The diversity and utility of arylthiazoline and aryloxazoline siderophores: challenges of total synthesis

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Siderophores are unique ferric ion chelators produced and secreted by some organisms like bacteria, fungi and plants under iron deficiency conditions. These molecules possess immense affinity and specificity for \( \text{Fe}^{3+} \) and other metal ions, which attracts great interest due to the numerous possibilities of application, including antibiotics delivery to resistant bacteria strains. Total synthesis of siderophores is a must since the compounds are present in natural sources at extremely small concentrations. These molecules are extremely diverse in terms of molecular structure and physical and chemical properties. This review is focused on achievements and developments in the total synthesis strategies of naturally occurring siderophores bearing arylthiazoline and aryloxazoline units.

1 Introduction

Iron is an exceptionally versatile cofactor that is indispensable for a plethora of biochemical reactions in both mammalian hosts and pathogenic microorganisms. Its acquisition and regulation is crucial for efficacious microbial growth and survival. Deficiency can hinder vital cellular processes such as respiration and proliferation, while an excess may cause toxic effects by inducing oxidative damage through reactive oxygen species produced in the Fenton and Haber–Weiss reactions. In the pre-oxygen era, microorganisms were able to exploit highly soluble \( \text{Fe}(\text{II}) \). Although iron is still abundant in the Earth’s crust, in the aerobic environment \( \text{Fe}(\text{III}) \) exists as insoluble ferric hydroxide, largely inaccessible to microorganisms.

To supply and regulate iron, microorganisms have evolved sophisticated iron acquisition and trafficking systems. Under iron depleted conditions, bacteria and fungi produce siderophores, low molecular weight (MW under 1500 Da) molecules with high binding affinity for ferric iron, capable of solubilizing the ferric hydroxide polymers and sequestering iron from a host’s proteins and ligands. Low iron concentrations trigger a “signal” to start biosynthesis of the appropriate siderophores and the proteins involved in siderophore uptake machinery. As soon as sufficient amount of iron is transported and accumulated inside the cell, its acquisition system is turned off.

Since the early 1950s, when the first three siderophores were isolated and identified as growth factors of bacteria, 270 different siderophores have been structurally characterized (from over 500 identified) and this number is growing.

The process of isolation of siderophores from natural sources is very tedious, inefficient, and thus expensive. The unique chemical structure diversity and numerous applications both in medicine and industry, prompted scientists to prepare these molecules by total synthesis (more in Sections 3.1 and 3.2). Over the last decades only two reviews concerning the synthesis of naturally occurring siderophores were published.

Total synthesis allows for obtaining analogs of naturally occurring siderophores – mimics, which are extremely important in biomedical applications, for example in the Trojan horse strategy (antibiotic therapy). This approach allows for a deeper investigation of the relationship between structure and metal complexing properties or bioactive functionality. In the retrosynthetic analysis essential to plan the total synthesis of siderophores, genetic and biochemical knowledge of siderophore biosynthesis is extremely useful. Siderophore retrosynthesis is based on finding the structure of target...
compound synthons that would correspond to the following stages of biosynthesis. The review covers total synthesis strategies of naturally occurring siderophores with arylthiazoline and aryloxazoline subunits. The keynote of this work is to present known strategies for preparation of this particular group of siderophores with a detailed analysis of the newest and most efficient approaches. This overview allows tracking the progress in this area made over the years, and identifying the possibilities for further development. In addition, the review describes the synthesis of analogues of some siderophores with arylthiazoline and aryloxazoline subunits, thus showing the impact of structural variations on the activity of these compounds.

Main classification of naturally occurring siderophores is based on the type of functional groups involved in the chelation of iron ions includes three basic groups such as catecholate, hydroxamate, and α-hydroxycarboxylate (Fig. 1). To date more than 100 siderophores bearing analogs of this type of donors have been isolated. In our review, we would like to focus on siderophores that have an aromatic phenolate and/or catecholate fragment in their structure linked directly to a thiazoline/oxazoline moiety, which will be called arylthiazolines/aryloxazolines (this nomenclature is not commonly used in siderophores classification).

