Electronic Supplementary Material (ESI) for Natural Product Reports.

Supporting information

Enzymatic Dimerization in the Biosynthetic Pathway of Microbial Natural Products

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Supplementary Figures

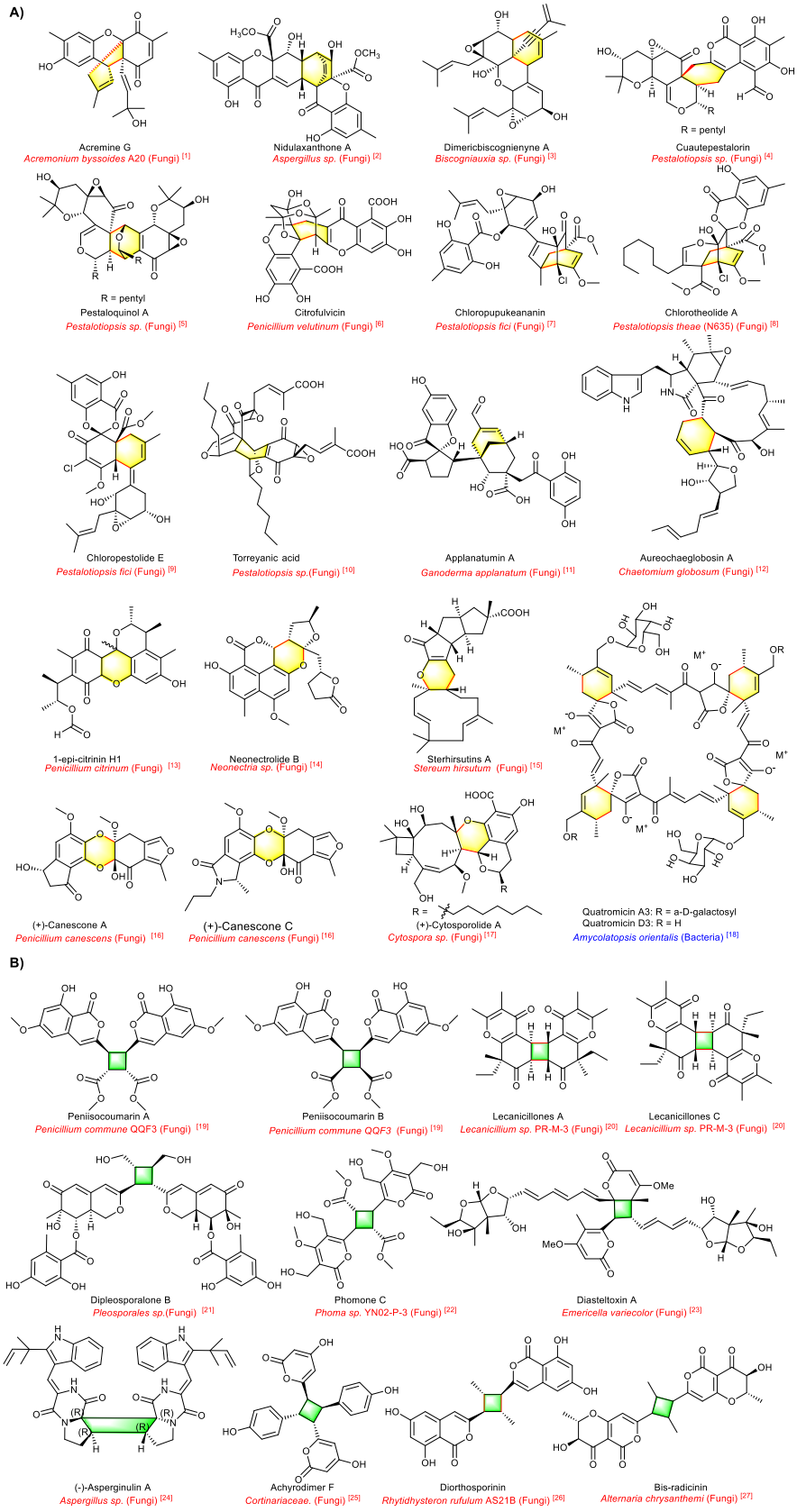

Fig. S1 Microbial natural products involved in a possible intermolecular cycloadditon reaction.[1-27] A). Potential intermolecular [4 + 2] cycloadditon; B). Potential intermolecular [2 + 2] cycloadditon.

