively) were examined. Antifungal activity of organic-soluble extracts of cultures for both strains was evaluated against the common human fungal pathogen *Can-*

*didia albicans*. The LS1 extract was active and activity-guided fractionation was used through a C<sub>18</sub> cartridge followed by reverse-phase HPLC to trace this activity to a molecule with a previously unreported molecular formula of C<sub>47</sub>H<sub>76</sub>O<sub>18</sub> (high resolution ESI-MS IM-HNar calcd 951.4924, expt 951.4928). The LS2 extract was examined by high resolution LC-MS and observed the same compound, although at approximately 5-fold lower abundance, clarifying this extract's lack of antifungal activity in our initial bioassay. The active compound's UV-vis spectrum is characteristic of a polyene, with three prominent peaks (319, 334, 352 nm) consistent with a chromophore of five conjugated double bonds (FIG. 2). Subsequent NMR analysis using a variety of two-dimensional methods (COSY, TOCSY, HMBC, H2BC, and ROESY) revealed this compound to be a novel polyene macrolide, which has been named selvamycin after the site of original collection.

COSY and TOCSY correlations allowed construction of two major fragments of the selvamycin macrolide: one from C2-C8 and another from C13 across the pentaene to the molecule's terminus at C31 (overlap of the polyene resonances prevented definitive assignments of C19-C24). HMBC couplings link the C2-C8 fragment to quaternary carbons at either end: an ester carbonyl at C1 (172.7 ppm) and a hemiketal at C9 (97.3 ppm). The hemiketal forms a 6-membered ring established by a series of HMBC couplings from the hemiketal OH at position 9, a tertiary alcohol and methyl substituent at C12, and the other bridgehead carbon at C13. H2BC correlations support the placement of substituents along the macrolide core of selvamycin (FIG. 3). A series of ROESY correlations establish an extended geometry for the C2-C8 aliphatic chain and a chair conformation for the hemiketal ring (FIG. 3). These correlations, corroborated by available scalar coupling constants, allowed the assignment of relative stereochemistry from C4 to C13.

The NMR analysis also revealed two sugars in the structure of selvamycin. COSY and HMBC couplings revealed their planar structures as 6-deoxy and 2,6-dideoxy hexoses, as shown in FIG. 1, Panel B. In order to better resolve the crowded sugar CH signals and reveal additional peak fine structure, selvamycin was reacted with acetic anhydride to modify its free hydroxyl groups. In the acetylation product, the hemiketal at position 9 was instead observed as a ketone, and with the exception of the tertiary alcohol at position 12, all OH groups were acetylated (FIG. 4). Scalar couplings and ROESY correlations allowed the acetylated sugars in this product to be assigned as (Ac)<sub>3</sub>-β-6-deoxymannose and Ac-α-4-O-methylidigitoxose (FIG. 5). The absolute configuration of the sugars was not determined.

A clear HMBC coupling from the anomeric proton of the β-6-deoxymannose places this sugar at position 15 of the selvamycin macrolide (FIG. 1, Panel B). While no HMBC couplings were observed for the anomeric proton of 4-O-methylidigitoxose, a series of POESY correlations (1<sup>H</sup>-H/27-H, 1<sup>H</sup>-H/33-H, 5<sup>H</sup>-H/34<sup>H</sup>-H) locate this sugar on the opposite side of the macrolide at position 27. The <sup>1</sup>H and <sup>13</sup>C, chemical shifts of the CH at position 27 support an oxygen substituent at this attachment point. From C25-C31, we observed broadened <sup>1</sup>H and <sup>13</sup>C resonances, which obscured scalar couplings to establish relative stereochemistry in this region. This peak broadening could reflect conformational exchange near the 4-O-methylidigitoxose glycosylation.

Selvamicin's structure diverges from the antifungal polyenes amphotericin B, nystatin A<sub>1</sub>, and natamycin in several key respects. Its 30-membered macrolide core is intermediate in size between that of the smaller antifungal natamycin and those of amphotericin B and nystatin A<sub>1</sub>.

Selvamicin's unusual glycosylation is notable. The 6-deoxymannose replaces the mycosamine sugar common to most antifungal polyenes, and a second glycosylation, observed here at C27, is also unusual. Selvamycin represents, to our knowledge, the first report of either 6-deoxymannose or 4-O-methylidigitoxose sugars in a polyene natural product.

