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REVIEW ARTICLE

Natural thiopeptides as a privileged scaffold for drug discovery and therapeutic development

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Abstract

Since the start of the 21st century, antibiotic drug discovery and development from natural products has experienced a certain renaissance. Currently, basic scientific research in chemistry and biology of natural products has finally borne fruit for natural product-derived antibiotics drug discovery. A batch of new antibiotic scaffolds were approved for commercial use, including oxazolidinones (linezolid, 2000), lipopeptides (daptomycin, 2003), and mutilins (retapamulin, 2007). Here, we reviewed the thiazolyl peptides (thiopeptides), an ever-expanding family of antibiotics produced by Gram-positive bacteria that have attracted the interest of many research groups thanks to their novel chemical structures and outstanding biological profiles. All members of this family of natural products share their central azole substituted nitrogen-containing six-membered ring and are classified into different series. Most of the thiopeptides show nanomolar potencies for a variety of Gram-positive bacterial strains, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and penicillin-resistant *Streptococcus pneumonia* (PRSP). They also show other interesting properties such as antiplasmodial and anticancer activities. The chemistry and biology of thiopeptides has gathered the attention of many research groups, who have carried out many efforts towards the study of their structure, biological function, and biosynthetic origin. Here we reviewed a total of 119 natural thiopeptides discovered during the last 50 years. Moreover, we summarized biological profiles, mechanisms of action, and biosynthesis of these thiopeptides.

Keywords Thiopeptides · Natural products · Antimicrobial activity · Biosynthesis

Introduction

Thiopeptides are sulfur-containing peptide antibiotics with highly modified heterocyclic rings (Bagley et al. 2005). A highly modified amino acid tail chain (C-terminal), assembled by cyclized/dehydrated cysteine (Cys), serine (Ser), and threonine (Thr) residues, extends outward along the core six-membered nitrogen heterocycle (Li and Kelly 2010; Just-Baringo et al. 2014a, b). Thiopeptides belong to ribosomally synthesized and posttranslationally modified peptides (RiPPs) that are characterized by a series of post-translational modifications including cyclization, dehydration, oxidation, methylation, and epoxidation. In 1948, the first member of the thiopeptide family, micrococcin (Su 1948), was discovered, but it was finally diagnosed as a mixture of two micrococcins (Bycroft and Gowland 1978). Later, thiostrepton was isolated (Dutcher and Vandeputte 1954) and characterized in 1970 (Anderson et al. 1970). For recent decades, owing to their complex structures and excellent bioactivities (Just-Baringo et al. 2014a, b), thiopeptides have inspired chemists and pharmacologists in academia and pharmaceutical industry (Myers et al. 2010; Aminake et al. 2011; Newman and Cragg 2016). Primarily, thiopeptides exhibit a wide range of biological activities against a variety of Gram-positive bacteria, such as MRSA, PRSP, VRE, etc. (Just-Baringo et al. 2014a, b). Moreover, there are many other good biological properties as follows. First, some thiopeptides show good anticancer activities (Radhakrishnan et al. 2006; Nicolaou et al. 2005; Kwok et al. 2008; Bowling et al. 2008; Bhat et al. 2008, 2009; Uppoor et al. 2013; Hegde et al. 2011; Barot et al. 2013;

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J Kim 2002). For example, siomycin A and thiostrepton target overexpressed transcription factor forkhead box M1 (FoxM1) in cancer cells, inducing apoptosis of cancer cells without affecting the activity of normal functional cells in organisms (Hegde et al. 2011). Second, some thiopeptides exhibit promising antifungal activity (Nowak-Jary and Andruszkiewicz 2009; Mizuhara et al. 2011; Sajid et al. 2014; Cha et al. 2015) by binding to the chitin of fungal cells (Mizuhara et al. 2011; Cha et al. 2015). Third, some thiopeptides exhibit antiparasitic activity (Clough et al. 1997, 1999; Sullivan et al. 2000; Schlitzer 2007; Aminake et al. 2011) by interfering with the normal action of proteasomes and apicoplast (specific organelle of parasite) of malaria parasites. Fourth, some thiopeptides are confirmed as RNA polymerase inhibitors so that they are good candidates for antiviral therapy (Hashimoto et al. 2006). Fifth, some thiopeptides were found to have immunosuppressive activity (Ueno et al. 2004) since siomycins inhibit rat B cell proliferation stimulated by the antigen DNP-LPS (dinitrophenyl-lipopolysaccharide) independent of T cells, resulting in the inhibition of T cell proliferation and antibody production. Sixth, some thiopeptides show renin inhibitory activity (Aoki et al. 1991a, b, c). For example, cyclothiazomycin is a renin inhibitor found in the process of hypertension cascade. To date thiostrepton has been used as a FDA-approved active pharmaceutical ingredient for animals (Wang et al. 2015) while nosiheptide has been widely applied in veterinary antibiotics and food preservation (Mak et al. 2015).

Isolation, purification, structure elucidation, and biological profiles of thiopeptides

On the basis of the oxidation state of the nitrogen-containing six-membered ring, thiopeptides can be divided into the following five series: "*a* series", a reduced piperidine ring; "*b* series", a piperidine ring with further 1,2-dehydrated oxidation; "*c* series", a piperidine ring fused with imidazoline; "*d* series", a trisubstituted pyridine ring after further oxidized; "*e* series", an oxidized *tetra*-substituted pyridine ring with a hydroxyl group, and a modified 3,4-dimethylindoleic acid of macrocycle attached to the core ring (Just-Baringo et al. 2014a, b) (Fig. 1 and Table 1). All structures of thiopeptides family in this review (119 compounds) are collected from previously published literatures.

Series *a*

In the late 1970s, thiopeptins series including A1, A3, A4, and B were isolated and characterized from a soil actinomycete strain *Streptomyces tideyamensis* No. 7906 (Toyama, Japan) (Miyairi et al. 1970; Imanaka et al. 1973; Mine et al. 1972). Thiopeptins series can be divided into two series: *a* and *b*, in which the series *a* contains A1a (**1**), A3a (**2**), A4a (**3**), and Ba (**4**) (Fig. 2) and series *b* comprises other four compounds (Fig. 3). The six-membered ring of series *a* and *b* is a saturated and dehydrogenated piperidine (Hensens and Albers-Sch Nberg 1978, 1983). Thiopeptin B has been reported to exhibit a strong activity against Gram-positive bacteria with no cross-resistance, and the minimum inhibitory concentration (MIC) for *Staphylococcus aureus* 209P and *Smith* can reach 0.125 μg/mL (Miyairi et al. 1970). In addition, thiopeptin B has been used as feed additives that prevent lactic acid poisoning in ruminants (Gill et al. 1979; Kezar and Church 1979; Muir et al. 1980a, b, 1981; Nagaraja et al. 1982; Stutz et al. 1983; Cromwell et al. 1984a, b).

In 1978, antibiotics 68-1147 I and II were isolated from *Micromonospora arborensis* NRRL 8041, of which 68-1147 I could inhibit a variety of Gram-positive bacteria in vitro, such as *S. aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Bacillus subtilis* and other pathogens, and the MIC on average reach 0.03 μg/mL (Weinstein et al. 1978). In 1980, 68-1147 I Sch 18640 (**5**) was renamed and its chemical structure was elucidated (Fig. 2) (Puar et al. 1981).

Series *b*

Thiostreptons were isolated from the soil strain *Streptomyces azureus* ATCC 14921 (Mexico) in 1954 (Dutcher and Vandeputte 1954) and the strain *Streptomyces laurentii* ATCC 31255 in 1977 (Trejo et al. 1977). Both bryamycin (A-8506) and thiactin, isolated from the *Streptomyces hawaiiensis* in 1955 and 1963, respectively, were found to be identical (Cron et al. 1956; Bodanszky 1963). Chemical structure of thiostreptons was elucidated by chemical degradation and X-ray diffraction in 1970 followed by the confirmation of dehydroalanine side chains by the ^{13}C NMR in 1976 (Anderson et al. 1970; Tori et al. 1976). Complete structure of thiostreptons (Fig. 3) was established by NMR (Hensens and Alberssch Nberg 1983; Hensens et al. 1983; Mocek et al. 1989) and the sulfur anomalous dispersion method (Bond et al. 2001). Moreover, a minor product of thiostrepton A (**6**) was also found by ^{13}C NMR analysis and was named as thiostrepton B(**7**) (Tori et al. 1981) (Fig. 3).

Thiostrepton A (**6**) not only inhibits the growth of Gram-positive bacteria, but also interrupts with the main metabolism of malaria parasite (apicoplast) including chloroquine-sensitive and resistant *Plasmodium falciparum*. Moreover, thiostrepton A (**6**) is capable for inhibiting precursor gemic cells, showing an extremely strong anti-

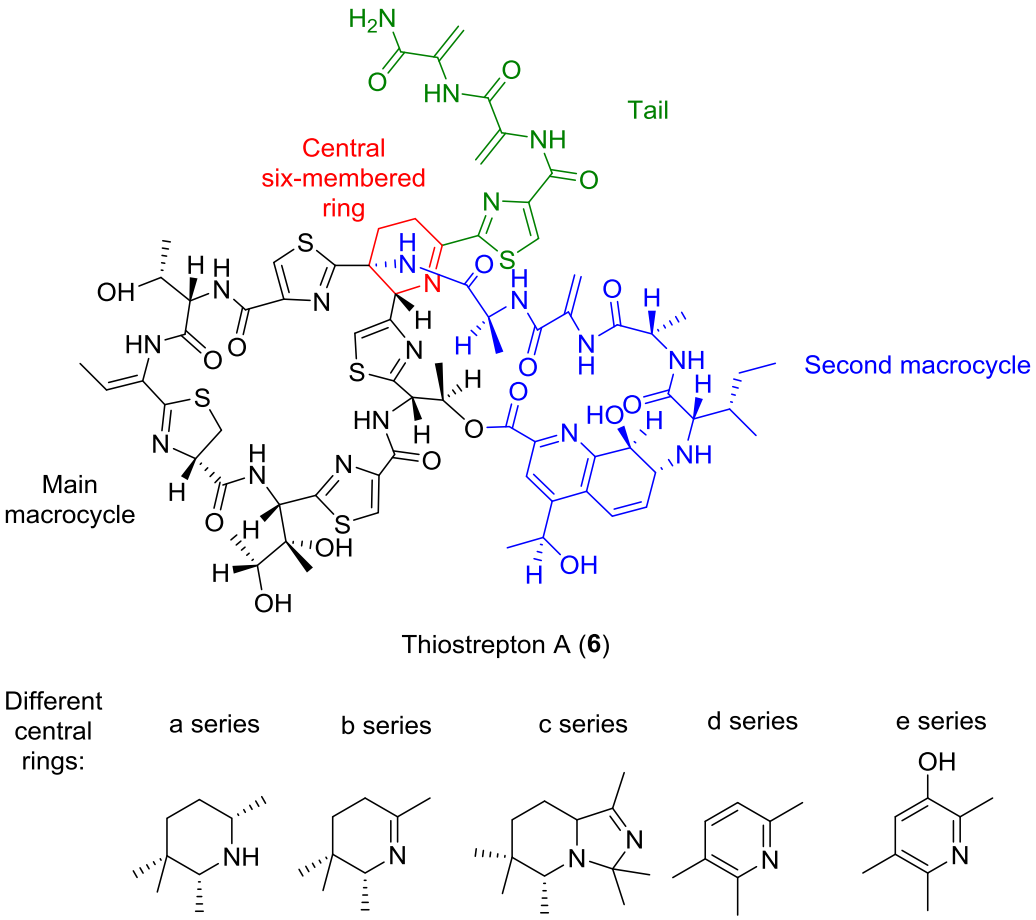


Fig. 1 Key regions of thiopeptides and classification into different series depending on their central six-membered ring

malarial performance with an IC_{50} of 8.9 µM (Aminake et al. 2011; Mcconkey et al. 1997; Rogers et al. 1997). Surprising, thiostreptons inhibit the transcription factor forkhead box M1 (FOXM1), thereby selectively inducing apoptosis in breast cancer and malignant tumor cells (Qiao et al. 2012).

Siomycins including A (**8**), B (**9**), and C (**10**) were isolated and characterized from *Streptomyces sioyaensis* Lv in 1959 (Nishimura 1961). Later siomycin D_1 (**11**) was isolated from *S. sioyaensis* and characterized in 1981 (Tori et al. 1981) (Fig. 3). Siomycin A (**8**), B (**9**), and C (**10**) exhibit similar biological profiles. They all show preferable resistance against Gram-positive bacteria, such as *B. subtilis*, *Bacillus anthracis*, *S. azureus*, *Diplococcus pneumonias* with MIC of up to 0.005 µg/mL (Nishimura 1961). Additionally, siomycin A (**8**) shows anticancer effects by targeting brain fatal glioblastoma (GBM) (Nakano et al. 2011) and restricting the overexpression of transcription factor Forkhead box M1 (FoxM1) (Gartel 2013; Guo et al. 2015). Siomycin A (**8**) also has an immunosuppressive effect compared with the typical immunosuppressant FK506 (Ueno et al. 2004). But it is noteworthy that, in contrast with siomycin A(**8**), its water-soluble derivatives showed better antibacterial activities in infected mice (Tokura et al. 1981), indicating a tremendous potential for the clinical antimicrobial application.

Additionally, thiopeptin *b* series, including thiopeptin A_{1b} (**12**), thiopeptin A_{3b} (**13**), thiopeptin A_{4b} (**14**), and thiopeptin B_b (**15**) (Fig. 3), also belong to this thiopeptide family.

Series *c*

Sch 40832 (**16**) was isolated and characterized from the complex 13-384 of *Micromonosporia carbonecea* ATCC 39149 (NRRL15099) in 1985 and was found to possess significant antibacterial activity (its MIC was between 0.1 and 1.0 µg/mL) in 1998 (Ganguly et al. 1987; Waitz et al. 1986). Its structure was elucidated by FAB-MS, PD-MS, Ion-Spray-MS, and 2D NMR while the stereochemistry of Sch 40832 (**16**) was finally confirmed through comparison with the known structure of thiostreptons (Puar et al. 1998).

Table 1 Thiopeptides classified according to central six-membered ring

Series *a*	Series *b*	Series *c*	Series *d*	Series *e*
Thiopeptins (*a* series)	Thiostreptons	Sch 40832 (13-384)	Micrococcin	Multhiomycin
Sch 18640 (68-1147)	Bryamycin (A-8506)		Sulfomycins	Nosiheptide
	Siomycin		Berninamycins	S-54832/A factors
	Thiactin		Thiocillins	Glycothiohexide α
	Thiopeptins (*b* series)		Thioxamycin	MJ347-81F4 factors
			Thioactin	Nocathiacins
			Cyclothiazomycins	Thiazomycins
			GE2270 factors (MDL 62,879) /LFF571/NAI003	Philipimycins
			A10255 factors	
			Promothiocins	
			JBIR-83 and JBIR-84	
			Geninthiocins	
			Amythiamicins	
			GE37468 factors	
			Promoinducin	
			Radamycin	
			QN3323 factors	
			YM-266183 YM-266184	
			Kocurin (PM181104)	
			Nocardithiocin	
			Thiomuracins	
			TP-1161	
			Baringolin	
			Lactocillin Lactazoles	

Bryamycin(A-8506) = Thiactin = Thiostreptons, Multhiomycin = Nosiheptide

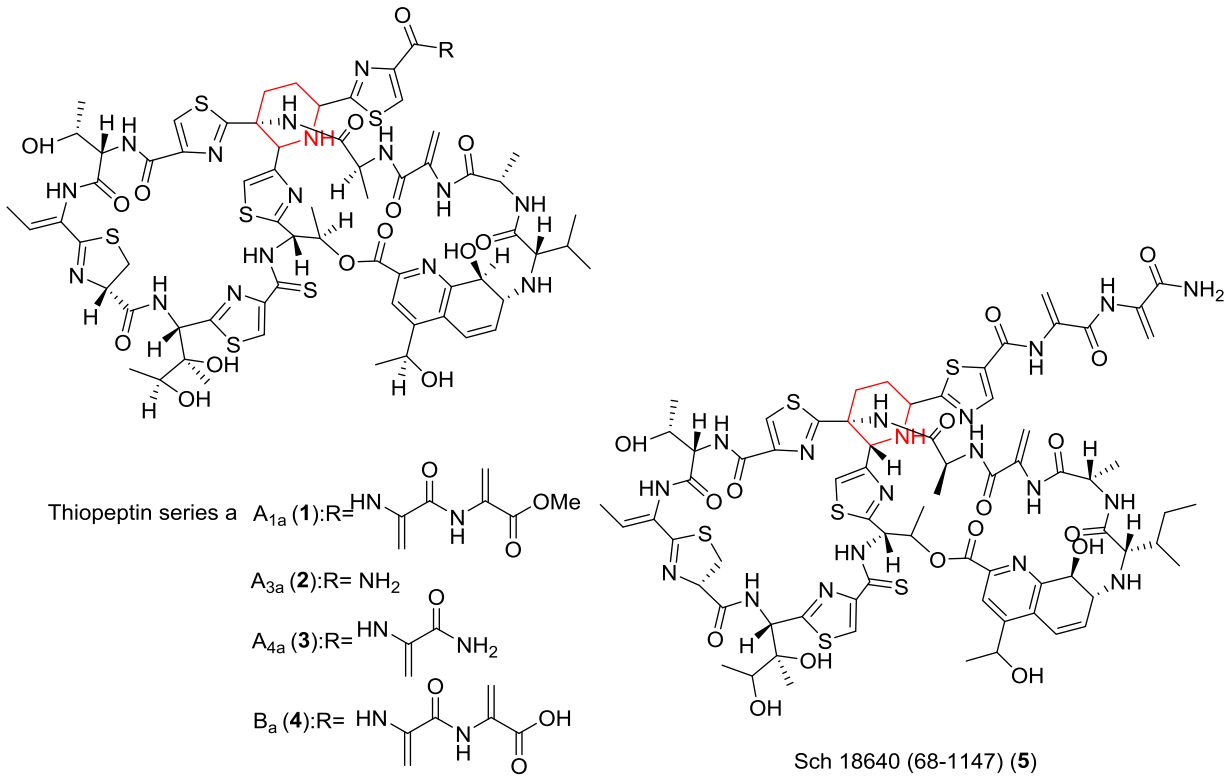


Fig. 2 Chemical structure of thiopeptin a series (**1**–**4**) and Sch 18640 (**5**)