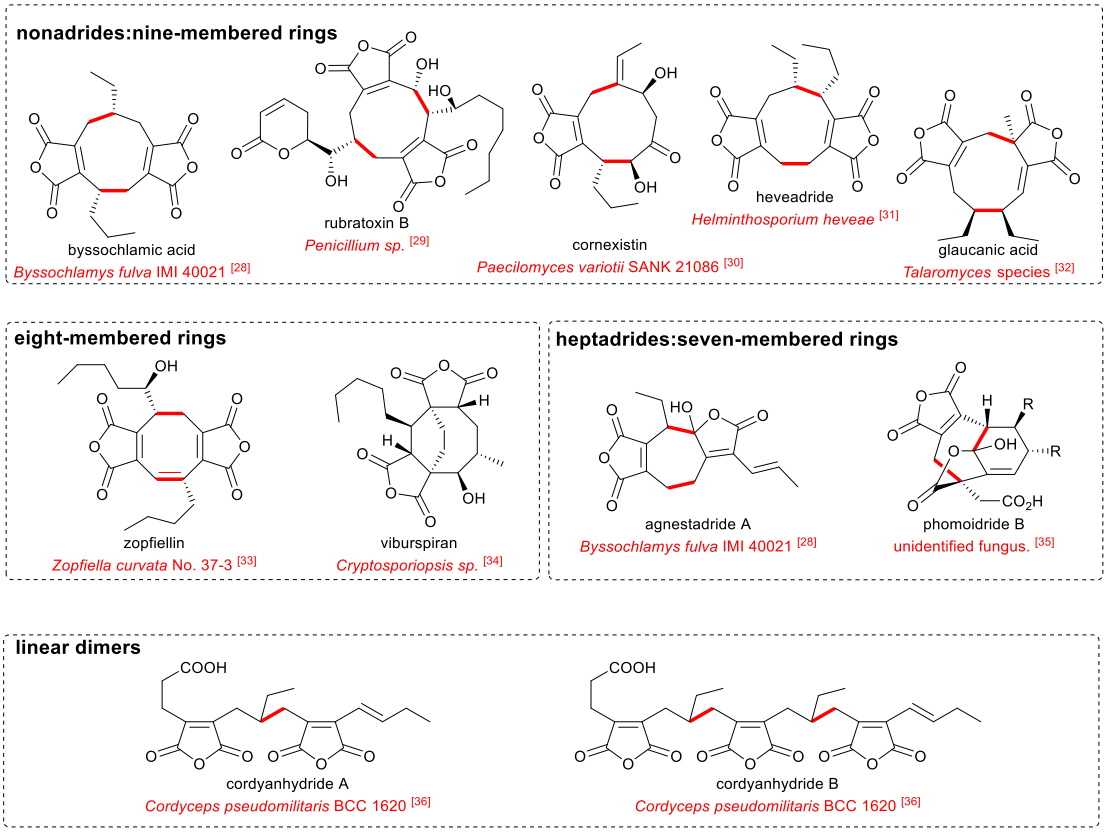

Fig. S2 Examples of fungal maleidrides.[28-36]