A second glycosylation located instead on the opposite end of the macrolide, as in selvamycin, has been observed among the minor fermentation products of the nystatin A<sub>1</sub> producer *Streptomyces noursei* (nystatin A<sub>3</sub>, FIG. 1, and NYST1070), and the candidin producer *Streptomyces viridoflavus* (candidoin), with the second sugar located at C35, the position corresponding to selvamycin's 4-O-methylidigitoxose attachment. While structurally distinct from 4-O-methylidigitoxose, these are also 2,6-dideoxy sugars (digitoxose, mycarose, and 2,6-dideoxy-L-erythro-hexopyranose-3-ulose, respectively). Notably, in contrast to fermentations of *Streptomyces noursei* and *Streptomyces viridoflavus*, we observe the diglycosylated polyene selvamycin as the major polyene species, and neither monoglycosylated analog is detectable by LC-MS in extracts of LS1 or LS2.

The presence of 4-deoxymannose in place of mycosamine represents the only example of a non-cationic sugar at that position in a glycosylated polyene natural product. Correspondingly, the usual paired carboxylate substituent (position 16 in nystatin and amphotericin B and position 12 in natamycin) is absent in selvamycin. There is instead a methyl group and a tertiary alcohol at position 12.

#### Example 2

##### Chemical Induction Affords Large Quantities of Selvamycin

The initial characterization and subsequent analysis of selvamycin was aided by the availability of large amounts of the compound (ultimately >100 mg) by chemical induction of *Pseudonocardia* isolate LS1 using sodium butyrate. The addition of high concentrations of sodium butyrate (150 mM) to cultures of LS1 and LS2 increased the production of selvamycin by approximately 20-fold (FIG. 8). Using mass spectrometry, <sup>13</sup>C labeling of selvamycin was observed when <sup>13</sup>C sodium butyrate was used, indicating that butyrate can also act as a metabolic precursor (FIG. 9). Sodium propionate also upregulated production in both LS1 and LS2, and <sup>13</sup>C labeling also demonstrated incorporation into selvamycin.

#### Example 3

##### Antifungal Activity and Solubility

Liquid broth-based activity testing confirmed selvamycin's antifungal activity against *Candida albicans* (MEC=23 μM), with similar activity observed across a panel of fungi (*Saccharomyces cerevisiae*, *Aspergillus fumigatus*, and *Trichoderma harzianum*, FIG. 10, FIG. 21, FIG. 23, Panel A). No activity was detected against either Gram-negative (*E. coli*) or Gram-positive (*B. subtilis*, *M. luteus*) bacteria. Selvamycin has more modest antifungal activity than clinically used polyene antifungals such as nystatin A<sub>1</sub> (MIC=1.0 μM against *C. albicans*). However, it has improved aqueous solubility (2.3 mM compared to 0.3 mM for nystatin A<sub>1</sub>), a major limitation of clinically available polyene antifungals. Selvamycin's improved solubility, despite its lack of charged carboxylate and ammonium groups, is probably contributed by its second sugar moiety.



The activity of known polyene antifungals derives from interactions with ergosterol, the primary sterol of fungal plasma membranes. Such interactions can compromise membrane integrity and inhibit the function of membrane proteins. Not wishing to be bound by theory, it is believed that ergosterol sequestration into extracellular aggregates may be the dominant mechanism of action, though several polyenes, including nystatin and amphotericin B, have also long been known to permeabilize membranes by the formation of ergosterol-dependent transmembrane channels. The presumed geometry of these channels situates the charged end of the molecule at the lipid-water interface, with the polyene and polyol interacting with ergosterol within the plasma membrane. The dramatically different electrostatic nature of selvatmicin would likely preclude channel formation, with a hydrophilic yet uncharged sugar at each end of the molecule. An interaction with ergosterol using an established isothermal calorimetry assay for binding to liposome-embedded ergosterol was probed. These experiments showed no evidence for binding, in stark contrast to control experiments using nystatin A<sub>1</sub>, suggesting that this interaction is much attenuated if present at all (FIG. 13).

#### Example 4

##### Biosynthetic Gene Cluster

To understand the genetic origins of selvamycin biosynthesis, the genomes of *Pseudonocardia* isolates LS1 and LS2, sequenced using PacBio technology, were examined. A large type I PKS gene cluster was identified in both genomes that satisfies the biosynthetic requirements for selvamycin (FIG. 11). The 109 kbp selvamycin biosynthetic gene clusters (BGC) from each isolate share perfect synteny and 98.4% nucleotide identity over their length. In contrast, the whole genomes differ more substantially. The average nucleotide identity (ANI) calculated across conserved replicons on both chromosomes is only 83% and a comparison of housekeeping gene sequences places LS1 and LS2 into distinct clades previously established for ant-associated *Pseudonocardia*. Overall, the two BGCs are much more similar to one another than are their bacterial hosts.