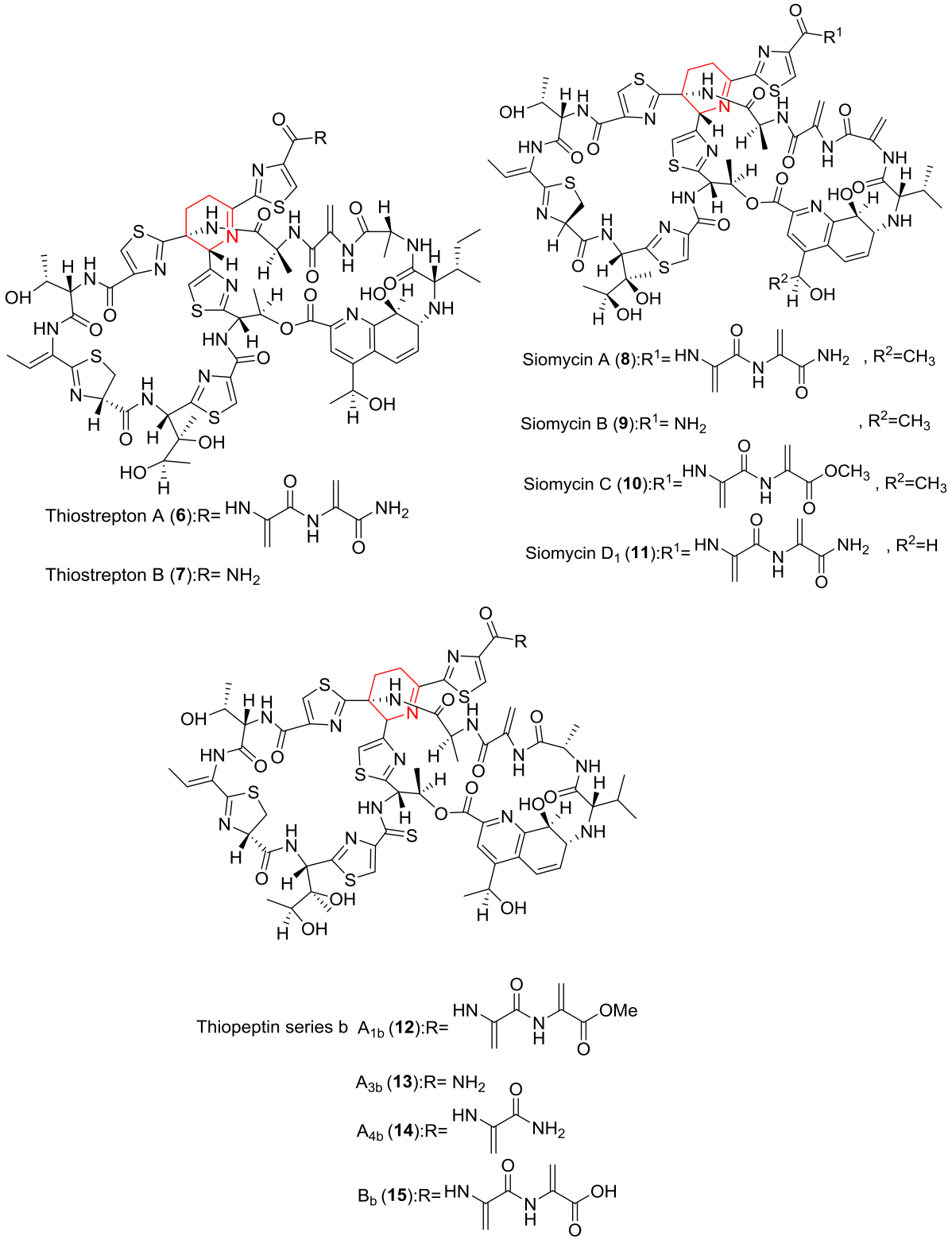


Fig. 3 The structures of b series thiopeptides

The core in the six-membered ring of Sch 40832 (**16**) is a bicyclic structure fused by a dihydroimidazopiperidine (Yoshimura et al. 1988; Puar et al. 1998) (Fig. 4). To date, Sch 40832 (**16**) has been the only *c*-series thiopeptide.

Series *d*

The first thiopeptide micrococcin was isolated from the sewage strain *Micrococcus* (Oxford, UK) in 1948, which is

capable of inhibiting a diversity of Gram-positive bacteria such as *S. aureus*, *Streptococcus faecalis*, *B. subtilis*, *Corynebacterium diphtheriae* with MICs of up to 0.025 μg/mL (Su 1948). Chemical structure of micrococcin P1 (**17**) and micrococcin P2 (**18**) were confirmed in 1978 (Bagley et al. 2005; Bycroft and Gowland 1978) (Fig. 5). Moreover, micrococcin P1 (**17**) was isolated and identified again in 2000 from a red fresh French cheese culture of *Staphylococcus equorum* WS 2733 (Carnio et al. 2000). Furthermore, micrococcin P1 (**17**) was found to have a broad spectrum of biological activities such as anti-cancer (J Kim 2002; SC Kim 2002), antimalarial (Clough et al. 1999; Schlitzer 2007), and anti-tuberculosis activity (Markham et al. 1951; Lee et al. 2016).

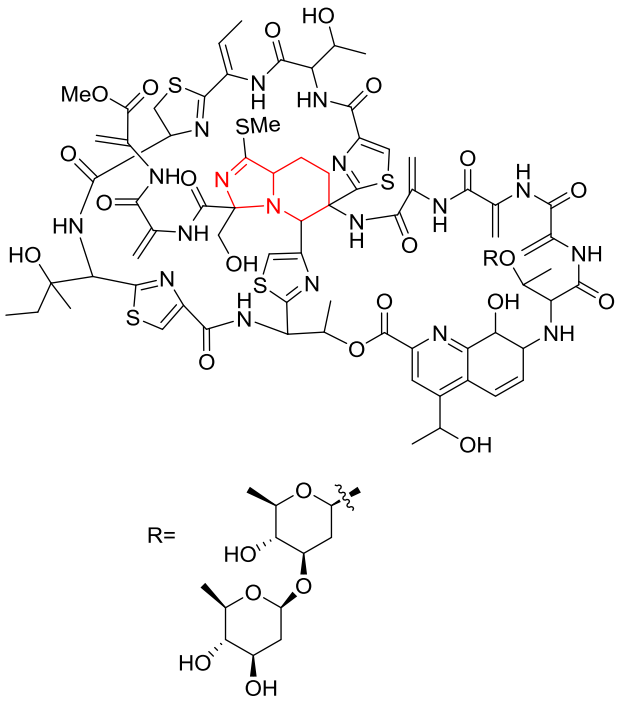


Fig. 4 The structure of c series thiopeptide

Subsequently, from *Streptomyces viridochromogenes* No. MCRL-0368 (*sulfomycini* ATCC 29776), three thiopeptides were isolated and named as sulfomycin I (**19**), II (**20**), and III (**21**) in 1969 (Egawa et al. 1969) and later their structures were elucidated by using chromatography, crystallization, FAB-MS, chemical degradation, and NMR (Abe et al. 1988; Kohno et al. 1996). In addition, a new compound, methylsulfomycin I (**22**) (Fig. 6), was isolated and identified from *Streptomyces* sp. HIL Y-9420704 in 1999. This compound exhibits excellent activity against Gram-positive bacteria, which are resistant to various antibiotics, such as vancomycin, teicoplanin etc., and the MIC values for several *Staphylococcus* and *Enterococcus* species ranged from 0.06 to 0.125 μg/mL (Kumar et al. 1999). Furthermore, sulfomycins was found to show strong activity against Gram-positive bacteria, such as cocci, bacilli, mycoplasma, and anaerobic bacteria, but less effective against *Neisseria*, *Bordetella*, and *Branches Mycobacteria*. It is noteworthy that sulfomycins exhibit cross-resistance with thiostrepton (Egawa et al. 1969).

In the same year, berninamycins A (**23**) was isolated from *Streptomyces bernensis sp. nova*. It exhibits promising activity against Gram-positive bacteria in vitro but has no inhibitory effect in vivo (Reusser 1969). A soluble amphoteric compound, berninamycinic acid (**25**), was identified during the acid degradation of berninamycin A (**23**). Chemical structure of berninamycin A (**23**) was initially proposed in 1976, revised in 1988, and confirmed in 1990 (Abe et al. 1988; Liesch et al. 1976a, b; Liesch and Rinehart 1977) (Fig. 7). Other three berninamycin B (**24**), C (**26**), and D (**27**) were isolated in 1994 and their structures were elucidated (Lau and Rinehart 1994) (Fig. 7). Furthermore, berninamycin A (**23**) (Ninomiya and Kodani 2011) and a novel analogue, berninamycin E (**28**), were characterized from *Streptomyces atroolivaceus* NBRC12741 (Kodani and Ninomiya 2013) (Fig. 7).

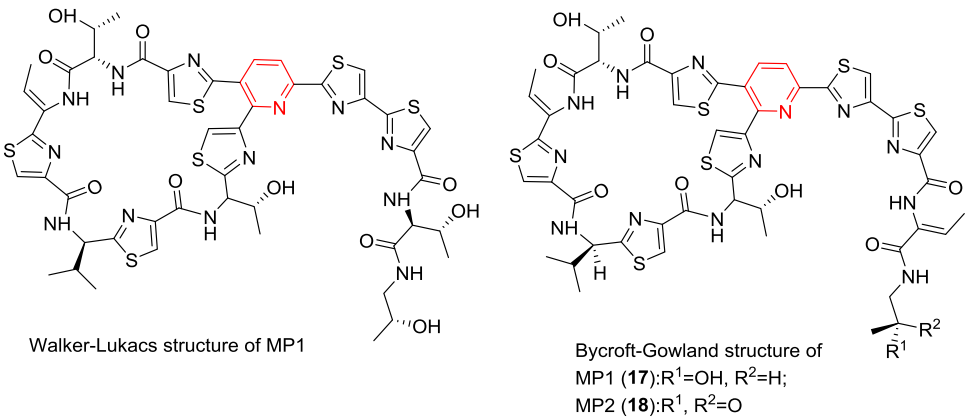
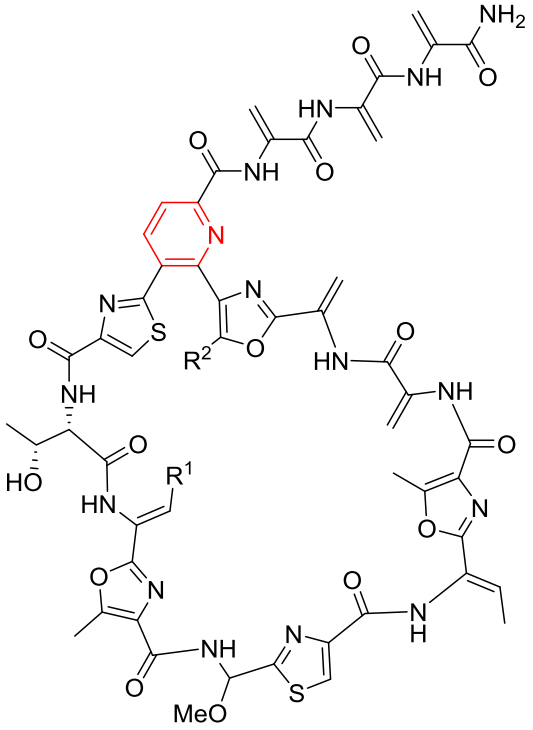


Fig. 5 The structures of micrococcins (**17**–**18**)



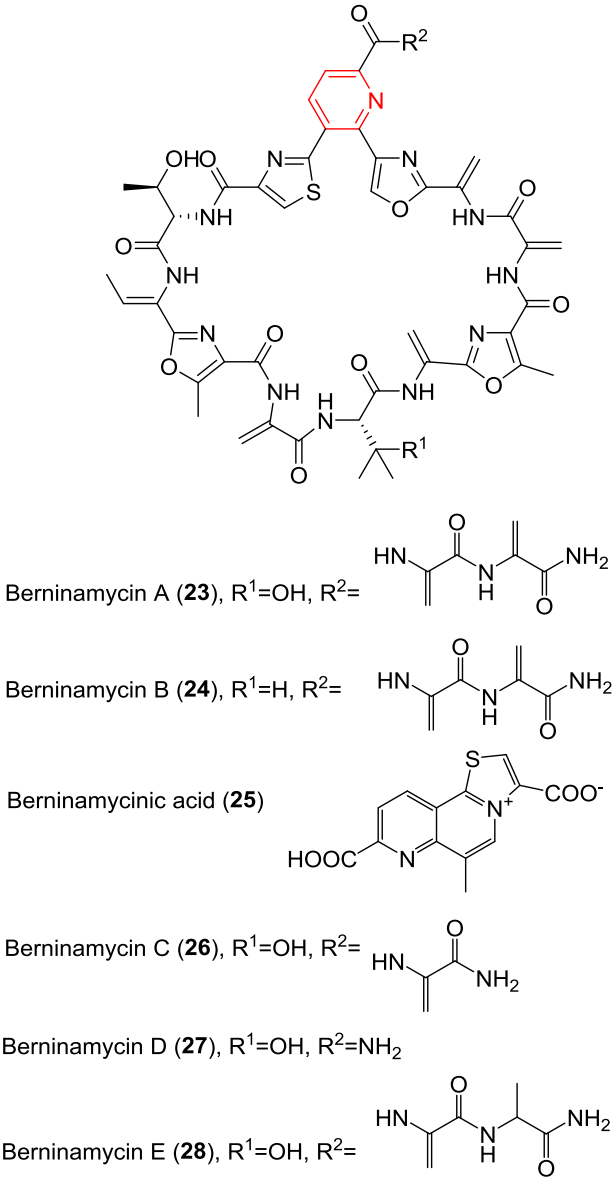
Sulfomycin I (**19**):R^1=CH(OH)Me, R^2=H

Sulfomycin II (**20**):R^1=CH2Me, R^2=H

Sulfomycin III (**21**):R^1=CH2OH, R^2=H

Methylsulfomycin I (**22**): R^1=CH(OH)Me, R^2=Me

Fig. 6 The structures of sulfomycins (**19**–**22**)



Berninamycin A (**23**), R^1=OH, R^2=

Berninamycin B (**24**), R^1=H, R^2=

Berninamycinic acid (**25**)

Berninamycin C (**26**), R^1=OH, R^2=

Berninamycin D (**27**), R^1=OH, R^2=NH_2

Berninamycin E (**28**), R^1=OH, R^2=

Fig. 7 The structures of berninamycins (**23**–**28**)

Berninamycin A (**23**) can effectively enhance the growth of domestic fowl and hogs (Pellegrino 1984).

Following the isolation of berninamycin A, thiocillin I (**29**) and II (**30**) were isolated from *Bacillus cereus* G-15 (also can be isolated from *Bacillus megatherium* I-13) while thiocillin II (**30**) and III (**31**) were identified from *Bacillus badius* AR-91 (Shoji et al. 1976, 1981) (Fig. 8). Thiocillin I (**29**) was chemically synthesized in 2011 and its complete structure was then determined (Aulakh and Ciufolini 2011) (Fig. 8). Thiocillins exhibit good antibacterial activities against Bacillus subtilis PCI 219, Bacillus anthracis (while thiocillin III (31) has no activity against these two kinds), Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae with MICs of 0.1–3.13 μg/mL (Shoji et al. 1976). Moreover, thiocillins can be used as a biofilm matrix inducer (Bleich et al. 2015).

Thioxamycin (**32**) was initially isolated from *Streptomyces* sp. strain PA-46025 in 1989 and it can effectively inhibit anaerobic and aerobic Gram-positive bacteria (Matsumoto et al. 1989). Then thioxamycin (**32**) and its derivative thioactin (**33**) were isolated from the mycelia of *Streptomyces* sp. DP94 by *tipA* screening (Fig. 9). Transcription of the *tipA* promoter can be induced by thiostrepton or related thiopeptide antibiotics (Murakami et al. 1989; Chiu et al. 1996). Besides, the minimum induction concentration of thioxamycin (**32**) and thioactin (**33**) to activate *tipA* promoters is 80 and 40 ng/mL, respectively, and the MIC values of thioactin (**33**) for *S. pyogenes*, *S. pneumoniae*, and *Micrococcus luteus* are 6.25 μg/mL (Yun et al. 1994a, b, c, d).

A structurally unique bicyclic thiopeptide, cyclothiazomycin A (**34**) was subsequently isolated from *Streptomyces* sp. NR0516 (Japan Kamakura Kanagawa) in 1990, followed by its structure elucidation via chemical degradation, FAB-MS, 1D NMR, and 2D NMR (Aoki et al. 1991a, b, c)

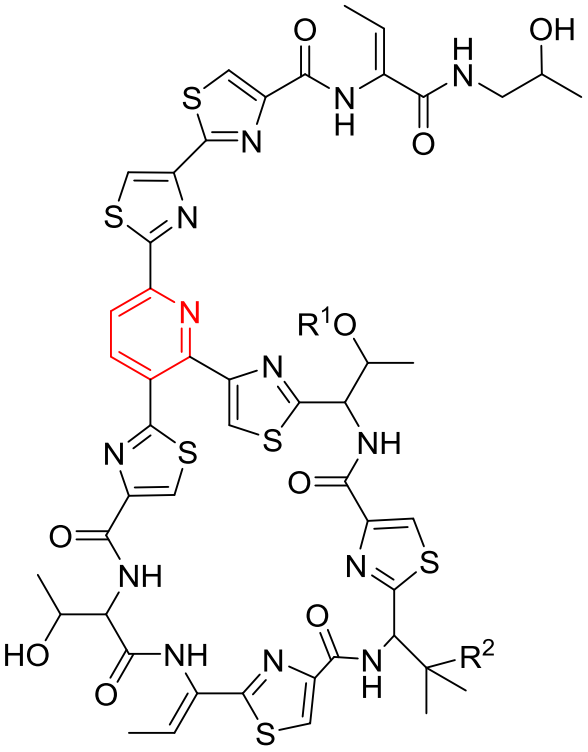


Fig. 8 The structures of thiocillins (**29**–**31**)

(Fig. 10). Cyclothiazomycin A (**34**) showed effective inhibitory activity against human plasma renin with IC_{50} of 1.7 µM (Aoki et al. 1991a, b, c). Two other cyclothiazomycin analogues, cyclothiazomycin B (**35**) and cyclothiazomycin C (**36**), were discovered from *Streptomyces* sp. A307 in 2006 and WC-3908 in 2014, respectively (Fig. 10). Cyclothiazomycin B (**35**) was confirmed to play a role in inhibiting RNA polymerase. In addition, cyclothiazomycin B (**35**) also possess antifungal effects by altering fungal morphology (Mizuhara et al. 2011). So far, the biosynthetic gene cluster for cyclothiazomycin A (**34**) has been identified (Wang et al. 2010) via tandem bioinformatics/reactivity-based (the covalent labeling of activated alkenes by nucleophilic 1,4-addition) screening method (Cox et al. 2014), which leads towards pathway engineering.