Numerous reviews have been published in the literature describing the types of siderophores produced by microbes, their properties, functions, as well as their acquisition machineries; for a comprehensive discussion, the readers are referred to selected reviews and the references therein. Arylthiazoline and aryloxazoline-type siderophores, so far have been only rarely discussed as a group, showing the diversity of the structures and the total synthesis approach, all illustrated by most prominent examples.

2 Origins and total synthesis of arylthiazoline and aryloxazoline siderophores and analogues

2.1 Arylthiazoline siderophores: origin and total synthesis

The group of arylthiazoline-based siderophores are characterized by the presence of a 2-thiazoline framework in the structure of a substituted aromatic ring and two or three linearly connected heterocyclic subunits. Phenolic hydroxyl group, the nitrogen atom of the thiazoline ring and usually a terminal carboxyl group are involved in iron coordination. The group members differ mainly in substituents of the phenolic ring, and modifications of the terminal thiazolidine fragment. Moreover, the configuration of the stereogenic centres should be also taken into account (Fig. 2).

2.1.1 Pyochelin. Pyochelin is a prototype of arylthiazoline-based siderophores. It was first isolated in 1978 from iron-deficient cultures of Pseudomonas aeruginosa ATCC 15692 by Liu and Shokrani. Cox and co-workers were pioneers in studying pyochelin properties, and established its structure in 1981.
Pyochelin is produced mainly by Gram-negative Pseudomonas and Burkholderia, highly aggressive opportunistic pathogenic bacteria that are common causative agents for severe respiratory infections affecting patients with compromised immunity. Moreover, P. aeruginosa is responsible for highly lethal hospital-acquired infections as it is unaffected by many disinfecting agents and its strains are often resistant to the majority of antibiotics. However, pyochelin was also isolated from Gram-positive bacteria, Streptomyces.

This unusual siderophore is built of one phenol moiety connected to thiazoline ring which is attached to thiazolidine part with a methyl-substituted nitrogen atom and a carboxylic group attached to the adjacent position. It has three chiral centres at positions C-4', C-2'' and C-4'' with absolute configurations (R,R,R) (pyochelin I), but the C-2''-centre readily isomerizes to the (S) form (pyochelin II) yielding a equimolar mixture of two epimers. On the other hand, Schalk et al. reported about four diastereoisomers which were obtained by organic synthesis: pyochelin I (4'R,2''R,4''R), pyochelin II (4'R,2''S,4''R), neopyochelin I (4'S,2''R,4''R) and neopyochelin II (4'S,2''S,4''R) with varying proportions depending on starting compound (Fig. 2).

The synthesis of pyochelin was first described in 1988 by Cox and co-workers in a three-step non-stereoselective procedure. The acid intermediate 1 was prepared by method of Mathur et al. and converted to the corresponding aldehyde 2, which was condensed further with y-N-methylcysteine 3, providing a mixture of pyochelin isomers 4, with an overall yield of approximately 5% (Scheme 1).

In a following paper, by optimising the reaction conditions, the overall yield was improved to 65%. The performed synthesis allowed to obtain four out of eight possible stereoisomers in the 4 : 1 : 1 : 4 ratio (Fig. 3). Based on the comparison of NMR spectra to the one of 4-methylpyochelin I methyl ester, whose structure was resolved by X-ray crystallography, Cox assigned the absolute configuration of four stereoisomers, i.e., pyoche- lins I and II and neopyochelins I and II.