Surprisingly, the selvamycin BGC is situated in completely different genomic contexts in the two selvamycin producers; in LS1 it resides on the 6.1 Mbp circular chromosome, while in LS2 it is on a 376 kbp plasmid, pLS2-1 (FIG. 11, Panel A). The presence of an identical BGC in two divergent *Pseudonocardia* isolates, and in different genomic contexts, points to recent horizontal transfer. In keeping with recent movement of this cluster, it is flanked by numerous mobile genetic elements in both genomes, including transposases and integrases (FIG. 11, Panel B). Such genes are prevalent across both genomes. On the pLS2-1 plasmid containing the selvamycin BGC, an impressive 24% of all RAST-annotated genes are mobile genetic elements.

Plasmid-encoded secondary metabolite biosynthesis in several other ant-associated *Pseudonocardia*. These plasmids are an unmatched source of genetic, chemical, and functional diversity. For example, an additional plasmid-borne cluster that encodes for an antibacterial rebeccamycin analog is thought to mediate niche defense between otherwise nearly indistinguishable *Pseudonocardia*. In contrast, here, a plasmid and a recent chromosomal insertion in two

distinct bacterial isolates that represent convergence on an unusual polyene macrolide was identified. These results mirror those observed for the gemmycins, cyclic depsipeptides of unknown function. Both selvamycin and gerumycin BGCs are found on the LS1 chromosome though in other strains they are found on plasmids. Overall, these observations continue to implicate plasmid-based genetic exchange between these bacterial symbionts and the environment with the *Pseudonocardia* acting as a reservoir for mobile BGCs that encode useful biological activities.

#### Example 5

##### Biosynthesis

The selvamycin cluster resembles known type I PKS-derived polyene BGCs, and a side-by-side comparison with the well-characterized nystatin BGC readily reveals the origins of selvamycin's unusual structural features (FIG. 12). Both natural products derive from type I iterative PKSs with polyketide elongation modules spread across five genes (selnysB, -C, -I, -J, and -K). Relative to the corresponding genes for nystatin, selC and selJ each lack two PKS modules, corresponding to the observed four-carbon truncations of selvamycin's polyene and polyol moieties opposite one another on the macrolide: The polyketide backbone of selvamycin can be traced through 14 PKS modules with ketoreductase (KR), dehydratase (DH), and enoylreductase (ER) domains dictating the oxidation state of each malonyl or methylmalonyl unit (FIGS. 14 and 15). As often observed in type I PKS modules, there are several presumably inactive vestigial domains with mutations and/or truncations at their active sites: a DH and ER in module 13 and a KR in module 11.

SelA, the putative PKS loading module for selvamycin's propionate starter unit, shares several unusual features with previously characterized polyene loading modules, the function of which are poorly understood. Unlike most type I PKS loading modules, SelA is a separate protein distinct from the first elongation module and a serine is found in place of the canonical KS active site cysteine. Like NysA, the nystatin loading module critical for initiation of its biosynthesis. SelA contains a presumably inactive DH domain with no obvious function. Most unusual, and without precedent in polyketide loading modules, the SelA AT domain lacks the critical active site histidine and has a large truncation of approximately 65 amino acids in the middle of the domain (FIG. 14), suggesting that an alternative means of loading the initial acyl starter unit may be operative.