Not long after the bicyclic thiopeptide discovered, a new family referred as inhibitors of protein synthesis was mined. First, the compound GE2270 A (**37**) was isolated from *Planobispora rosea* ATCC 53773 in 1991 and it was found to inhibit all Gram-positive bacteria including *Mycobacterium tuberculosis*, especially the anaerobic *Propionibacterium acnes* with MICs of 1 µg/mL by inhibition of elongation factor Tu (EF-Tu) (Selva et al. 1991). Later GE2270 A (**37**) was found to inhibit effectively the growth of many bacteria, such as *Staphylococci* (MIC_{90}, 0.125 µg/mL), *Streptococci* (MIC_{90}, 1 µg/mL), *Enterococci* (MIC_{90}, 0.03 µg/mL), *Clostridium difficile* and *P. acnes* (MIC_{90} 0.06 µg/mL) (Goldstein et al. 1993; King et al. 1993). Chemical structure of GE2270 A (**37**) was elucidated with IR, NMR, acid–base ionization, elemental analysis and FAB-MS-MS (Kettenring et al. 1991), and finally determined by a number of research groups in 1995 (Colombo et al. 1992; Tavecchia et al. 1994, 1995). During the same period, GE2270 A (**37**) homologues, GE2270 Bl (**38**), B2 (**39**), C1 (**40**), C2a (**41**), C2b (**42**), D1 (**43**), D2 (**44**), E (**45**), and T (**46**) were isolated from *P. rosea* ATCC 53773 (Selva et al. 1995) (Fig. 11). GE2270 A (**37**) derivatives have enhanced bioactivity, such as the semisynthetic thiopeptide LFF571 (**47**) (Fig. 12) which was more potent, more tolerant while less recurrent than vancomycin when administrated thimbleful to the mice infected with *C. difficile* (Leeds et al. 2011; Mullane et al. 2014). Remarkably, a new GE2270 A (**37**) derivative, NAI003 (**48**), (Fig. 12) is highly selective against *P. acnes*, with MIC values range from 4 to 250 ng/mL (Fabbretti et al. 2015), which is of great significance for the treatment of skin diseases.

In the same year, an A10255 complex was isolated from the soil strain *Streptomyces gardneri* NRRL 15537 (Holfano County, Colorado) and the complex was composed of B (**49**) (80–85%), C (**50**), D (**51**), E (**52**), F (**53**), G (**54**) (15–29%), H (**55**), and J (**56**) (Boeck et al. 1992). Debono et al. (1992) used chemical degradation, NMR, FAB-MS, and CID to elucidate the structures of A10255 B (**49**), G (**54**), and J (**56**). The isotope-labeled precursor incorporation was used to determine the structure of E (**52**) (Favret et al. 1992) (Fig. 13).

According to the previous *tipA* screening, promothiocins A (**57**) and B (**58**) were isolated and characterized from *Streptomyces* sp. SF2741 in 1994 (Fig. 14). The MICs for promothiocins A (**57**) and B for *tipA* promoter (**58**) were 0.2 and 0.1 µg/mL, respectively (Yun et al. 1994a, b, c, d). Two other derivatives a (**59**) and b (**60**) were obtained during chemically degradation to study their stereochemistry (Yun et al. 2001) (Fig. 14). In addition, melamine-formaldehyde resin (MF) method was used to isolate two promothiocin derivatives JBIR-83 (**61**) and JBIR-84 (**62**) from a soil strain *Streptomyces* sp. RI19 (Okinawa Prefecture, Japan) (Takagi et al. 2010) (Fig. 14).

Thiotipin (**63**) (Fig. 15) was isolated from the mycelia *Streptomyces* sp. DT31 by *tipA* screening in 1994 with a MIC of 80 ng/mL, and a MIC of 3–6 µg/mL against *S. pneumoniae*, *S. pyogenes*, and *M. luteus* (Yun et al. 1994a, b, c, d).

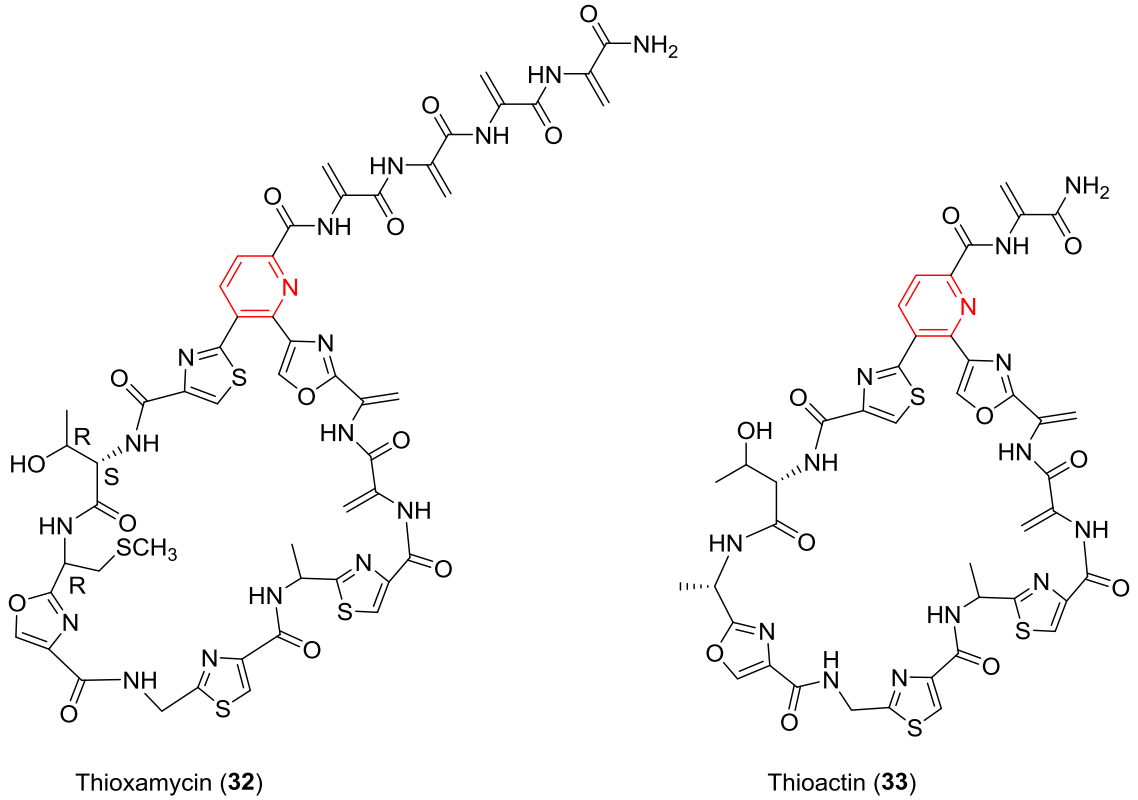


Fig. 9 The structures of thioxamycin (**32**) and thioactin (**33**)

Geninthiocin (**64**) was isolated from the mycelia of the soil strain *Streptomyces* sp. DD84 (Japan's Izu Island) by *tipA* screening in 1994 (Fig. 15) and the MIC of geninthiocin (**64**) is 1.2 ng/mL (Sajid et al. 2014, 2008). A new geninthiocin analogue, Val-Geninthiocin (**65**), was isolated from the mycelium of *Streptomyces* sp. RSF18 in 2008 (Fig. 15) and has both antibacterial and antifungal activities (Sajid et al. 2014, 2008).

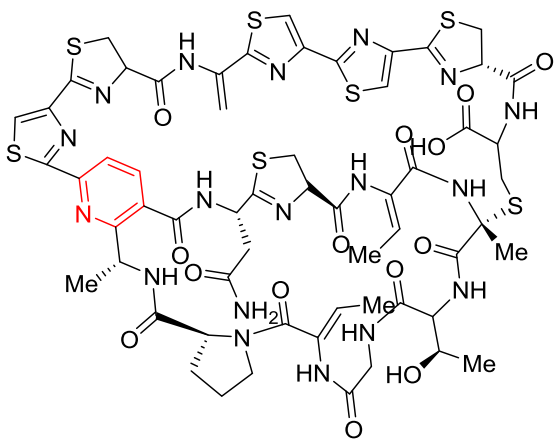
Furthermore, four thiopeptides amythiamicin A (**66**), B (**67**), C (**68**), and D (**69**) were isolated and characterized from *Amycolatopsis* sp. MI481-42F4 (No. FERMP-12739) (Kanagawa, Japan) in 1994 (Shimanaka et al. 1994a, b, 1995) (Fig. 16). Amythiamicin A (**66**), B (**67**), C (**68**), and D (**69**) all have good inhibitory activities against Gram-positive bacteria and amythiamicin A (**66**) with the most prominent effect. The MIC of amythiamicin A for *S. aureus* FDA209P can reach 0.1 µg/mL (Muraoka et al. 2000).

GE37468A (**70**), another inhibitor of protein synthesis, was isolated and identified from *Streptomyces* sp. ATCC 55365 (Fig. 17) in 1995 (Stella et al. 1995; Ferrari et al. 1995; Marinelli et al. 1996). GE37468A (**70**) possesses good in vivo antibacterial activity and protects mice from the pathogen *S. aureus* with ED_{50} (median effective dose) value of 3.2 mg/kg. Furthermore, two derivatives GE37468B (**71**) and GE37468C (**72**) were characterized in 1997 (Fig. 17) with MICs of from 0.016 to 0.25 µg/mL (Stella et al. 1997).

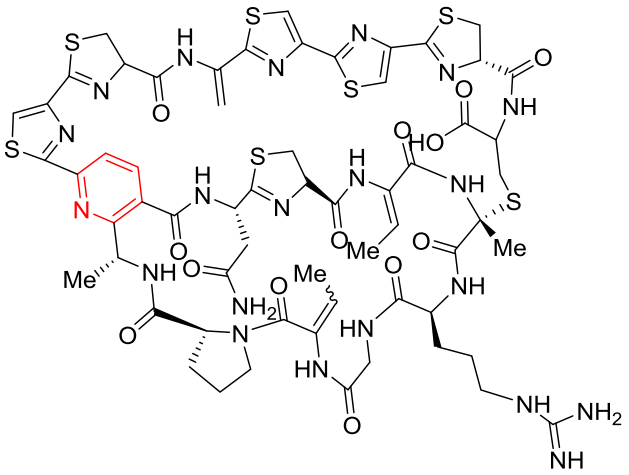
In the same year, *tipA* screening method was used to isolate promoinducin (**73**) from a strain *Streptomyces* sp. SF2741 (Fig. 17) and the MIC value was 40 ng/mL. Promoinducin (**73**) also showed strong anti-Gram-positive bacterial activity in vitro, such as *M. luteus* (MIC: 0.39 µg/mL), *S. pneumoniae* (MIC: 0.1 µg/mL), and *S. pyogenes* (MIC: 0.1 µg/mL) and so on. It was found that the thiopeptides without dehydroalanine moiety, such as amythiamicin A (**66**), cyclothiazomycin (**34**), and GE2270 A (**37**), had no promoter-induced activity, indicating the role of dehydroalanine in the induction of promoter (Yun and Seto 1995).

In the next year, Alexomycin (U-82,127), produced by *Streptomyces arginensis*, was found to be an effective growth stimulant for poultry and domestic hogs with the optimum dose varying from 2.3 to 6.2 mg/kg (Cromwell et al. 1996; Jones et al. 1998; Marshall and Jones 1999). But later on, it turned out to be a mixture of sulfomycin I (**19**) and promothiocin B (**58**) (Ashraf-Khorassani et al. 2000).

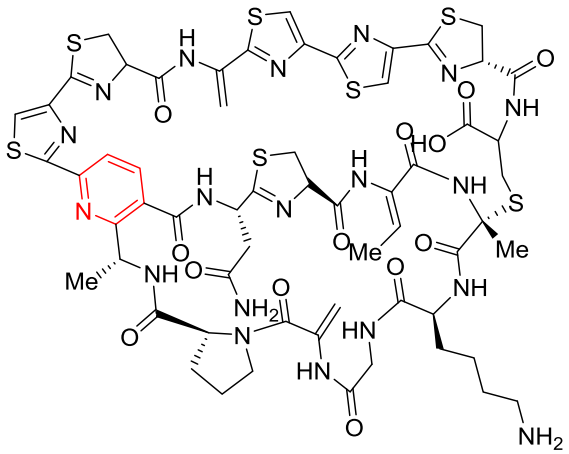
Two 35-membered thiopeptides, isolated from *Streptomyces* sp. RSP9 in 2001, were confirmed to be methylsulfomycin I (**22**) (Fig. 6) and radamycin (**74**) (Fig. 18), respectively. Radamycin (**74**) has no inhibitory effect on Gram-positive bacteria, but it is capable of inducing the



Cyclothiazomycin (**34**)



Cyclothiazomycin B (**35**)



Cyclothiazomycin C (**36**)

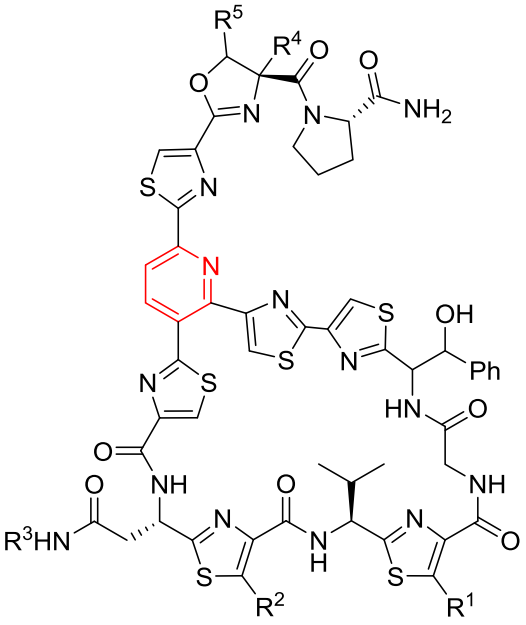
Fig. 10 The structures of cyclothiazomycins (**34**–**36**)

expression of the *tipA* promoter (**22**). Radamycin (**74**) has an induction concentration of 10 µg/mL for *tipA* promoter and is more efficient than thiostrepton and methylsulfomycin I at the same concentration (González et al. 2002; Castro et al. 2002).

New thiopeptides QN3323 A (**75**), B (**76**), and Y1 (**77**) were discovered from *Bacillus* sp. and characterized in 2002 (Fig. 19). The QN3323 series had a better inhibitory effect on Gram-positive bacteria, such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), with MIC values ranged from 0.05 to 2 µg/mL (Kamigiri et al. 2006).

Analogous to QN3323 compounds, thiocillins I (**29**), II (**30**) (Fig. 8) and two new thiopeptides YM-266183 (**78**), YM-266184 (**79**) (Fig. 19) were isolated from *B. cereus* QN03323 in 2005. YM-266183 (**78**) and YM-266184 (**79**) are the rare few thiopeptides isolated from the marine sources and are similar to thiocillins I (**29**) and II (**30**). Moreover, YM-266183 (**78**) and YM-266184 (**79**) exhibit very strong in vitro antibacterial activity against MRSA, VRE, *B. subtilis*, etc. with MIC values between 0.025 and 1.56 µg/mL (Nagai et al. 2003; Suzumura et al. 2003).

After the bottleneck in the mining history of thiopeptides, a compound PM181104 (kocurin) (**80**) (Mahajan et al. 2007) (Fig. 19) with antimicrobial activity was isolated from the marine-derived *Kocuria* sp.(ZMA B-1/MTCC5269) (southern Spain) in 2007. It was confirmed that PM181104 (**80**) has good inhibitory activity against *Staphylococcus* sp. (MIC: 0.00781–0.0625 µg/mL), *Bacillus* sp. (MIC: 0.00391–0.01563 µg/mL), *E. faecalis* (MIC: 0.00391–0.3125 µg/mL) and so on. Moreover, the salts of kocurin (**80**) can be used for the treatment of bacterial infection with the acceptable dose between 0.01 and 100 mg/kg (Martín et al. 2013; Palomo et al. 2013).



GE2270

Factor	R^1	R^2	R^3	R^4, R^5
A (**37**)	CH_2OMe	CH_3	CH_3	H
B1 (**38**)	CH_2OMe	CH_3	H	H
B2 (**39**)	CH_3	CH_3	CH_3	H
C1 (**40**)	H	CH_3	CH_3	H
C2a (**41**)	CH_2OMe	CH_2OH	CH_3	H
C2b (**42**)	CH_2OMe	H	CH_3	H
D1 (**43**)	H	CH_3	H	H
D2 (**44**)	CH_2OH	CH_3	CH_3	H
E (**45**)	CH_2OH	CH_3	H	H
T (**46**)	CH_2OMe	CH_3	CH_3	π-bond

Fig. 11 The structures of GE2270 factors (**37**–**46**)

Guided by antimicrobial bioassay, nocardithiocin (**81**) (Fig. 20) was isolated from the pathogens *Nocardia pseudobrasiliensis* IFM 0757 in 2009. The compound exhibits strong bacteriostatic activity against a variety of aciduric bacilli *Mycobacterium* sp., *Gordonia* sp., rifampicin-resistant bacteria and the sensitive *M. tuberculosis* with MICs of 0.025–1.56 μg/mL. But nocardithiocin (**81**) showed no activity against Gram-negative bacteria and fungi (Mukai et al. 2009). The predicted nocardithiocin (**81**) biosynthetic gene cluster was confirmed by gene disruption and complementation in 2015, which will lead to a number of nocardithiocin analogues by genetic engineering (Sakai et al. 2015).