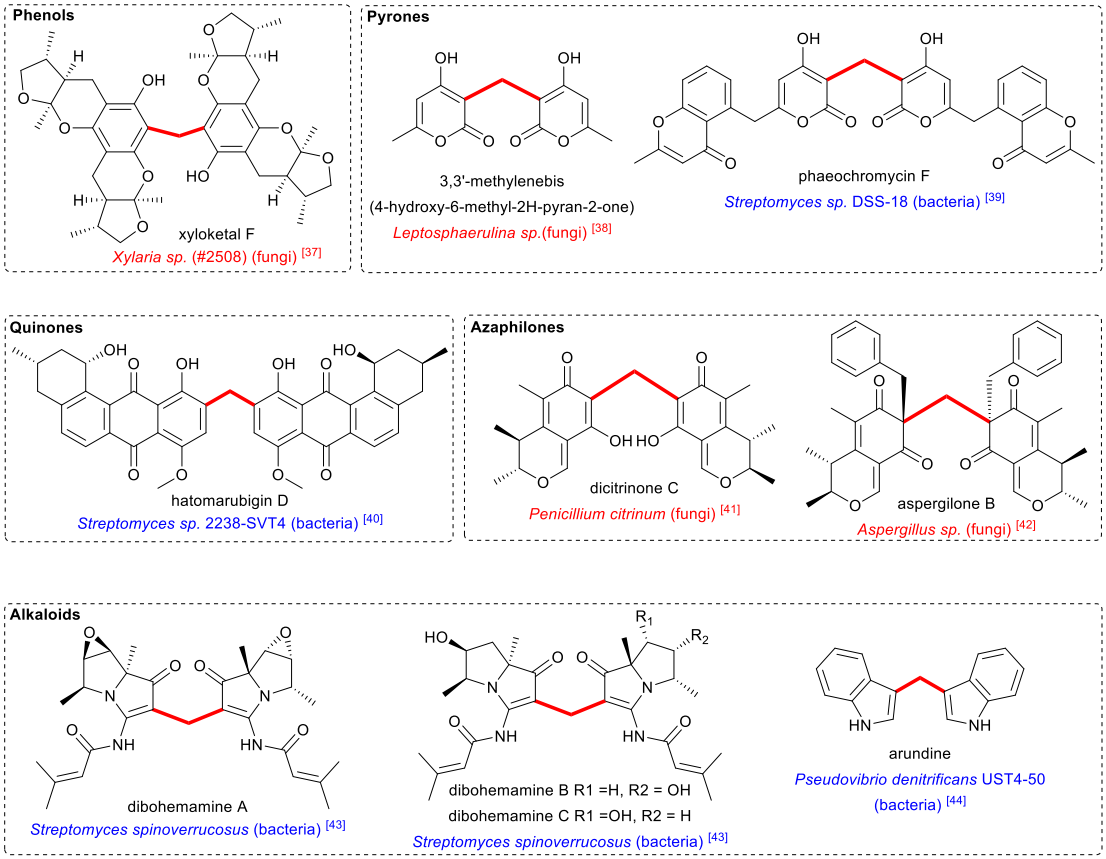

Fig. S3 Representative examples of microbial methylene bridged dimeric natural products.[37-44]

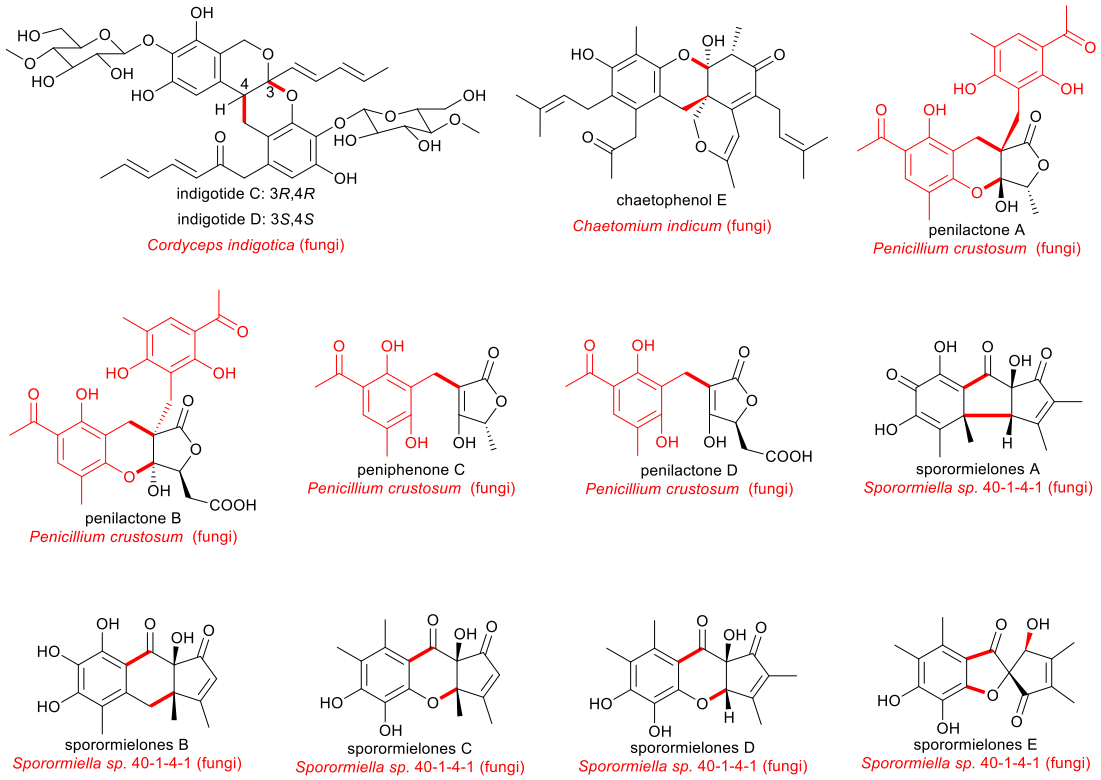

Fig. S4 Representative examples of methylene bridged natural products derived from spontaneous dimerization.