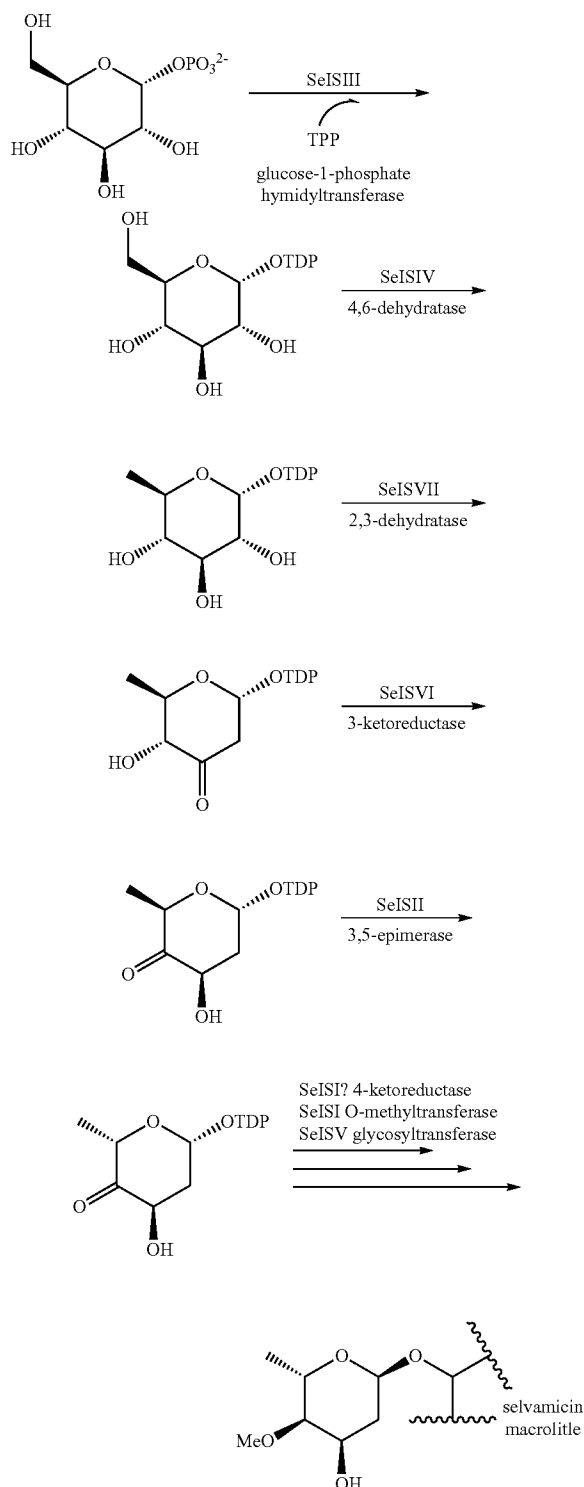
Tailoring of the polyketide core of selvamycin requires hydroxylations at C4 and C12. SelL, a cytochrome p450 with homology to the p450 NysL that installs nystatin's C10 hydroxyl, is the most probable oxidase for C4. SelP, a 2-oxoglutarate-dependent oxygenase with homology to phytanoyl-CoA dioxygenases was also identified. No homologous enzyme has been observed in other polyene clusters and this oxidase could be responsible for selvamycin's unusual C12 hydroxylation.

The canonical paired carboxylate and ammonium in polyene antifungals are both lacking in selvamycin. Notably, both the p450 NysN and ferredoxin NysM believed to install nystatin's carboxylate at C16 are absent in the selvamycin cluster, consistent with selvamycin's unoxidized methyl substituent at C12. The aminotransferase responsible for ammonium installation on the mycosamine sugar, NysDII, is also absent from the selvamycin cluster. The remaining sugar-related enzymes in the nystatin BGC, the mannose 4,6-

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dehydratase NysDIII and the glycosyltransferase NysDI, both have homologs in the selvamicin cluster and are consistent with the 6-deoxymannose found at C15.

Scheme 2: Proposed reactions carried out by the selvamicin 4-O-methyldigitoxose sugar subcluster



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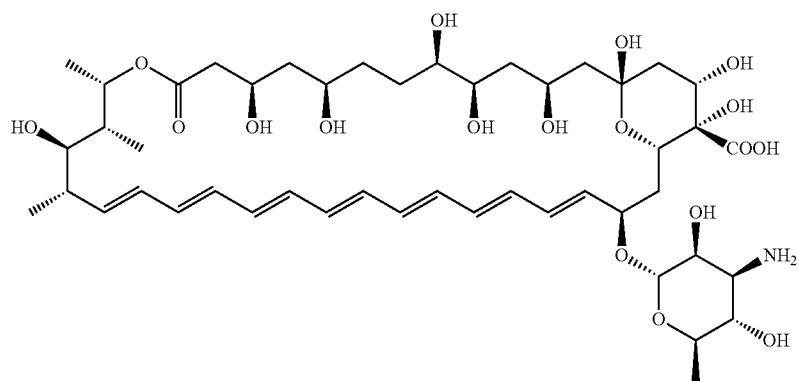
selSVII, found in the middle of the selvamicin BGC. These include a glycosyltransferase gene, selSV, and six genes consistent with 4-O-methyldigitoxose biosynthesis as a TDP-sugar from glucose-1-phosphate (Scheme 2). The putative 4-O-methyldigitoxose biosynthesis proteins are homologous to a similar suite of proteins responsible for digitoxose biosynthesis in the BGC for jadomycin B in *Streptomyces venezuelae* ISP5230. However, the selvamicin sugar subcluster additionally contains an O-methyltransferase gene selSI, and it curiously lacks an NDP-sugar 4-ketoreductase which should be required for digitoxose formation. Recently, 4-ketoreductase activity has been reported for a bifunctional SAM-dependent methyltransferase involved in the biosynthesis of methramycin's sugars. Similar bifunctional activity could be operative for the SelSI methyltransferase or alternatively this activity could require a separate 4-ketoreductase outside the selvamicin BGC in both the LS1 and LS2 genomes.