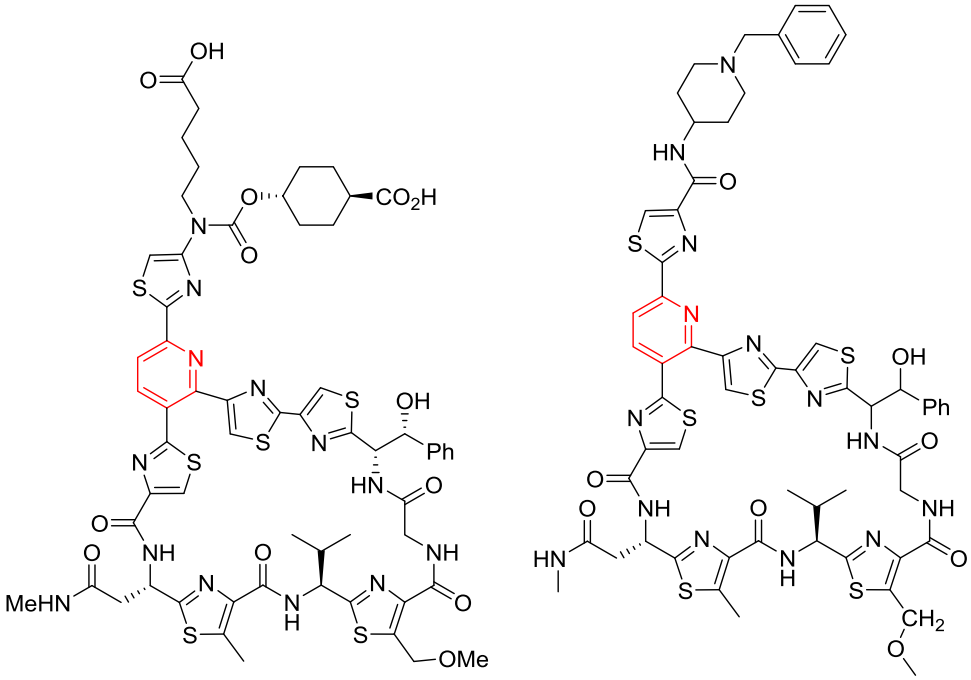
High-throughput screening bioassay was applied to exploit a number of novel series *d* thiopeptides which were designated as thiomuracins A–I (**82**–**90**) (Fig. 20) which were isolated from the strain *Nonomuraea* Bp3714-39. Among them, the main compound thiomuracin A (**82**) is an acid-labile compound and possess similar features to GE2270 A (**37**). Thiomuracin A (**82**) showed good inhibitory effects against *E. faecalis* and *S. aureus* with MICs of 0.25–4 μg/mL and 0.5–2 μg/mL (thiomuracin E has MIC of 16 μg/mL), respectively. Thiomuracin A and I have the highest activity against *E. faecalis* (MIC of 0.25 μg/mL) and thiomuracin A, B, D, F have the same activity against *S. aureus* (MIC of 0.5 μg/mL). However, all compounds did not show obvious activity against Gram-negative bacteria, indicating that such substances might have poor permeability through Gram-negative bacterial outer membrane (Morris et al. 2009). Notably, structural optimization of thiomuracin A (**82**) was achieved in 2012 (LaMarche et al. 2012) to promote its physicochemical properties.

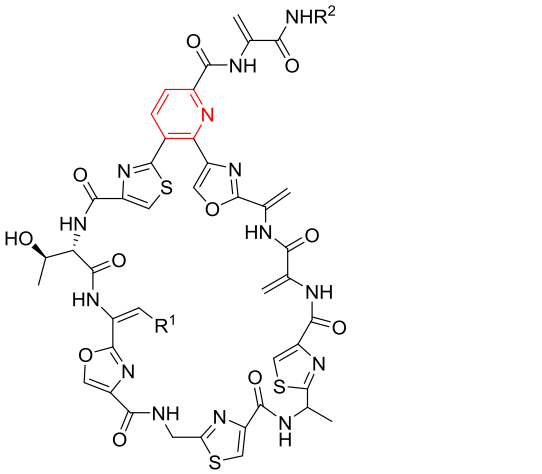
In a high-throughput campaign to discover novel antibiotics from the marine organisms, a new thiopeptide TP-1161 (**91**) was isolated and characterized from the strain *Nocardiopsis* sp. TFS65-07 (Trondheim, Norway) (Fig. 21). TP-1161 (**91**) has MICs of 0.25–4 μg/mL for most Gram-positive strains, which is almost near to those of the reference antibiotic vancomycin. In addition, TP-1161 (**91**) also inhibits the growth of vancomycin-resistant strains *E. faecalis* 560 and *E. faecium* 569 with a MIC of 1 μg/mL (Engelhardt et al. 2010a, b). Later genome mining revealed the biosynthetic gene cluster responsible for TP-1161 (**91**), which laid the ground for the study of novel thiopeptides analogues and their derivatives (Engelhardt et al. 2010a, b).

In 2012, a new member of thiopeptide, baringolin (**92**) (Compound I) (Fig. 21), was discovered from the bacteria *Kucuria* sp. MI-67-EC3-038 (CECT-7337) (the southern Alicante coast of Spain). Baringolin (**92**) shows good inhibitory effects against a variety of Gram-positive strains, such as *S. aureus*, *B. subtilis*, *M. luteus*, *P. acnes*, etc., with MIC values between 0.015–161 μg/mL and 0.33–0.66 mM for the clinical isolated MRSA (Ca Edo Hernández et al. 2012). In addition, a series of baringolin (**92**) analogues were chemically synthesized for SAR studies (Just-Baringo et al. 2013, 2014a, b).

A systematic strategy combining bioinformatics, genetics, and chemistry was applied to study secondary metabolites which are capable of mediating interspecies communications in complex biosystems, leading to novel antibiotics from human microbiota. The thiopeptide antibiotic lactocillin (**93**) was isolated and characterized from human vaginal microbial flora in 2014 (Donia et al. 2014) (Fig. 22), demonstrating the widespread occurrence of gene clusters responsible for secondary metabolites in the human microbiota.

Fig. 12 The structure of LFF571 (**47**) and NAI003 (**48**)





A10255 B (**49**):R^1=Et, R^2=
A10255 E (**52**):R^1=^{i}Pr, R^2=
A10255 G (**54**):R^1=Me, R^2=

A10255 J (**56**):R^1=Me, R^2=H

*The structures of compound 50, 51 and 53 were not elucidated yet.

Fig. 13 The structures of A10255 (**49**, **52**, **54**, and **56**)

Further genomics analysis revealed the occurrence of a silent thiopeptide biosynthetic gene cluster in *Streptomyces lactacystinaeus* OM-6519 (Hayashi et al. 2014). The target silent gene cluster was heterologously expressed in *Streptomyces lividans* TK23 and three thiopeptides lactazole A (**94**), B (**95**), and C (**96**) (Fig. 22) were isolated and characterized. Lactazoles are a kind of unique thiopeptides which contains a 32-membered macrocycle linked to a 2-oxazolyl-6-thiazolyl pyridine core, while others own a smaller macrocyclic ring with a 2-thiazolyl-6-thiazolyl or 6-thiazolyl pyridine core. Lactazoles are biosynthesized through six unidirectional genes with a DNA size of only 9.8-kb. It is the smallest thiopeptide gene cluster known to date.

Series *e*

Multhiomycin (**97**) (in 1970) was isolated from the mycelia of *Streptomyces antibioticus* 8446-CC_1 (Gifu Prefecture, Japan) and is capable of inhibiting the nucleic acid synthesis of *B. subtilis* 168 (Tanaka et al. 1970a, b). Later multhiomycin (**97**) was identified to be the same as nosiheptide (**97**) (Benazet et al. 1980; Endo and Yonehara 1978) (Fig. 23). Multhiomycin (Nosiheptide) (**97**) exhibits impressive activity against a variety of Gram-positive strain, such as *Bacillus* sp. with MIC values between 0.003 and 25 μg/mL, *S. aureus* with the MIC value between 0.0009 and 0.103 μg/mL, *S. faecalis* with MIC values between 0.00028 and 0.0065 μg/mL and so on (Tanaka et al. 1970a, b; Benazet and Cartier 1980; Benazet et al. 1980). Multhiomycin (nosiheptide) (**97**) inhibits the binding of T factor and GTP-dependent phenylalanyl-tRNA (phe-tRNA) to the aminoacyl site (site A) of the 30S ribosomal subunit ($Mg^{+2} \geq 10$ mM), thereby inhibiting protein synthesis (Tanaka et al. 1970a, b, 1971a, b; Cundliffe and Thompson

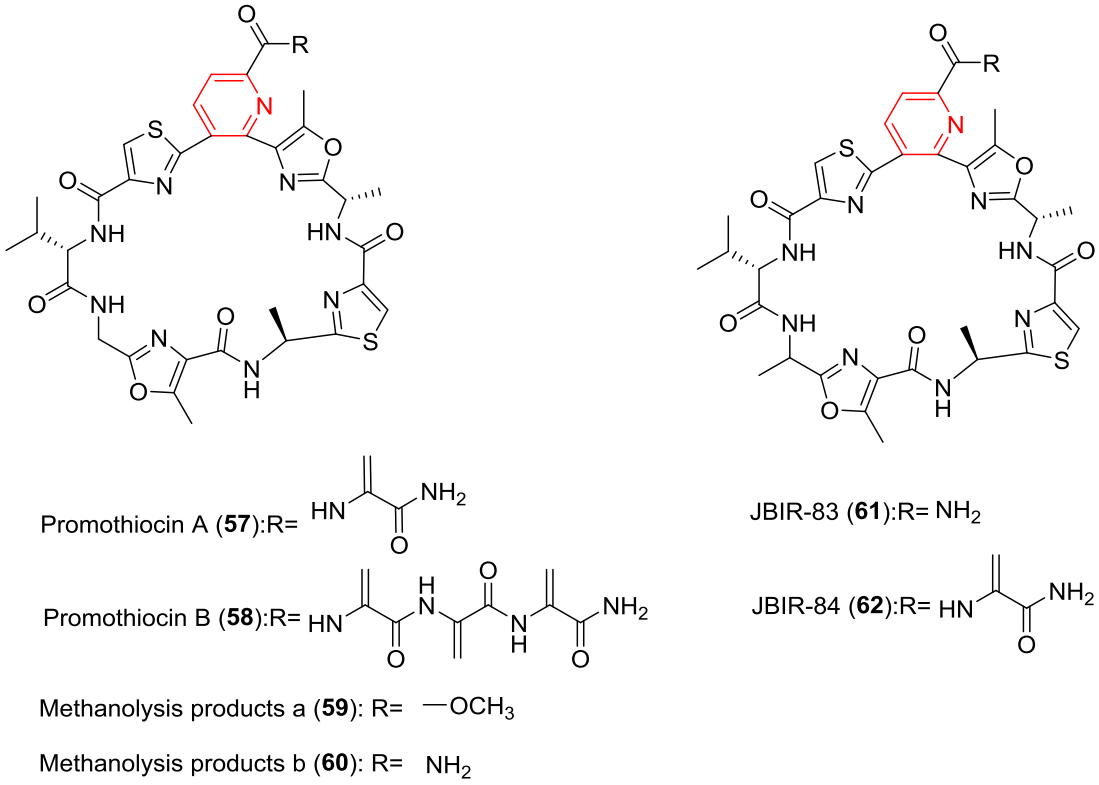


Fig. 14 The structures of promothiocins (**57**–**58**), JBIR-83 (**61**), and JBIR-84 (**62**)

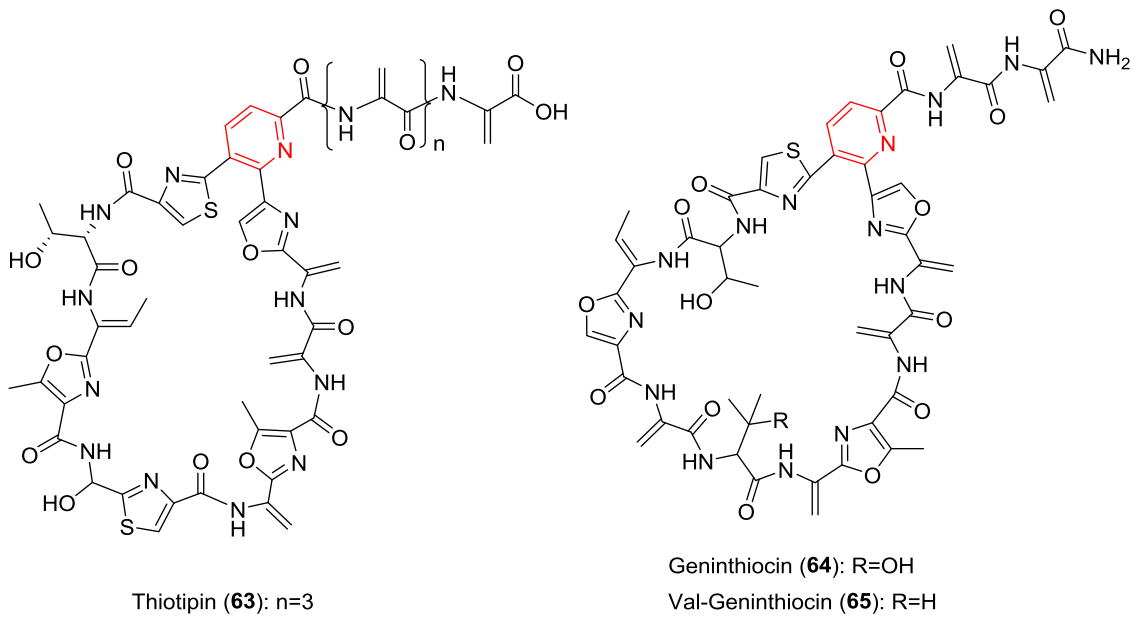


Fig. 15 The structures of thiotipin (**63**) and geninthiocins (**64**–**65**)

1981a, b). At present, multhiomycin (nosiheptide) (**97**) is used as a growth enhancer for poultry and hogs (Benazet et al. 1980; Cromwell et al. 1984a, b). Nosiheptide (**97**) also has prominent inhibitory activity against hepatitis B virus in vitro (Feng et al. 2008). Furthermore, nosiheptide (**97**) has been totally synthesized by multiple research groups and its biosynthetic genes have been elucidated (Koerber-Plé and Massiot 1995; Wang et al. 2013), which provides a solid basis for the discovery of new derivatives of the nosiheptide family.

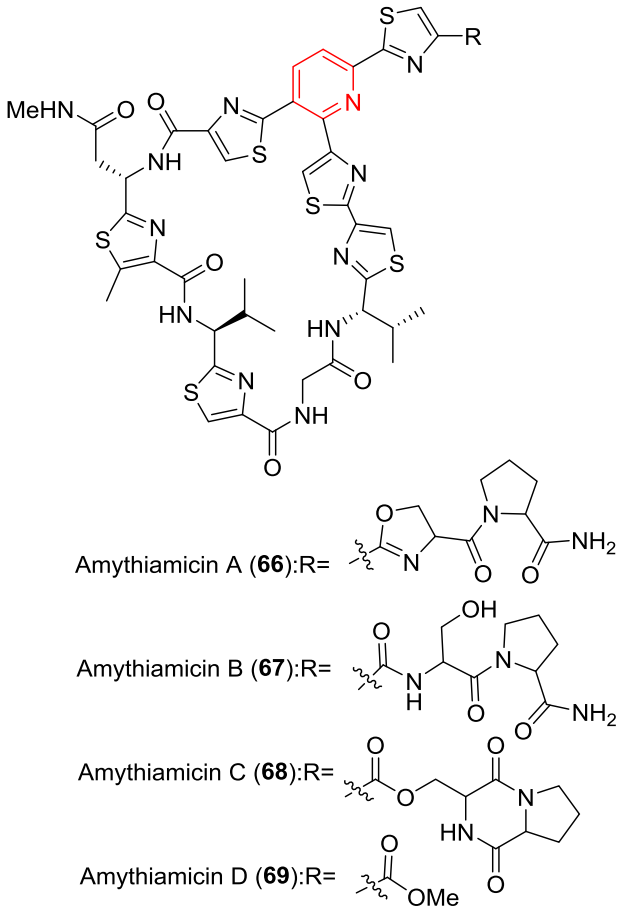


Fig. 16 The structures of amythiamicins (**66–69**)

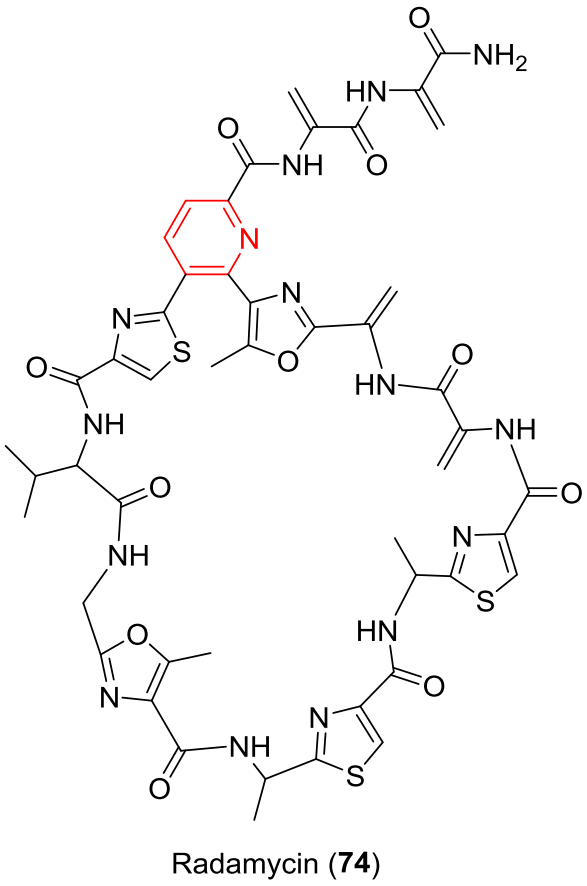
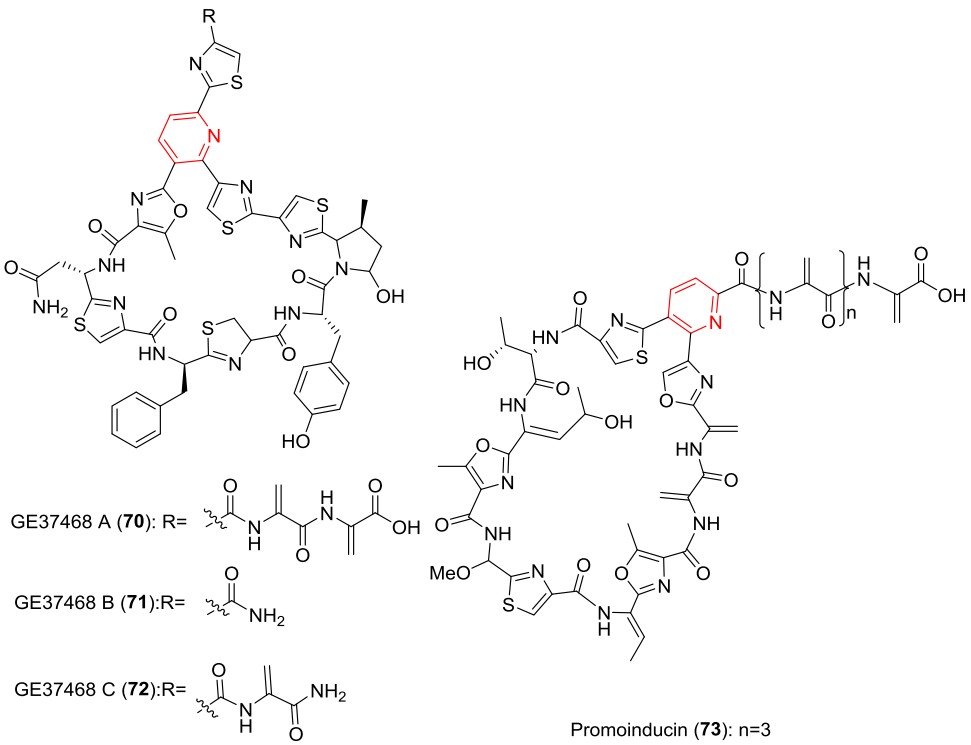