Table S1 Experimentally characterized enzymes involving in dimerization

Category	Names	*in vivo*		*in vitro*	Crystal structure	Bioinformatic analysis	Biosynthetic pathway
		Heterologous expression	Knockout				
P450s:	ClaM	Y	Y	N	N	Y	cladofulvin
	SKY_4059	N	N	N	N	Y	skyrin
	JulI	Y	Y	Y	N	Y	julichrome $Q_{6\text{-}6}$
	SetI	N	N	N	N	Y	setomimycin
	SptI	N	N	N	N	Y	spectomycin B1
	JuiI	Y	Y	Y	N	Y	julichrome $Q_{6\text{-}6}$
	NsrP	N	Y	N	N	Y	neosartorin
	CPUR_05431	N	N	N	N	Y	ergochromes
	DmxR5	N	Y	N	N	Y	cryptosporioptides
	pc16g10670 or pc16g10820	N	N	N	N	Y	chrysoxanthones A
	P-450mel	Y	Y	Y	N	Y	melanin
	CYP158A1	Y	Y	Y	Y	Y	flaviolin dimers
	CYP158A2	Y	Y	Y	Y	Y	flaviolin dimers
	AunB	Y	N	N	N	Y	aurasperone B
	BfoB	Y	N	N	N	Y	bifonsecin B
	KtnC	Y	N	N	N	Y	*P*-orlandin
	AfvE	N	Y	N	N	Y	aflavarin
	HmtS	Y	Y	N	N	Y	himastatin
	ClpS	Y	N	N	N	Y	alboflavusins
	BmP7	Y	Y	N	N	Y	Polybrominated marine products
	Dit1	Y	N	N	N	Y	bisformyl dityrosine
	XanG	N	Y	N	N	Y	xanthocillin
	DtpC	Y	N	Y	N	Y	ditryptophenaline
	TtpB1	Y	N	Y	N	Y	tetratryptomycin A
	TtpB2	Y	N	Y	N	Y	tetratryptomycin B
	ChaE	N	N	N	N	Y	chaetocin A
	NascB	Y	N	Y	N	Y	naseseazine C
	NznB	Y	N	Y	N	Y	naseseazines B
	NzeB	Y	N	Y	Y	Y	naseseazine C
	NasB	Y	N	Y	N	Y	naseseazine A
	AspB	Y	N	Y	N	Y	aspergilazine A
	DuxL	Y	N	Y	N	Y	duclauxin
	CnsC	Y	Y	Y	N	Y	communesin A

Table S1 (continued)

Category	Names	*in vivo*		*in vitro*	Crystal structure	Bioinformatic analysis	Biosynthetic pathway
		Heterologous expression	Knockout				
Laccases:	VdtB/ Av-VirL	Y	Y	Y	N	Y	viriditoxin
	MCE	Y	N	Y	N	Y	dinapinone A
	UstL	N	N	Y	N	Y	ustilaginoidin A
	SpoL	Y	N	Y	N	Y	sporandol
	CTB12	N	Y	N	N	Y	cercosporin
	AshL	Y	N	Y	N	Y	
	CheL	Y	N	Y	N	Y	
	MytL	Y	N	Y	N	Y	
	Gip1	N	Y	N	N	Y	aurofusarin
	ElcG	Y	N	N	N	Y	elsinochrome A
Inter-DA:	Macrophomate synthase	Y	N	Y	Y	Y	macrophomic acid
	Riboflavin synthase	Y	N	Y	Y	Y	riboflavin
	AsR5	Y	N	N	N	Y	xenovulene A
	EupF	Y	N	Y	N	Y	eupenifeldin
	EupfF	Y	N	Y	N	Y	eupenifeldin
Others:							
PKS:	AN7909	Y	N	Y	N	Y	diorcinol
NRPS-like:	$AtrA_{At}$	Y	N	N	N	Y	atromentin
	ApvA	Y	Y	N	N	Y	aspulvinone E
	MelA	Y	N	Y	N	Y	aspulvinone E
	BtyA	Y	Y	N	N	Y	butyrolactone IIa
	AtqA	N	Y	N	N	Y	asterriquinone CT5
	PgnA	Y	N	N	N	Y	phenguignardic acid
	TdiA	N	N	Y	N	Y	terrequinone A
	BpsA	Y	N	Y	N	Y	indigoidine
	MinA	Y	Y	Y	N	Y	minimycin
KI-like:	bfL6 / bfL10	Y	N	N	N	Y	byssochlamic acid
	rbtR	N	N	N	N	Y	rubratoxin A
	ZopC	Y	N	N	N	Y	zopfiellin
Flavin-dependent halogenases	Mpy10-Mpy11	Y	N	N	N	Y	marinopyrrole A
Hemolysin-type protein:	CylK	N	N	Y	N	Y	cylindrocyclophane A

Table S1 (continued)

Category	Names	*in vivo*		*in vitro*	Crystal structure	Bioinformatic analysis	Biosynthetic pathway
		Heterologous expression	Knockout				
Cytochrome b2:	RebD	Y	N	Y	N	Y	rebeccamycin
	StaD	Y	N	Y	N	Y	staurosporine
NmrA-like	ActVA-ORF4	N	Y	N	N	Y	actinorhodin
	Lom19/Strop2191	N	N	N	N	Y	lomaiviticin A
FMO	SorD	Y	Y	N	N	Y	sorbicillinoids

(Y: Yes; N: No).

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