This sugar subcluster's insertion within a cluster of familiar polyene biosynthetic genes fits well with the paradigm of modular subclusters recombining over the course of natural product evolution to generate new products. Presumably, a similar suite of genes synthesizes and attaches the digitoxose sugar to nystatin A<sub>3</sub>, though no such subcluster occurs in the nystatin BGC from *Streptomyces noursei*. Whole genome sequencing of this strain may eventually reveal the location of these genes. Nystatin A<sub>3</sub>'S occurrence as a minor product of the nystatin BGC contrasts with selvamicin's occurrence as the principal product of the selvamicin cluster. The 4-O-methyldigitoxose subcluster's incorporation into the selvamicin BGC likely reflects selection for diglycosylation in the principal product. If this subcluster is truly modular it should present a biosynthetic engineering opportunity for appending 4-O-methyldigitoxose to other polyene scaffolds. Encouragingly, diglycosylated nystatin analogs, currently available only as minor products from *Streptomyces noursei* fermentation, have comparable anti-*Candida* potency to nystatin A<sub>1</sub>. A boost in solubility from an additional sugar would address a major pharmacological limitation of antifungals such as nystatin A<sub>1</sub> and amphotericin B.

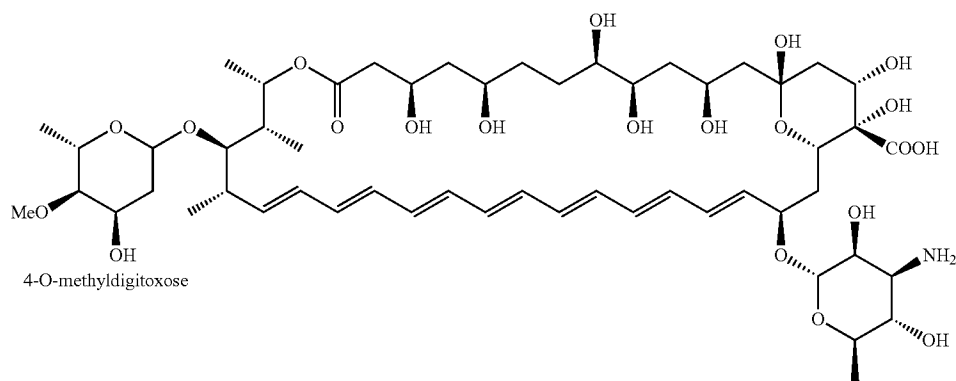
### Example 6

#### Creation of Solubility-Improved Polyene Antifungals Using Selvamicin's Subcluster of Sugar Biosynthetic Genes (Prophetic)

The subcluster of sugar biosynthesis genes found in selvamicin's biosynthetic gene cluster (SelSI-SelSVII, FIG. 12) should contain all genes required to synthesize the sugar 4-O-methyldigitoxose and attach it to a polyene macrolide. It is predicted that this suite of genes could be transferred to the producing organism of a structurally related polyene antifungal and would act in the same fashion, allowing for the creation of new glycosylated analogs of existing antifungal agents. Glycosylation should increase aqueous solubility, which is currently a major limitation of the clinically important antifungals amphotericin B and nystatin A<sub>1</sub>, shown below:

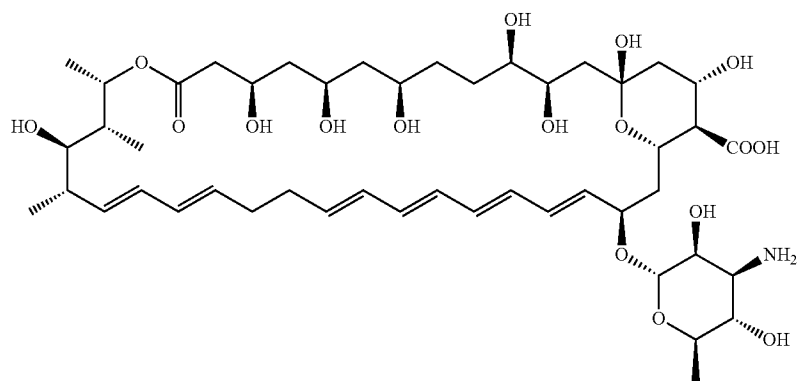


Amphotericin B

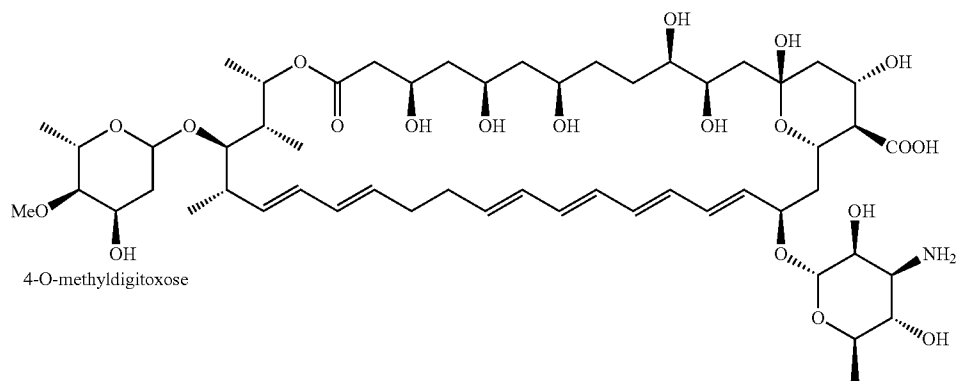


4-O-methyl-D-glucopyranose

Amphotericin analog



Nystatin A<sub>1</sub>



4-O-methyl-D-glucopyranose

Nystatin analog

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## Example 7

Generation of Non-Natural Selvamycin Analogs  
(Prophetic)

Non-natural analogs of selvamycin may be generated with retained or possibly improved antifungal activity by manipulating its biosynthetic gene cluster using gene knockouts. There are many possibilities here, including knockouts of the oxidases SelP or SelL to yield analogs lacking hydroxyl substituents at C4 or C12, respectively.

Selvamicin is a type I polyketide natural product whose macrolide core is generated by the iterative action of polyketide modules. The types of domains comprising each module dictate the final polyketide structure, as depicted in FIG. 16, Panel A.

Selvamicin analogs could be generated by deleting or disrupting individual modules (rather than entire genes), an approach that has been widely used to generate analogs of other polyene natural products. In one example, the ketoreductase domain of module 13 could be disrupted to generate analog 1 shown in FIG. 16, Panel B.

In another example, the dehydratase domain of module 14 could be disrupted to generate analog 2 shown in FIG. 16, Panel C.

## Example 8

## Selvamycin In Vivo Antifungal Activity

Selvamicin was tested in the neutropenic mouse disseminated candidiasis model. Briefly, mice were infected with an inoculum of  $5.70 \log_{10}$  cfu/ml of *Candida albicans* K1. Two hours after infection, the mice were administered either saline or selvamycin at 80 mg/kg via the intraperitoneal route. Eight hours after therapy, the burden of *Candida albicans* in mouse kidneys was measured by viable plate counts of organ homogenates. Selvamycin demonstrated efficacy in preventing *Candida albicans* growth following a single administration. No animal toxicity was apparent throughout the study.

## Example 9

## Selvamycin In Vivo Antifungal Activity

Selvamicin was tested in the neutropenic mouse disseminated candidiasis model. Mice were infected with an inoculum of *C. albicans*, *C. glabrata*, and *C. auris*. After infection, the mice were administered either saline or selvamycin at 20 mg/kg or 80 mg/kg via an intraperitoneal route. After therapy, the burden of *Candida albicans* in mouse kidneys was measured by viable plate counts of organ homogenates. Selvamycin demonstrated efficacy in preventing *C. albicans*, *C. glabrata*, and *C. auris* growth in a dose dependent fashion following administration (FIG. 23, Panel B and C).

While the present disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the disclosure.