Fig. 18 The structure of radamycin (**74**)

Fig. 17 The structures of GE37468 factors (**70–72**) and promoinducin (**73**)



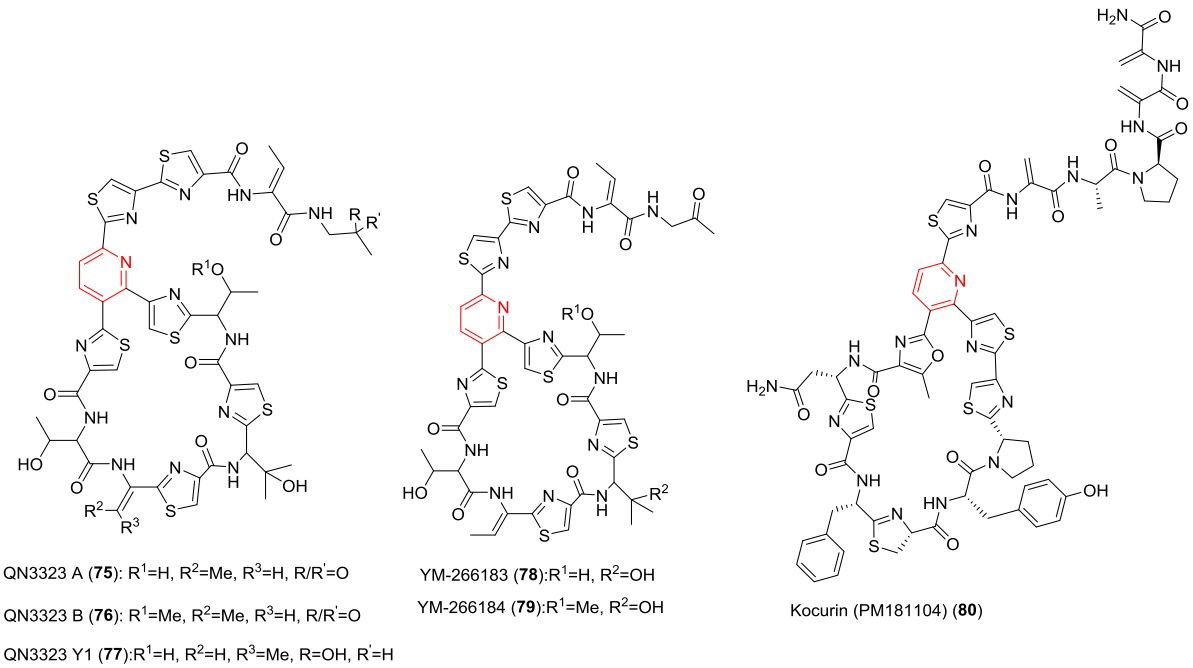


Fig. 19 The structures of QN3323 factors (**75–77**), YM-266183 (**78**), YM-266184 (**79**), and kocurin (**80**)

Four compounds, S-54832/A-I (**98**), II (**99**), III (**100**), and IV (**101**) were isolated from the strain *Micromonospora globosa* (Kurrayi paddy field, Spain) and characterized (Keller-Juslen et al. 1984). They were found to have a strong inhibitory activity against Gram-positive strains including penicillin-resistant *S. aureus* (MIC ≤ 0.3 μg/mL), erythromycin-resistant strains like *B. subtilis*, *Clostridium pasteurianum*, *Mycobacterium smegmatis*, *Neisseria catharalis* (MIC ≤ 0.3 μg/mL), and rifamycin-resistant *Streptococcus* sp. (MIC ≤ 0.03 μg/mL) and so on.

A nosiheptide-related new compound, glycothiohexide α (**102**) was isolated from the mycelium of the soil actinomycetes *Sebekia* Strain LL-14E605 (NRRL 21083) in 1994 (Steinberg et al. 1994). Another *O*-methyl- glycothiohexide α (**103**) was also isolated and characterized (Fig. 23) (Northcote et al. 1994a, b). Glycothiohexide α (**102**) shows excellent inhibitory activity against Gram-positive strains including MRSA and VREF with MIC value ranged from 0.03 to 0.06 μg/ml. In addition, nocathiacin II (**107**) was mildly hydrolyzed and nocathiacin IV (**109**) was deoxygenated into glycothiohexide α (**102**) lactone compounds which exhibit antibacterial activity in mice (Connolly et al. 2005).

Two thiazole cyclopeptides, MJ347-81F4 A (**104**) and B (**105**), were isolated from the mycelia of *Amycolatopsis* sp. MJ347-81F4 in 1998 (Sasaki et al. 1998) and their structures were elucidated by chemical degradation, 2D NMR, and LC-MS (Fig. 24). MJ347-81F4 A (**104**) shows good antibacterial activity against Gram-positive bacteria including MRSA and VREF with MIC values between 0.006 and 0.01 μg/mL.

Nocathiacin I (**106**), II (**107**), and III (**108**) were isolated from *Nocardia* sp.WW-12651 (ATCC 202099) in 2000 (Leet et al. 2001, 2003; Li et al. 2003) (Fig. 24) and they have a broad spectrum of anti-Gram-positive bacterial activities against many strains including *Staphylococcus* sp. (MIC: 0.001–0.03 μg/mL), *Streptococcus* sp. (MIC ≤ 0.002 μg/mL), *Enterococcus* sp. (MIC: 0.015–0.03 μg/mL) and *Moraxella* sp. (MIC: 0.06–0.25 μg/mL). Nocathiacin IV (**109**) (Fig. 24) was obtained by incubating the protease of *Streptomyces geriseus* with nocathiacin I (**106**) and DMF. Nocathiacin I (**106**) and IV (**109**) have both in vitro and in vivo inhibitory activity against Gram-positive bacteria (Wenying et al. 2002). In addition, the derivatives of nocathiacin I (**106**), BMS-411886, BMS-461996 (Pucci et al. 2004) and various other water-soluble derivatives (Naidu et al. 2004a, b, 2006) were found to have good in vitro and in vivo antibacterial as well as anti-malarial activity (Sharma et al. 2015).

A novel compound thiazomycin (**110**) and four known compounds nocathiacins I–IV (**106–109**) were isolated from *Amycolatopsis fastidiosa* MA7332 (ATCC 202099) in 2007 and the structure was elucidated with NMR (500 or 600 MHz), IR, Perkin-Elmer spectra, LTQ-FT MS, etc. (Fig. 25) (Jayasuriya et al. 2007). In vitro experiments (Singh et al. 2007) showed that thiazomycin (**110**) significantly inhibited Gram-positive pathogens such as *S. aureus* Smith, *S. pneumoniae*, *S. pyogenes*, *Enterococci* and *Enterococcus faecium*, with MIC values between 0.002 and 0.064 μg/mL. In addition, mouse subcutaneous injection experiments also showed a highly effective anti-*S. aureus*

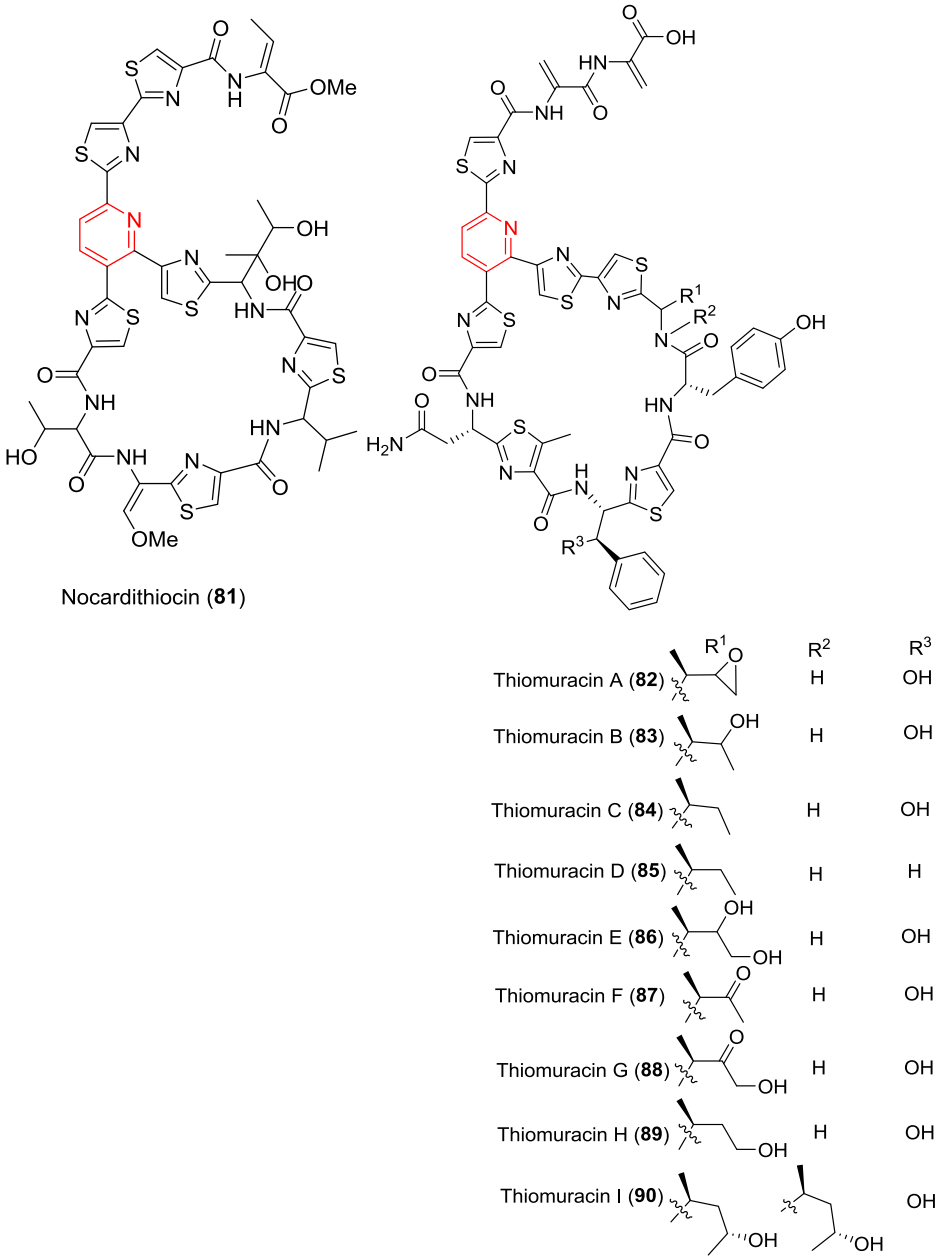


Fig. 20 The structures of nocardithiocin (**81**) and thiomuracins (**82–90**)

infection (ED_{99} value of 0.15 mg/kg). Thiazomycin (**110**) is capable of targeting the L11 protein and the 23S rRNA of ribosomal 50S subunit, which has an IC_{50} of 0.031 μg/mL for protein synthesis. Furthermore, another thiazomycin analogue thiazomycin A (**111**) was isolated and characterized from *A. fastidiosa* MA7332 in 2008 (Fig. 25). The methine on the oxazole ring of thiazomycin's aminoglycoside is substituted by a methyl group in thiazomycin A (**111**). In vitro and in vivo activity experiments showed that the MIC value for Gram-positive bacteria was 0.002–0.25 μg/mL and the IC_{50} inhibiting the synthesis of protein was 0.7 μg/mL (Zhang et al. 2008a, b). A group of six new thiazole peptides thiazomycins B–D (**112–114**) and thiazomycins E1–E3 (**115–117**) (Fig. 25) (Zhang et al. 2009) were discovered from *A. fastidiosa* MA7332. Thiazomycins B–D (**112–114**) also shows inhibition of Gram-positive pathogens in vitro experiments, such as *Streptococcus* sp. (MIC: 0.004–0.03 μg/mL), *S. aureus* (MIC: 0.02–0.1 μg/mL) and *Enterococcus* sp. (MIC: 0.004–0.1 μg/mL) (**112–114**). In addition, it has been reported that thiazomycins, nocathiacins, and related derivatives show potent activity against drug-resistant clinical tuberculosis mycobacteria (Singh et al. 2017).

In the year of 2008, two new glycosidic thiazolidic compounds, philipimycins a (**118**) and b (**119**), were isolated from the *Actinoplanes philippinensis* MA7347

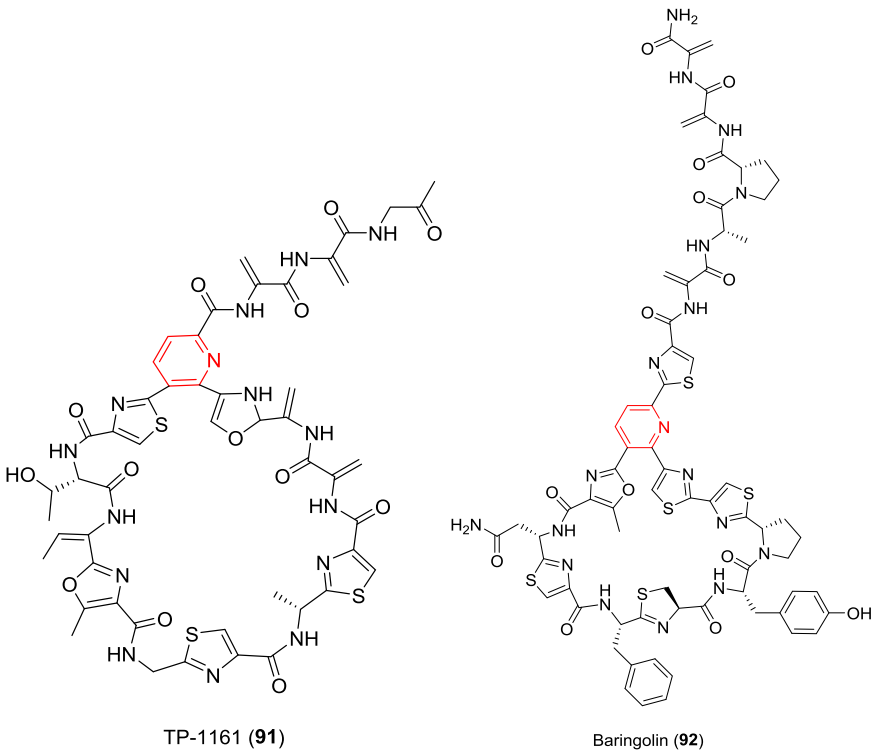


Fig. 21 The structures of TP-1161 (**91**) and baringolin (**92**)

(Namakrancan, South Africa) (Fig. 25) and both have effective inhibitory activity against Gram-positive bacteria with MIC values between 0.015 and 1 μg/mL. Subcutaneous injection of mice showed that philipimycin had a significant effect on *S. aureus* with ED_{50} of 8.4 mg/kg (Zhang et al. 2008a, b).

Unidentified thiazole peptides

Chemical structures of many thiopeptides have not been elucidated, such as saramycetin (X-5079C/Sch43057) isolated from *Streptomyces nov*. sp. X-5079 in 1961 (Berger et al. 1962; Grunberg et al. 1961; Bennett et al. 1969; Cooper et al. 1990; Kirschbaum and Aszalos 2010), sporangiomycin from *Planomonospora parontospora* (strain B987) in 1968 (Thiemann et al. 1968; Watanabe 1972; Cundliffe and Dixon 1975; Thompson and Cundliffe 1980) and kimorexin A (90-GT-302) from *Kitasatospora kimorexae* (90-GT-302) (Yeo et al. 1994a, b). The initial IR, UV, MS, and other structural data revealed that these compounds contain multiple thiazole heterocyclic structure, but the NMR or X-crystal diffraction detailed data did not illuminate complete structure. In addition, the neoberninamycin isolated from *M. luteus* ATCC 53598 (New Jersey, USA) in 1987 was very similar to berninamycin according to the ^1H NMR (400 MHz) data but was significantly different from berninamycin with TLC (silica gel), in which the R_f values of the two compounds were 0.23 and 0.27, respectively. In addition, neoberninamycin has inhibitory activity against aerobic Gram-positive bacteria and anaerobic Gram-negative bacteria by targeting 50S subunit of the ribosome, similar to berninamycin and thiostrepton. Thus, it may also be a member of berninamycin family (Biskupiak et al. 1988).

Mechanisms of action

Thiopeptides possess broad therapeutic potential including antibacterial, antifungal, anticancer, antiplasmodial, immunosuppressive, renin inhibitory, RNA polymerase inhibitory, which results from the macrocyclic scaffold of thiopeptides, as a veritable privileged structure, with interesting mode of actions.

Inhibition of ribosomes

All bacterial ribosomes (relative deposition rate is 70S) contain two different size subunits: a large 50S and a small 30S subunit. These two subunits acts synergistically with each other in the form of non-covalent bonds and are the major sites for bacterial protein synthesis. Among them, the 30S subunit consists of 21 proteins of S1–S21 and 16S rRNA fragments, while the 50S subunit is comprised of 31 proteins of L1-L31, and 23S as well as 5S rRNA fragments. The interconversion of the elongation factors EfTu•GTP •aa-tRNA to EfTu•GDP and Ef G•GTP to Ef G•GDP, supplying energy via phosphate hydrolysis for protein translation. These hydrolysis reactions

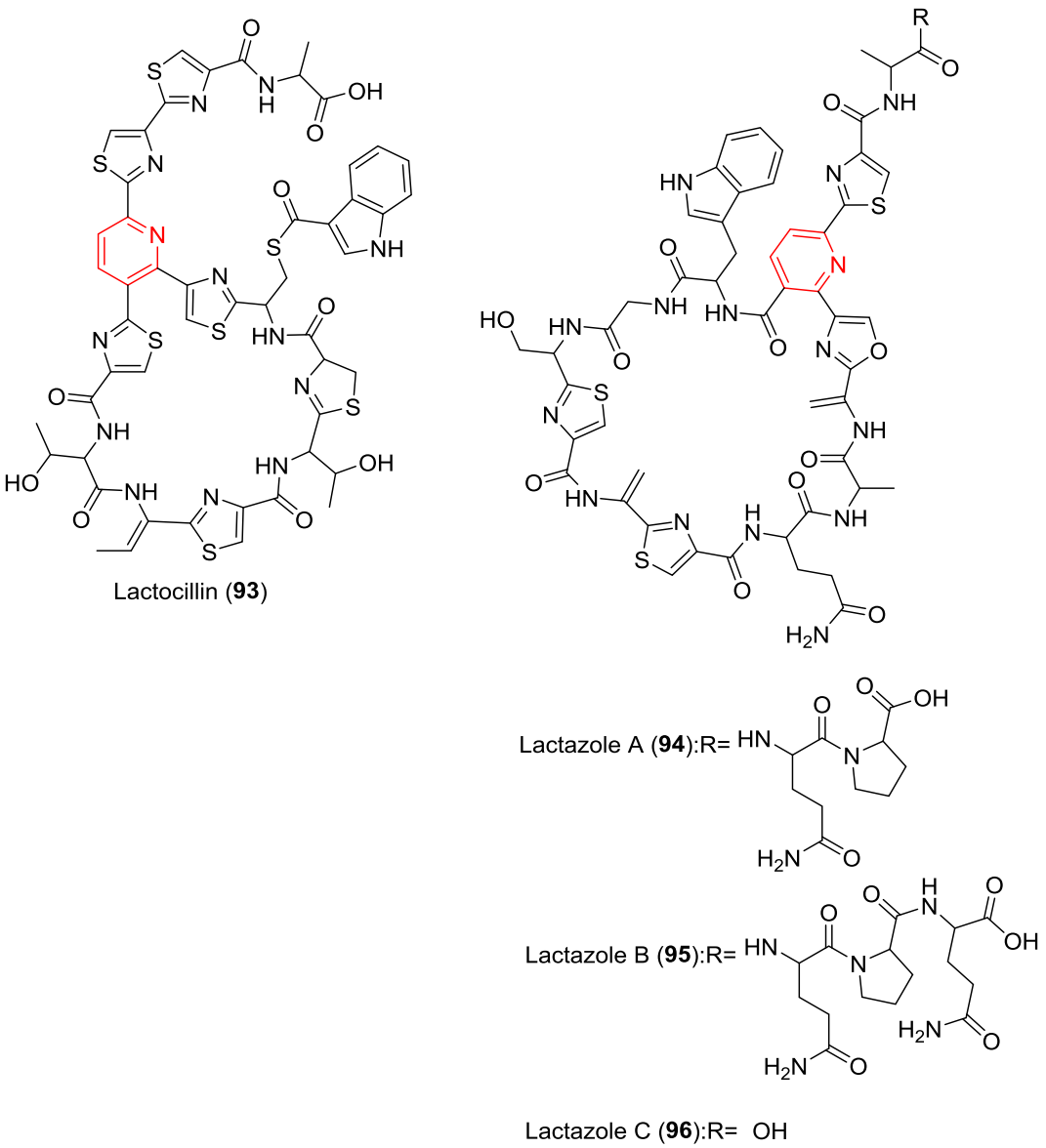
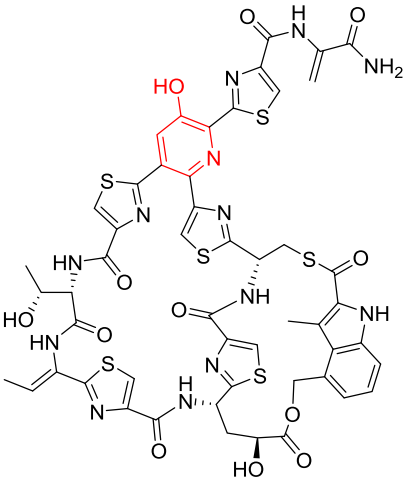


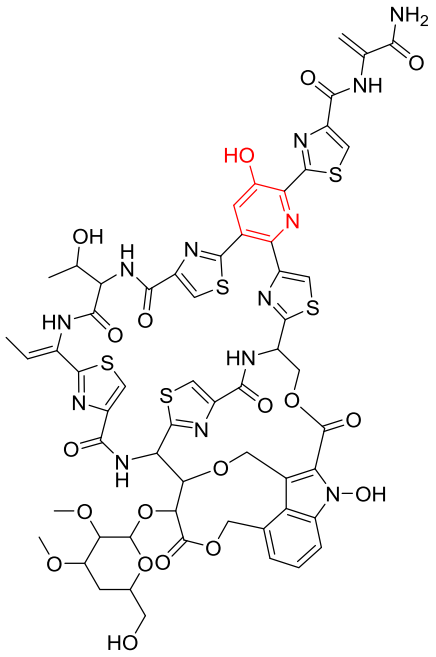
Fig. 22 The structures of lactocillin (**93**) and lactazoles (**94**–**96**)

occur in the double hairpin structure within the 50S subunit's 23S rRNA domain II (ribosomal protein L11 and pentamer complex L10•$(L12)_4$ co-package) and ribosomal N-glycosidase hairpin loops in domain VI (L11 binding domain (L11BD)). Ribosome inhibitors such as some thiopeptides bind adenosine A-1067 and A-1095 on L11BD to prevent conformational changes in L11, a key motion that is stimulated by elongation factor. This directly affects the directional movement of tRNA and mRNA on ribosomes, thereby inhibiting extension of the peptide, of which the most typical mechanism of antibacterial activity cover thiostrepton, micrococcins (Rosendahl and Douthwaite 1993, 1994; Xing and Draper 1996; Porse et al. 1998; Rodnina et al. 1999; Cameron et al. 2002; Harms et al. 2008; Cundliffe and Thompson 1981a, b; Porse et al. 1999) and siomycins (Modolell et al. 1971; Watanabe and Tanaka 1971) and so forth.

However, the thiopeptide resistance to some Gram-positive resistant strains such as *Bacillus megaterium* results from the mutation of the gene encoding the protein L11 substituted by the protein BM-L11 (Cundliffe et al. 1979), which is the major cause of obvious resistance to thiopeptide antibiotics in vitro. The resistance exhibited by Gram-negative bacteria to thiopeptide antibiotics is mainly being unable to penetrate into the bacterial cell wall (Arnison et al. 2013). In addition, producers of thiopeptide antibiotics also have a self-protective mechanism against the product, which is mainly derived from the auto-immune

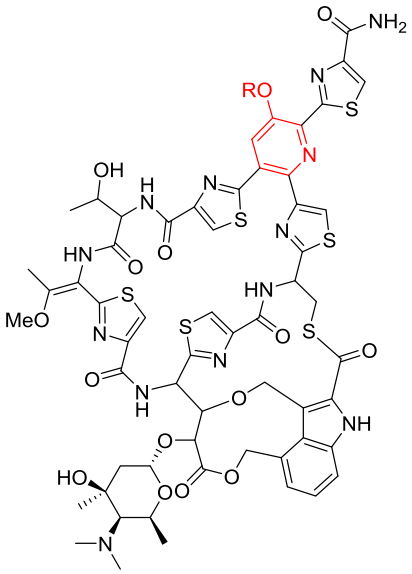


Nosiheptide (**97**)



S 54832/A-I (**98**)

*The structures of compound 99, 100 and 101 were not elucidated yet.



Glycothiohexide a (**102**): R=H

O-methyl-Glycothiohexide a (**103**): R=Me

Fig. 23 The structures of nosiheptide (**97**), S54832/A-I (**98**), and glycothiohexide α (**102**)

protective effect of RNA-pentose methylation of methionine (Cundliffe and Thompson 1979; Cundliffe et al. 1979; Cundliffe 1978).

Heterologous expression in *Escherichia coli* (Mankin et al. 1994) shows that thiopeptide-resistant methylase introduces a single methyl group on the A-1067 residue of the GTP hydrolase domain of the 23S rRNA, resulting in a modified 2′-*O*-methyladenosine ribosomes, which is resistant to thiopeptides. Furthermore, the study of thiostrepton resistance gene (tsr) from *S. aureus* that was overexpressed in *E. coli* to characterize enzyme reaction demonstrates that its recognition is indeed dependent on the ribosome hairpin loop secondary structure containing nucleotide 1067 (Bechthold and Floss 1994).

Similarly, inhibition of *P. falciparum* by thiopeptides mainly relies on binding to plasmodium plastid rRNA (a

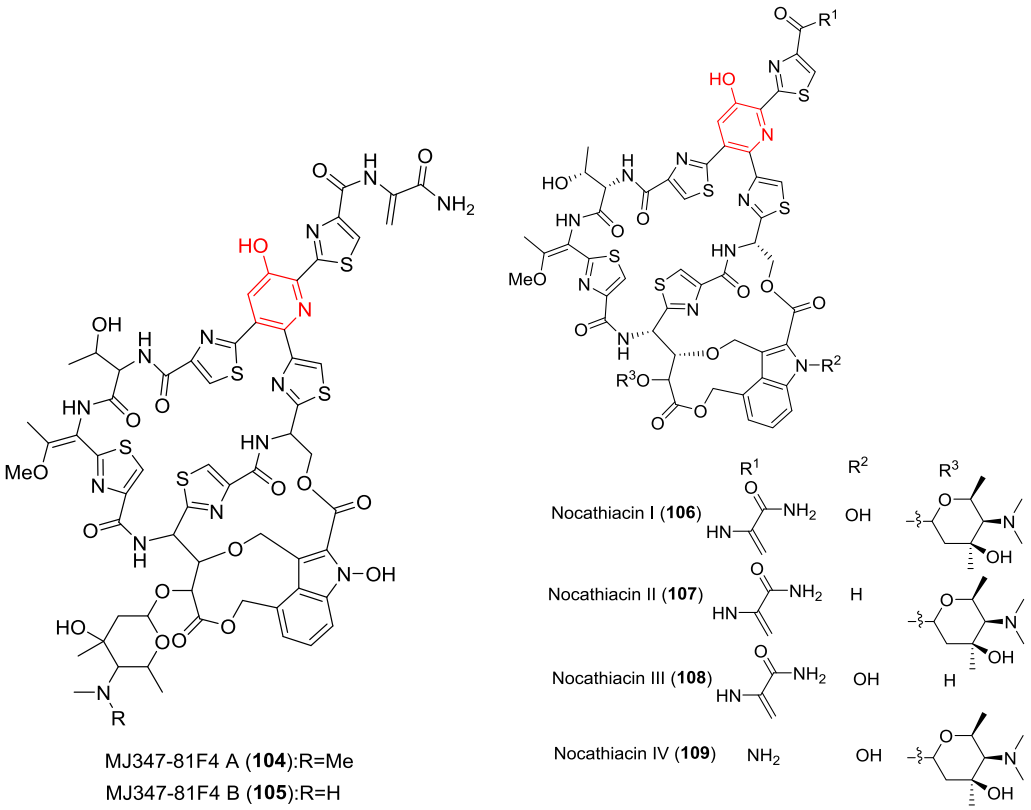


Fig. 24 The structures of MJ347-81F4 factors (**104**–**105**) and nocathiacins (**106**–**109**)

large subunit component encoded by extrachromosomal 35-kb DNA) (Mcconkey et al. 1997; Clough et al. 1997).

Inhibition of elongation factor Tu

The elongation factor Tu, an important element of ribosome function, is also a target of the direct action of some thiopeptide compounds. Direct binding of thiopeptide compounds to Ef-Tu prevents the binding of aa-tRNA to its GTP dimer to interrupt the transfer of aminoacyl-tRNA to ribosome (Anborgh and Parmeggiani 1991), and also limits the spatial conformation of GTP in conversion of Ef-Tu•GTP to Ef-Tu•GDP (Heffron and Jurnak 2000), thus blocking the elongation of peptide chains in the synthesis of bacterial proteins.All of GE2270 A **(37)** (Zuurmond et al. 2000; Möhrle et al. 1997), thiomuracin A (**82**) and amythiamicin A (**66**) (Shimanaka et al. 1995a, b) inhibits the elongation factor Tu.

TipA promotion

TipA is the transcriptional regulatory protein induced by thiostrepton in the multidrug resistance mechanism of actinomycetes. In the process of resistance induction, with the accumulation of the inducing protein (Tip), the strain produces resistance to a variety of different antibiotics including thiopeptides. Among them, there are two main types of TipA, namely TipAL (253 amino acids) and TipAS (144 amino acids), both of which stem from transcription and translation of the same gene *tipA*. TipAS is located on the *C*-terminal region of TipAL. During transcription, the TipAL-thiopeptide complex activates the transcription of monocistronic mRNA from the *tipA* promoter (*ptipA*) and thus triggers the self-expression of its own promoter. When resistant strain encounters thiopeptide, TipAS (a thiopeptide recognition binding domain) accumulates and recognizes the thiopeptide, then sequestrates thiopeptide in the cytosol at a high concentration, regulating its own independent translation and expression in the form of positive feedback (Murakami et al. 1989; Holmes et al. 1993). The conformational changes within TipAL strengthen its binding to *ptipA*, decrease the rate of dissociation from the binding site, and increase the affinity of RNA polymerase (RNAP) for *ptipA*, thereby activating transcription (Chiu et al. 2001). It is worth noting that TipAL can binds to its target site and activates transcription in the absence of ligands, and increased external osmotic pressure leads to an increase in intracellular negative DNA supercoils, which enhances the expression of *ptipA*. In the presence of thiopeptide antibiotics, the *N*-terminal coiled linker of the TipAL complex becomes rigid, clinches the dimeric DNA-binding domain, and twists the DNA helix of the promoter, which drives the

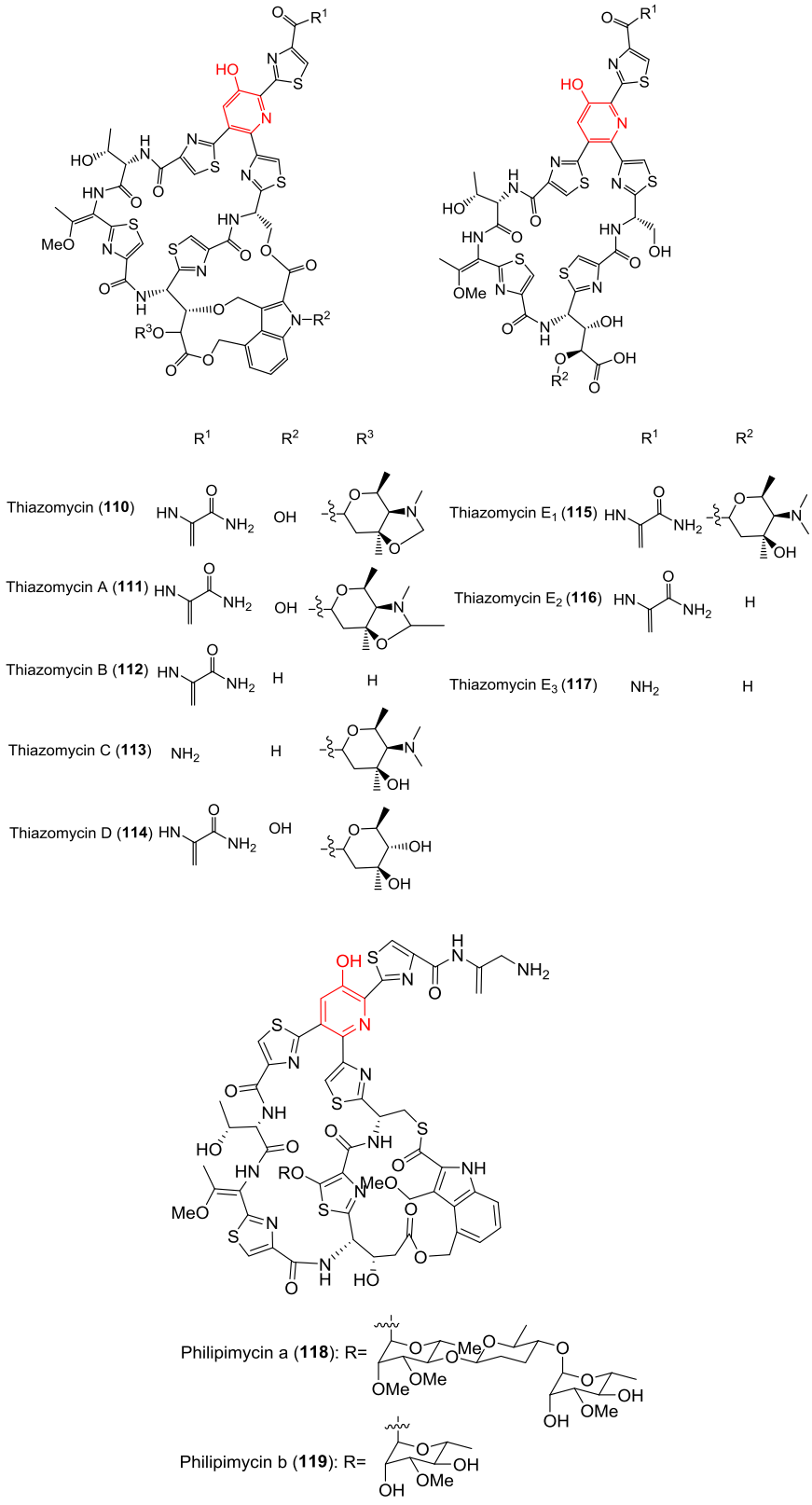


Fig. 25 The structures of thiazomycins (**110–117**) and philipimycins (**118–119**)

alignment of two mutual recognition sequences so that RNAP initiates transcription (Higashibayashi et al. 2004). Thiopeptide compounds induce the transcription of *ptipA* in the strain and translate to express a series of induced proteins so that the bacteria can make themselves resistant to thiopeptides or to other antibiotics. Thiostrepton (Murakami

et al. 1989; Chiu et al. 1996; Holmes et al. 1993), thioxamycin (**32**) (Yun et al. 1994a, b, c, d), thiotipin (**63**) (Yun et al. 1994a, b, c, d), and geninthiocin (**64**) (Yun et al. 1994a, b, c, d) all have *tipA* induction activity.