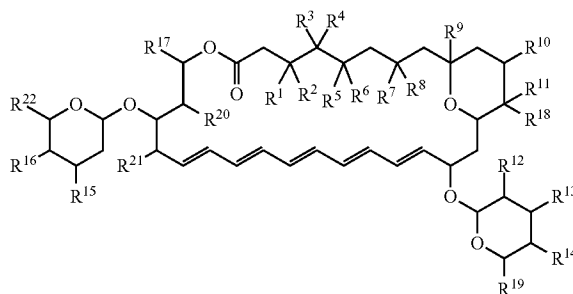
## 42

All publications, patents, patent applications and sequence accession numbers mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

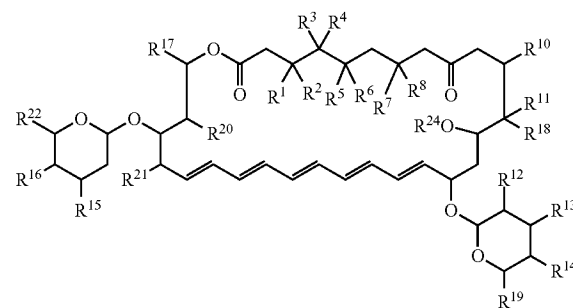
What is claimed is:

1. A compound having a structure of Formula I or Formula II or a pharmaceutically acceptable salt thereof:

Formula I



Formula II



wherein

$R^1$  and  $R^2$  are, independently for each occurrence, H or  $OR^{23}$ , or  $R^1$  and  $R^2$  together with the carbon to which they are bound form a carbonyl moiety;

$R^3$  and  $R^4$  are, independently for each occurrence, H or  $OR^{23}$ , or  $R^3$  and  $R^4$  together with the carbon to which they are bound form a carbonyl moiety;

$R^5$  and  $R^6$  are, independently for each occurrence, H or  $OR^{23}$ , or  $R^5$  and  $R^6$  together with the carbon to which they are bound form a carbonyl moiety;

$R^7$  and  $R^8$  are, independently for each occurrence, H or  $OR^{23}$ , or  $R^7$  and  $R^8$  together with the carbon to which they are bound form a carbonyl moiety;

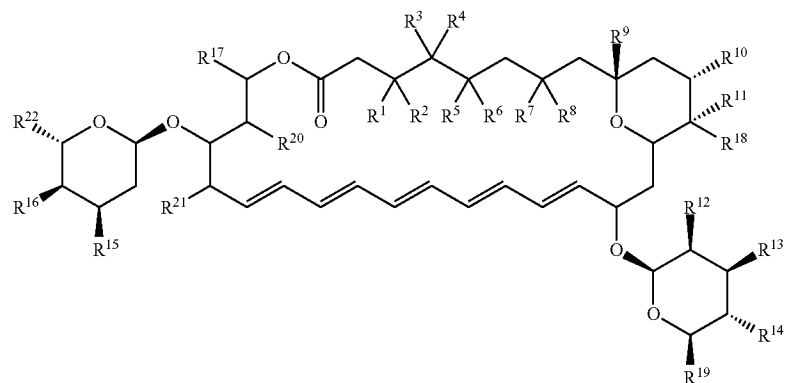
$R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ , and  $R^{16}$  are, independently for each occurrence, H or  $OR^{23}$ ;

$R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are, independently for each occurrence, H or optionally substituted alkyl;

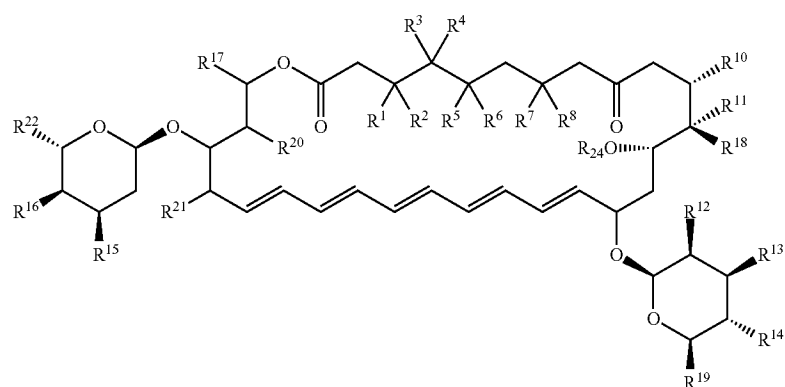
$R^{23}$  is, independently for each occurrence, H, optionally substituted alkyl, or optionally substituted acyl; and

$R^{24}$  is, independently for each occurrence, H, optionally substituted alkyl, or optionally substituted acyl.