Inhibition of forkhead box M1

Recent studies have not only focused on the antibacterial and antimalarial effects of thiopeptides but also more on the anticancer mechanism. Forkhead box M1 (FOXM1), a transcription factor associated with the proliferation of many malignant tumors. It assists cell cycle progression into S and M phases and is an indispensable element for normal mitosis. The expression and transcriptional activity is increased through proliferation signals and decreased by anti-proliferative signals (Wierstra 2013). The apoptosis induced by down-regulation of FOXM1 which is affected by thiopeptides, mainly involves endogenous apoptotic pathways. However, overexpression of FOXM1 protects cancer cells from thiopeptide-mediated cell death (Bhat et al. 2009). Thiostrepton binds directly to FOXM1 protein, thus preventing the regulation of transcription factor FOXM1 on the promoters of related genes (*MYC*, *CDC25B*, *CCNB1*, *XBP1*, *GREB1*, and *ESR1*) involved in cancer progressions (Hegde et al. 2011). The typical representatives of this mechanism of action are thiostrepton (Hegde et al. 2011) and siomycin A (Bhat et al. 2009). Overall, the role of thiopeptide-FOXM1 suggests that thiopeptide may become an effective drug candidate for cancer treatment in the future.

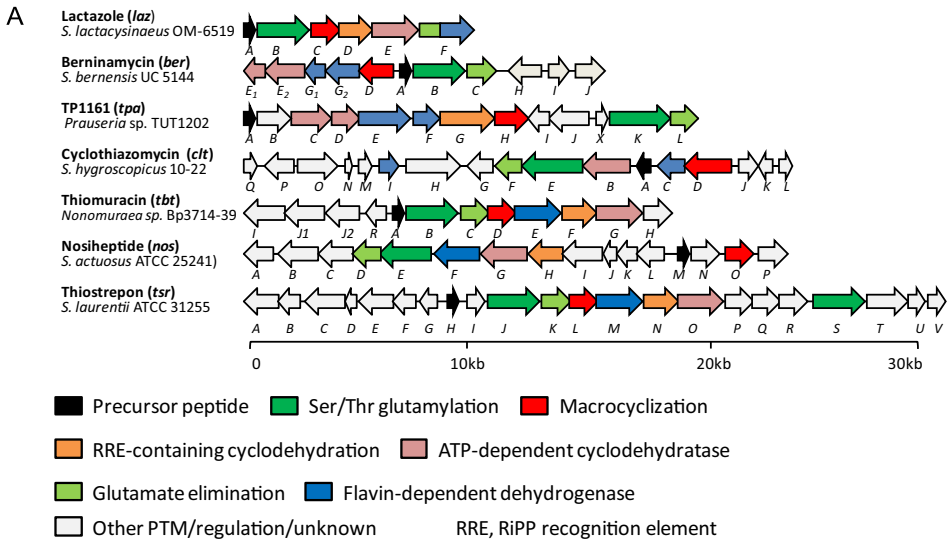
Inhibition of proteasome

Thiostrepton can exert antiplasmodial activity by targeting the apicoplast of malarial parasite (Schoof et al. 2010). Furthermore, thiopeptides possess the capacity of interfering with the normal function of proteasome (Aminake et al. 2011) which is a kind of indispensable polyprotein complex in eukaryotes and can degrade and recycle the nonfunctional ubiquitin-proteins (Etlinger and Goldberg 1977). Thiostrepton and its derivatives were proved to interfere with 20S proteasome in *P. falciparum* (Schoof et al. 2010) and kill the parasite at trophozoite stage when administrated during *P. falciparum* bloodstages. And there was no opportunity of survival for the escaped fragment of the parasite from the first reproductive cycle because of the arrest by apicoplast-mode in the schizont stage of the second cycle, resulting in a delayed death. It is a dual-killing effect that dramatically impairs drug resistance of the parasite. Thus, from the perspective of proteasome-targeting mode, this kind of thiopeptides will be developed to be superior therapeutic candidates for malaria parasite and cancer (Reynolds et al. 2007).

Biosynthesis

Thiopeptide belongs to the RiPPs family. The initial precursor is synthesized by ribosomes and then post-translationally modified by relatively few conserved enzymes to a mature product. Thiopeptide contains a nitrogen-containing core six-membered ring and a 26, 29, 32, or 35 atoms (9–12 amino acid residues) peptide macrocycle extending from the position 2,6 of pyridine tetrapyridine/dehydropiperidine ring. Studies have shown that its biological profile is related to the macrocyclic types: the 26-atom species binding to the 50S ribosomal subunit, the 29-atom type binding to EF-Tu, and the 35-atom variants may resemble 26 atomic species (Malcolmsona et al. 2013), while the 32-atom type is not detected with antimicrobial activity (Hayashi et al. 2014). However, the known biological mechanism and complex biological activity of thiopeptides is more influential and their biosynthetic mechanisms have a potential for drug development and pathway engineering.

With the advancement of bioinformatics, genome of microorganism is successively carried out to predict the corresponding enzymes and facilitate the elucidation of biosynthetic pathway. Several representing gene clusters, encoding the 26-membered, 29-membered, 32-membered, and 35-membered thiopeptides, are shown in Fig. 26a. The gene clusters of each thiopeptide contain an open reading frame (ORF) coding for precursor peptide (Fig. 26b) and some for typical post-translational modification enzymes (PTMases) which catalyze three major biotransformations: heterocyclization, Cys/Ser/Thr dehydration, and macrocyclization (Bennallack and Griffitts 2017) (Fig. 26c). Among these biotransformations, heterocyclization involves two conservative cyclization reactions (Hudson et al. 2015; Dunbar et al. 2014). For the first step, Cys or Ser/Thr residues are cyclized to form a heterocyclic thiazolines (oxazolines) moiety; then, cyclization dehydration as well as dehydrogenation is committed to further develop a more stable thiazole (oxazole) (Fig. 26c1). The reactions above all can be catalyzed by the enzymes encoded by the genes not only associated with ATP-dependent cyclization dehydratase which includes LazE, BerE1/E2, TpaC/D, CltB, TbtG, NosG and TsrO (Encoding by purple ORF in Fig. 26a), but also associated with another flavin-dependent cyclodehydrogenase such as LazF, BerG1/G2, TpaE/F, CltI/C, TbtE, NosF and TsrM(Encoding by blue ORF in Fig. 26a), along with the RRE-containing cyclodehydrogenase required for substrate recognition (Encoding by orange ORF in Fig. 26a). After the heterocyclization, the Ser/Thr dehydration is mediated by PTMases to form dehydroalanine (Dha) and dehydrobutyrine (Dhb), involving the side chain dependent glutamylation and glutamate elimination reaction (Fig. 26c2). These PTMases mainly include tRNA-Glu-dependent glutamylation enzyme (Bewley et al. 2016), such asLazB, BerB, TpaK, CltE, TbtB, NosE, and TsrJ



B

Precursor	Leader peptide	Core peptide
LazA (lactazole)	MSDITASRVESLDLQDLDLSELTVTSLRDTVALPENGA--	SWGSCSCQASSSCAQP-QDM
BerA (berninamycin)	MEQQIELDVLEISDLIAGAGENDDLAQVMAA--	SCTTTSVSTSSSSSSS-S
TpaA (TP-1161)	MNKDIDLSAIEISDLISETEQSDDALSQVMAA--	SCTTTGCACSSSSSST
CltA (cyclothiazomycin)	MEKELVLDLADLSVDELDVLPTSPGAGLESINVGHAMVEIGA--	SNCTSTGTPASCCSCCCC
TbtA (thiomuracin)	MDLSDLPMDVFELADDGVAVESLTAGHGMTEVGA--	SCNCFCYICCSCSS-A
NosM (nosiheptide)	MDAAHLSDLDIDALEISEFLDESRLEDSEVVAKVMSA--	SCTTCECCCSCS-S
TsrH (thiostrepton)	MSNAALEIGVEGLTGLDVDTLEISDYMDETLLDGEDLTVTM--	IASASCTTCICTCSCSS

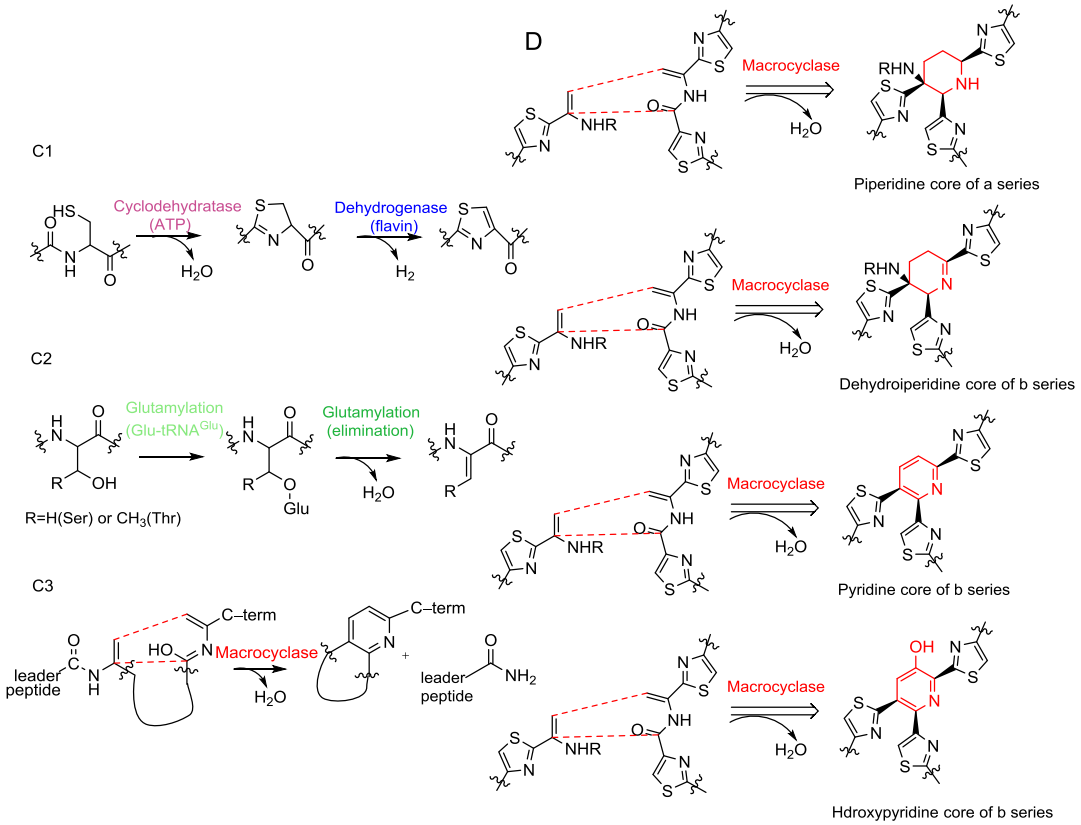


Fig. 26 Biosynthesis of related thiopeptides. **a** Gene information and predicted function of gene clusters encoding the four representative thiopeptides. **b** Precursor peptide sequences of four featured thiopeptides. (In core peptide sequences, red residues go through heterocyclization, green residues go through dehydration and those with the underline bear the 6-atom nitrogenous ring. C-terminal core peptide residues will be removed during processing), **c1** Proposed heterocyclization (Cys), **c2** Ser/Thr dehydration, **c3** Macrocyclization. **d** Proposed cyclization to be the six-member ring

(Encoding by the dark green ORF in Fig. 26a), and Glutamate elimination enzyme which includes LazF, BerC, TpaL, CltF, TbtC, NosD, and TsrK (Encoding by the light green genes in Fig. 26a). This dehydration usually involves 2–9 Ser/Thr residues along the thiopeptide skeleton. According to the sequence of core peptides, the site of Ser incorporated into the six-membered ring and the distance between anteroposterior Ser and Cys remain highly conservative (Fig. 26b). Subsequently, macrocyclization forms the main skeleton of thiopeptide. It is mainly accomplished by cycloaddition of two dehydroalanine residues and a neighboring carboxyl group to form a nitrogen-containing six-membered ring (Wever et al. 2015) (Fig. 26c3). It is proposed that this cycloaddition, hetero-Diels–Alder cycloaddition reaction, could be facilitated by macrocyclization (Encoding by red ORF in Fig. 26a) and may either be concerted or an asynchronous sequence of stepwise $\{2+4\}$ additions (Li and Kelly 2010), according with the draft of Bycroft (Bycroft and Gowland 1978) and Floss (Mocek et al. 1993). However, the minor macrocycle apparently does not arise from encoding precursor amino acid but an indirect further operation. Integration of quinaldic acid moiety of thiostrepton into the main skeleton is proposed to be derived from tryptophan and is achieved by coenzyme A activation (Liao et al. 2009) and NRPS-type adenylation domains (Kelly et al. 2009). Moreover, the overexpression of the gene tsrV support the putative diketone mode that 2-methyltryptophan is transformed into α-keto acid (Li and Kelly 2010). Remarkably, the biosynthesis of lactazoles just contains the seven basic PTM enzymes of the three-step biochemical reaction without any other structural modifications, so the lack of antibacterial activity may also be related to the structure of the thiopeptide that has not been modified. However, it is worth mentioning that the gene cluster consists of only 6 ORFs, which allows the glutamate eliminating enzyme to fuse with the azole dehydrogenase.

Furthermore, in addition to the synthesis of main structure, many thiopeptides are also accompanied by additional functional modifications such as methylation, epoxidation, cyclization of side chains, and the integration of indolyl (Bennallack and Griffitts 2017).

Structure–activity relationship

Although the in vitro antibacterial activities of most thiopeptides are excellent, the low aqueous solubility limits their further development. The medicinal chemistry effort of thiopeptides focused on enhancing aqueous solubility relative to that of the natural product and improving antibacterial activity. With the rapid development of chemical synthesis and biosynthesis of thiopeptides (Just-Baringo et al. 2014a, b), a lot of researches have been conducted on structure–activity relationship of thiopeptides.

Structure–activity relationship of thiostrepton-type thiopeptides

Early studies have reported that macrocycle of siomycin A was modified with dicarboxylic acids to produce some half-esters and their salts, some of which increased their aqueous solubility and therefore exhibited better therapeutic profiles in vivo with reserving in vitro antibacterial activities (Tokura et al. 1981). Wendy L. Kelly group explored the mutations of thiostrepton A through heterologous expression and verified that two amino acid residues (Ala2 and Ala4) were not important for retaining the antibacterial activity, but the residue Thr7 was the critical role in the antibacterial activity (Fig. 27a) (Li and Kelly 2010; Zhang and Kelly 2015), which provides an available approach for the modification of thiostrepton, thiocillin I, micrococcin P1 and nosiheptide. Furthermore, the same group subsequently performed the mutation of Ala2 and removed the Ile1 to generate 10 derivatives, which indicated that the contracted quinaldic acid loop could significantly affect biological activity (Fig. 27b) (Zhang et al. 2016). Otherwise, the group of Wen Liu designed and biologically synthesized 5′-fluoro-Thiostrepton and 5′-fluoro-Siomycin which were quinaldic acid (QA)-modified analogues *via* exogenous related chemical feeding of synthetic QA analogues into the corresponding mutant strains and found that 5′-fluoro-Siomycin exhibited better antibacterial properties and higher aqueous solubility (Fig. 27c) (Wang et al. 2019). Several tail modified analogues of thiostrepton A were designed and synthesized, which highlight an dramatic contribution by the tail part to antibacterial activity (Fig. 28a) (Myers et al. 2010). Modification of macrocycle and C-terminal tail of thiostrepton including oxidization of the thiazoline rings and attachment of lipophilic thiols to the terminal dehydroamino acid led to a series of potent analogues agents against *P. falciparum*, which established a promising nontoxic scaffold for antimalarial drug discovery (Schoof et al. 2010; Aminake et al. 2011). The pharmaceutically important fluorine and methyl groups were introduced onto the the biologically tunable quinaldic acid moiety thiostrepton, which strongly promoted the antibacterial activity and water solubility (Fig. 28b) (Wang et al. 2015).