2. The compound of claim 1, wherein the compound has a structure of Formula III or Formula IV or a pharmaceutically acceptable salt thereof:

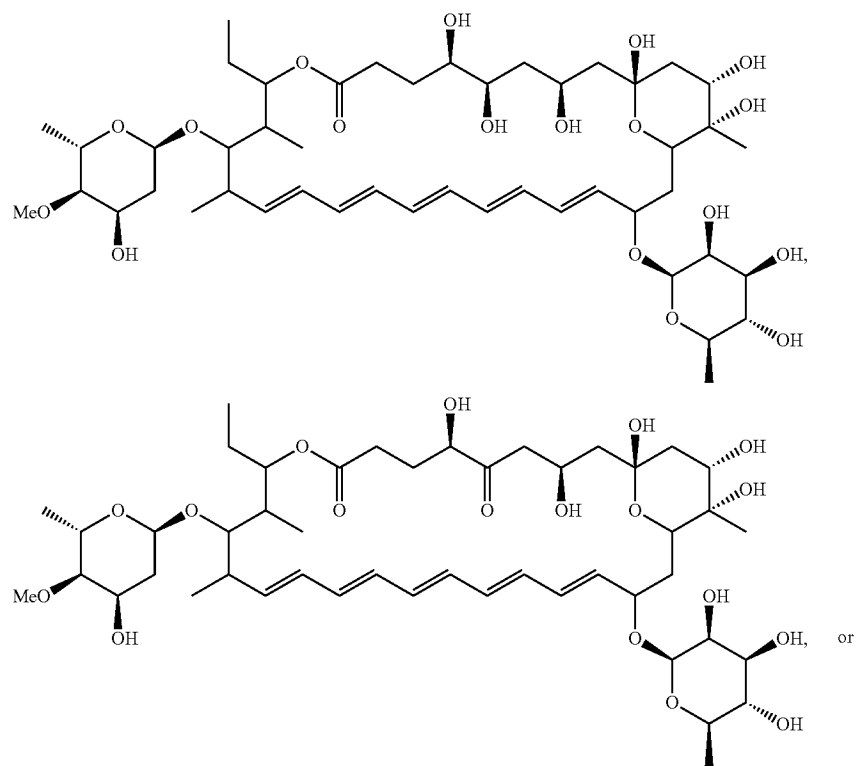


Formula III



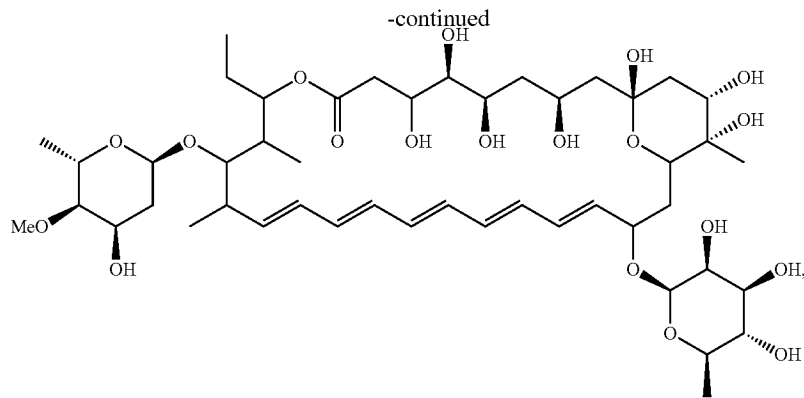
Formula IV

3. The compound of claim 1, wherein the compound has the structure



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or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier. 20

5. A method of inhibiting the growth of a fungus, the method comprising contacting a fungus with a compound of claim 1.

6. The method of claim 5, wherein the fungus is selected from *Candida albicans*, *Candida glabrata*, *Candida auris*, *Saccharomyces cerevisiae*, *Trichoderma harzianum*, and *Aspergillus fumigatus*. 25

7. A method of treating or lessening the severity of a fungal infection in a subject, the method comprising administering to the subject a compound of claim 1.

8. The method of claim 7, wherein fungal infection is infection with a fungus selected from *Candida albicans*, *Candida glabrata*, *Candida auris*, *Saccharomyces cerevisiae*, *Trichoderma harzianum*, and *Aspergillus fumigatus*.

9. A method of treating candidiasis in a subject, the method comprising administering to the subject a compound of claim 1.

\* \* \* \* \*