Structure–activity relationship of GE2270 A-type thiopeptide

Previous study showed that β-phenylserine residue is important for retaining antibacterial activity of GE2270 A (Lociuro et al. 1997). Remarkably, a prepeptide-coding region randomization of thiopeptides conducted by Walsh and co-workers developed 29 GE37468 variants and 12 of the variants retained antibacterial properties. They found that both Asn3 and β-hydroxylated Phe8 were conserved in GE37468, GE2270 A and thiomuracin, and the macrocyclic

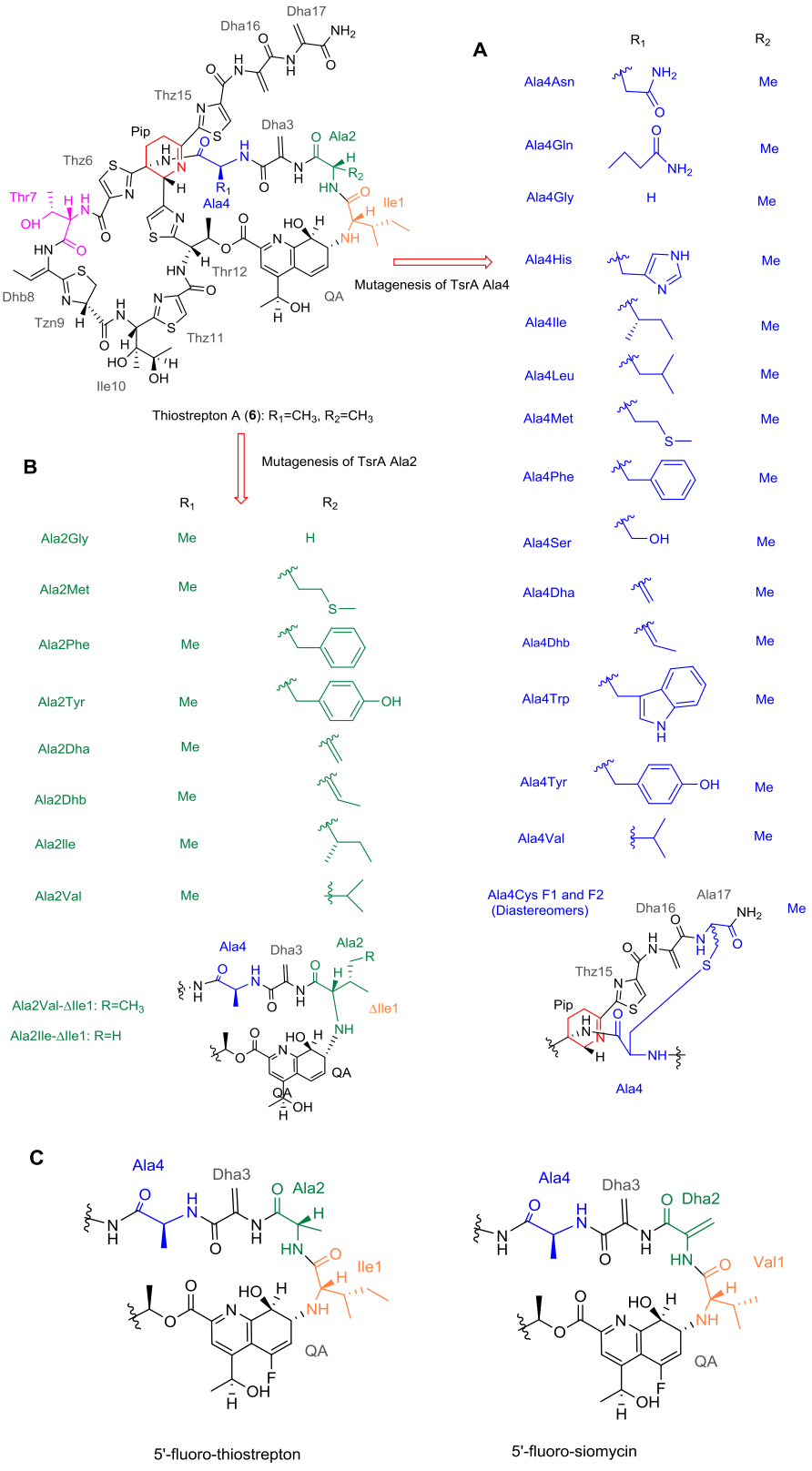


Fig. 27 Biosynthetic modification of thiostrepton

ring was important for antibacterial activity. Mutant T2S showed similar activity to GE37468 (0.016 mg/mL), whereas T2C exhibited 2-fold enhanced activity (0.0078 mg/mL) suggesting that the methyloxazole, thiazole, and oxazole residues have important effects on antibiotic activity (Young et al. 2012). The in vitro antibacterial

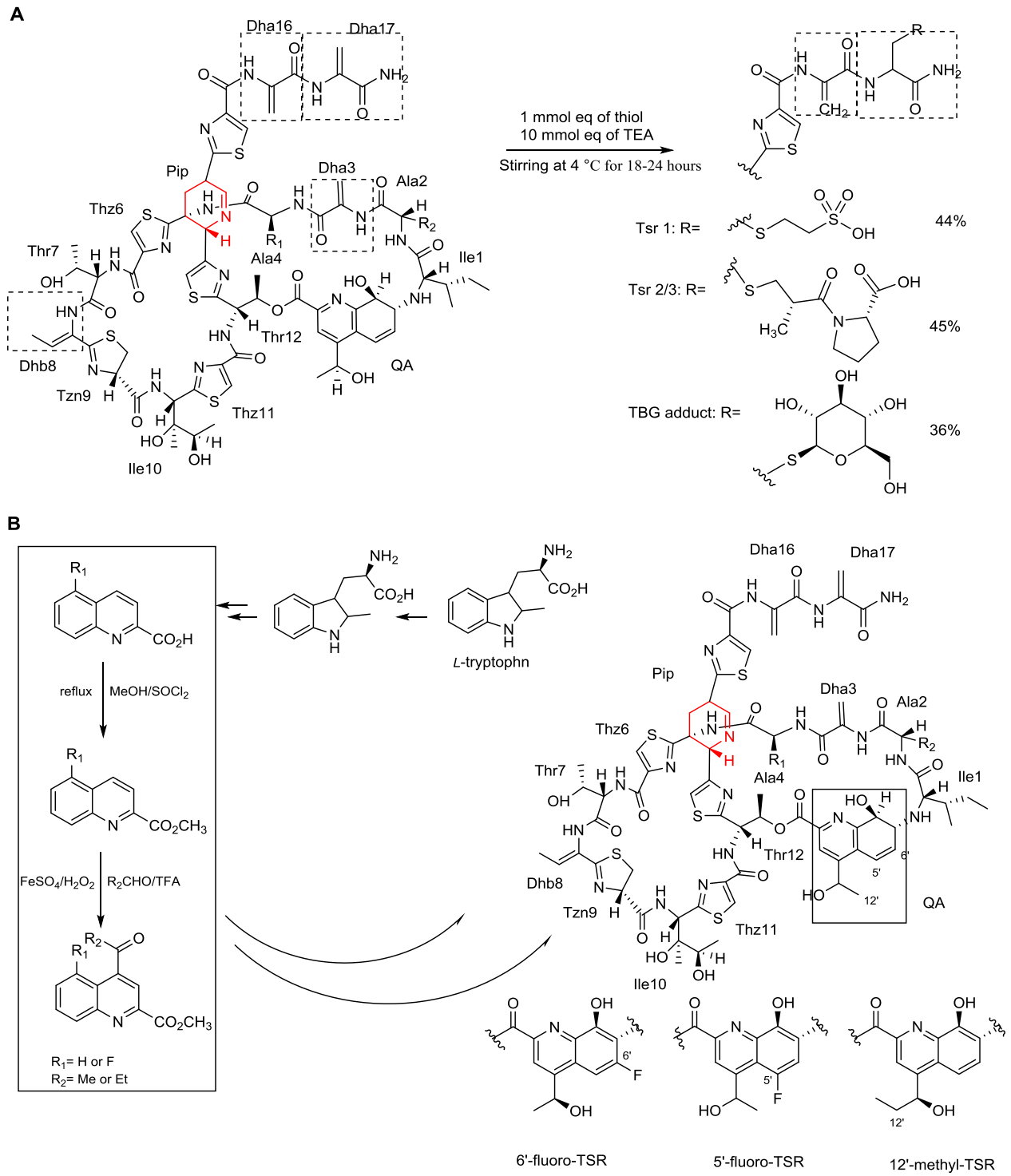


Fig. 28 Chemical modification of thiostrepton

activities of GE2270 A are potent, the aqueous solubility was limited for further drug development (<0.005 nM). 4-Aminothiazolyl analogues of GE2270 A were designed and optimized for the treatment of *C. difficile* infection in order to improve its pharmacokinetic profile. Finally, several cycloalkylurethane-based diacid and triacid analogues exhibited good antibacterial activity against a panel of Gram-positive organisms both in vitro and in vivo (Fig. 29). LFF571 has been selected in clinical trials for moderate *C. difficile* infection because of promising in vitro and in vivo potency and high aqueous solubility (LaMarche et al. 2011, 2012).

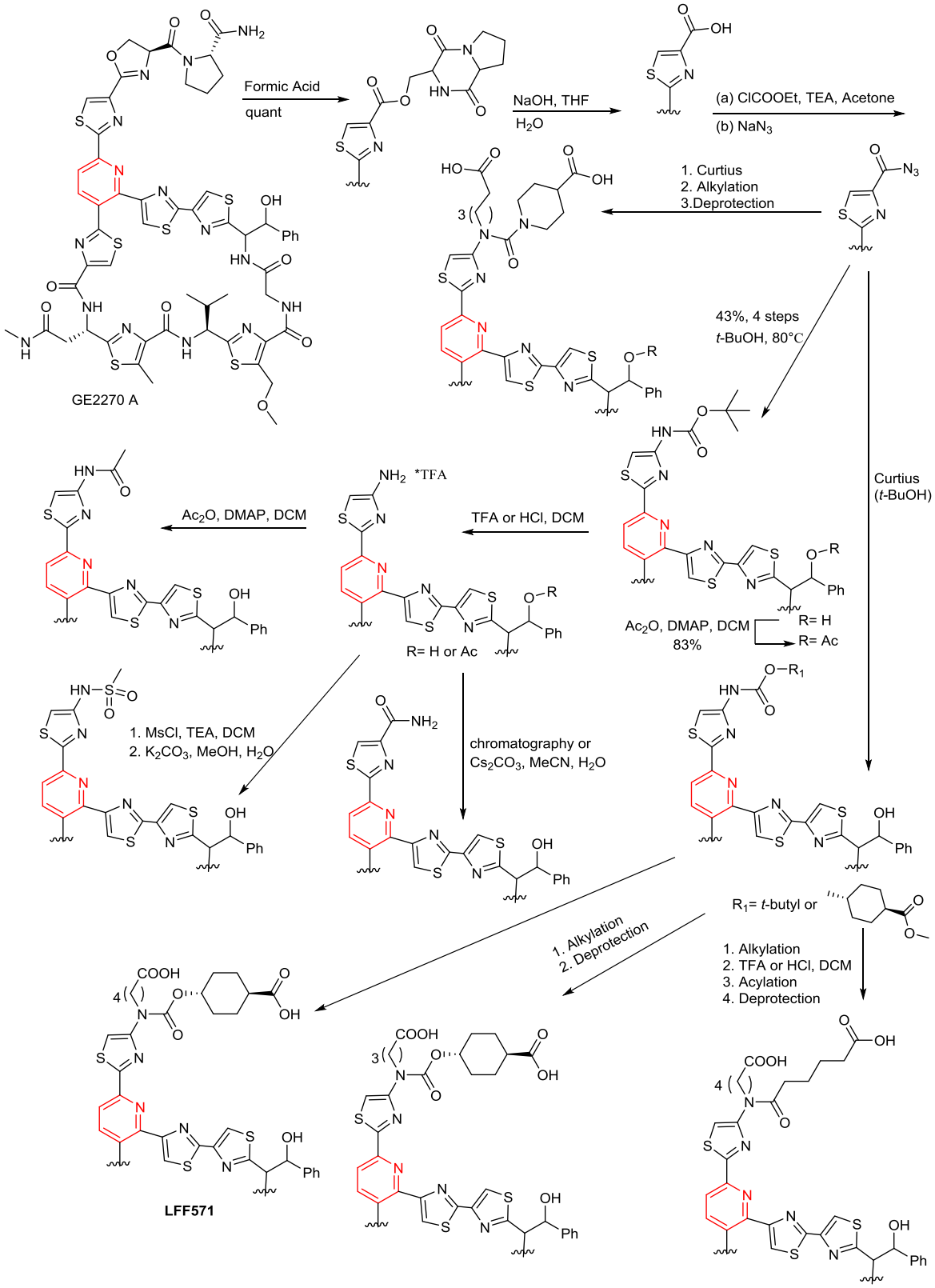


Fig. 29 Modification of GE2270 A

Structure–activity relationship of thiocillin-type thiopeptides

Prepeptide gene replacement with overall alanine scan of all 14 amino acid residues of thiocillin was used to study structure–activity relationship of thiocillin (Acker et al. 2009; Bowers et al. 2010). First, serines 1 and 10 are crucial for the formation of the core pyridine ring which is important for the antibiotic activities. Second, threonines 3 and 4 are conserved in the 26-member macrocycle because these two residues are responsible for binding the protein L11 are essential for antibacterial activity. Third, the residues cysteines 2, 5, 7, 9 (the position of thiazoles) are responsible for sustaining the rigidity of macrocycle, which is crucial for inhibition of translation elongation at the ribosome. Then, the other residues are flexible with modification at a certain extent. For example, the residues valine 6, threonines 8 and 14 could accept hydroxylation, methylation and β-oxidation/decarboxylation and reduction, indicating that the future direction of structural optimization of thiocillin for enhancing antibacterial activity and water solubility (Fig. 30) (Luo et al. 2016). In accord with thiocillin, the threonines 3 of nosiheptide is flexible for retaining antibacterial activity (Wang et al. 2016).

Analogues of thiomuracin A were designed and synthesized through removing the C-terminal tail, modifying epoxide region and altering the hydroxyphenylalanine motif. All analogues retained the antibacterial activity and cyclization of the C84 epoxide to a pyrrolidine led to a structurally simplified, chemically stable analogue, which retained antibacterial activity in vitro and in vivo, and allowed for further exploration. Importantly, the systematic SAR studies of thiomuracin generated two promising analogues, *C*-linked cyclohexylcarboxylic acid and *N*-linked dicarboxylic acid analogues, both of which proved significantly more soluble than thiomuracin A and more potent antibacterial activity in vitro and in vivo than vancomycin (LaMarche et al. 2012, 2016).

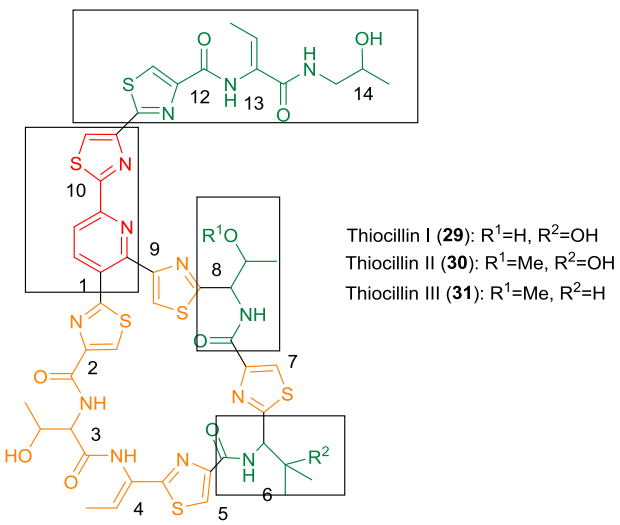


Fig. 30 SAR of thiocillin distribution. The red zone is indispensable for the antibiotic production, the orange scaffolds are conservered for antibiotic production and activity properties, and green residues could be modified or mutated for antibiotic analogues with almost or more considerable activity

Several analogues of baringolin were chemically synthesized to assess the role of the thiazoline ring and pentapeptidic tail in order to define structure–activity relationships for these moieties. The thiazoline ring was found to be crucial to retain inhibitory activities against various Gram-positive bacteria. the peptidic tail was not a crucial moiety and its substitution for a *trans*-4-aminocyclohexane-1-carboxilyc acid moiety improved the antibacterial potency against most strains (Just-Baringo et al. 2014a, b).

The discovery of a number of thiopeptide analogues has illuminated structure–activity relationship of some types of thiopeptides and allowed some of the limitations inherent to this promising class of peptide to be overcome. Chemical synthesis, semi-synthesis, and engineering of the biosynthetic pathway have independently led to structural modifications of various thiopeptides. Some of the new analogues have exhibited enhanced profiles, not only as antibacterial, but also as antiplasmodial agents. The design, synthesis and optimization of novel agents based on the thiopeptide scaffold is supposed to be the only strategy to exploit the high potential in vitro for drug discovery and development.

Conclusion and outlook

Notably, thiopeptide compounds also have anti-fungal, anti-tuberculosis and other therapeutical potentials, and it has shown least toxicity in mice. Despite their promising biological profile in vitro, their poor pharmacokinetic properties, especially poor aqueous solubility, have limited their use as therapeutic agents, which leads to the restriction of these potent agents in the treatment of animal infections. To date, only thiostrepton and nosiheptide have been in the market. Thiostrepton is used for the treatment of cats and dogs skin infections and nosiheptide is used as an animal growth promoter. To overcome the physicochemical drawbacks of thiopeptides, various approaches including chemical synthesis, biosynthetic pathway engineering, and semi-synthesis have been used to determine structure–activity relationship to evaluate key structural features responsible for their unique biological profile in order to produce structural analogues of thiopeptides with enhanced aqueous solubility that can retain biological activity in vitro and in vivo. The large differences between

the three above strategies lead to that structural modifications are distinct, which has allowed different areas of chemical space to be explored. Among those three methods, chemical synthesis is of a huge potential and is likely to provide comprehensive insights into structure–activity relationship of thiopeptides because total synthesis of many thiopeptides have been achieved through the development of powerful synthetic methods and strategies which are amenable for synthesis of any analogue that can be designed. Therefore, chemical synthesis allows the introduction of various modifications that are impossible used in the other two approaches. However, it is noteworthy that the complexity and high cost do not make it always feasible for the preparation of libraries with sufficient production. Biosynthetic pathway engineering allows alteration of the enzymatic machinery function and makes amino acid residue replacement possible to produce structural analogues in vivo. The structure of the thiopeptides originating from extensive posttranslational modification of a ribosomally synthesized pre-peptide makes this approach a great potential for the easy rapid production of thiopeptide analogues. However, some disadvantages have limited the application of pathway engineering of thiopeptide in the study of structure–activity relationship. First, culture condition has to be optimized to achieve efficient amounts of thiopeptide analogues because product yields are often dramatically low when even just one amino acid residue is changed through mutation. Second, many mutations are not successfully accomplished by the biosynthetic machinery so that only a small fraction of the chemical space can be studied by this approach. The enzymatic machinery responsible for the biosynthesis of thiopeptides cannot produce analogues that are very different from natural thiopeptides. A semisynthetic approach effectively introduces new structural fragments or degradation at the specific positions of the natural product. However, this approach is mainly limited by the inherent reactivity of the thiopeptides and all chemical modifications have to be accomplished at the most chemically reactive positions of thiopeptides. As previously stated, they all have some inherent limitations so that appropriate strategy or a combination of different strategies should be thoroughly considered to effectively produce new thiopeptide analogues.

Continuously exploring the new water-soluble thiopeptide compounds is a critical task. In addition, it is also imminent to use a bioengineering method to alter and modify the biosynthetic pathways of thiopeptide compounds in microorganisms and to chemically modify certain functional groups of known thiopeptides to semi-synthesize analogues with water-soluble structures. During the upcoming years it is highly possible for us to see new advances on design, synthesis and optimization of new thiopeptide analogues with excellent biological profile and enhanced pharmacokinetic property, which will guarantee the development of these fantasticating and sophisticated natural product into the clinic. The new advances to come in the near future will unambiguously provide a deeper understanding of the chemistry and biology of thiopeptides through the combination of different approaches in a multidisciplinary strategy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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