An improved synthesis of pyochelin was described by Zamri and Abdallah, who proposed a stereocontrolled synthetic pathway and obtained a mixture of four diastereoisomers in the 2 : 2 : 5 ratio (Scheme 2). In the new proposed synthesis, the method of Mathur et al. for acid preparation (1, Scheme 2) was replaced by a protocol described by Bergeron et al. to avoid epimerization of the C-4' stereogenic centre. The acid 1 was converted to N-methoxy-N-methyl hydroxamate intermediate 7; N,O-dimethylhydroxylamine was coupled to compound 1 using diethyl cyanophosphonate (DECP) as coupling reagent, providing hydroxamate 7 in excellent yield (94%); reduction of
the hydroxamate 7 by excess LiAlH₄ afforded an aldehyde 2. The final condensation step was accomplished by the known methodology between aldehyde 2 and L-N-methylcysteine hydrochloride 3 in a 4:1 mixture of ethanol and water in the presence of potassium acetate, and yielded 70% of pyochelin 4 as a mixture of four diastereoisomers. In natural pyochelin, the absolute configurations are (4₀₀⁰R) and (4₀₀₀R). During the synthesis of pyochelin, partial epimerization occurs at C-4₀ while the absolute configuration at C-4₀₀ remains unaffected thus providing a mixture of pyochelin isomers: pyochelin I and II, and neopyochelin I and II.

Synthetic analogs of pyochelin can enrich the library of biologically active molecules, to tune the chemical or physical properties of the pyochelin, as well as to provide a tool for the investigation of the structure–function relationship of the transporters. An appropriate architecture of ligands and the geometry of complexes allow a control of efficient iron coordination and bacterial recognition. However, the epimerization at the C-2₀₀ chiral centre shows the difficulty in preparing enantiopure synthetic pyochelin analogs.

The first pyochelin analogs were only accessed by mutasynthesis (Fig. 4).²⁹ The mutasynthetic pyochelin analogs as mixtures of two rapidly interconverting isomers I (4₀₀⁰R,2₀₀₀R,4₀₀₀R) and II (4₀₀₀R,2₀₀₀S,4₀₀₀R) were compared to pyochelin in their ability to transport iron in P. aeruginosa. Isomeric forms were transformed into methyl esters and separated (in case of 8c only one form I was obtained). 4-Methylpyochelins 8b and epi-8b were more active than pyochelin in ⁵⁵Fe(III) transport, while the other two analogs 5-fluoropyochelin 8a and epi-8a and 6-azapyochelin 8c demonstrated a decreased iron uptake.

Extensive work in the field of synthetic pyochelin analogs was performed by the group of Schalk, Mislin and their co-workers. The Schalk group focused on studying the properties of several biologically active analogs and conjugates of pyochelin 9a–c, as will be described on several examples. In the first generation, the effect of the configuration on bacterial uptake was tested (Fig. 7).³⁰ Uptake rates of ⁵⁵Fe(III), tested on P. aeruginosa (ATCC 15692) as well on its pyoverdine defective mutant CDC5 (pPVR2), suggested that the configuration at carbon C-4₀ has no effect on the biological properties of pyochelin. Zinc complexation of the mixture (4₀₀⁰R,2₀₀₀R,4₀₀₀R) and (4₀₀₀R,2₀₀₀S,4₀₀₀R) pyochelins provided exclusively (2₀₀₀R) diastereomer, which indicated template direction effect. Moreover, substitution in the aromatic part (R¹, Fig. 7) or amine group in thiazolidine part (R², Fig. 5) did not affect dramatically the biological properties of the corresponding analogs compared to pyochelin.
In an additional series of pyochelin analogs, the thiazoline ring was replaced by a thiazole moiety (Fig. 6). The series was prepared using the synthetic protocol for pyochelin analogs through Weinreb amide intermediate, and tested for \( {^{55} \text{Fe}} \) uptake by \( \text{P. aeruginosa} \), strains PAO1 and PAD07. As phenol function is crucial for the coordination of Fe(III), analogs bearing a methylated hydroxyl group failed to transport Fe(III), and only analogs 10a, 10c, 10e and 10f were able to transfer iron inside the bacteria.

2.1.2 **Yersiniabactin, micacocidin and piscibactin.** Micacocidin belongs to a well-known family of zinc-containing metallophores. It was isolated from \( \text{Pseudomonas} \) culture primarily as Zn(II) complex together with Cu(II) and Fe(III) analogs, and extensively studied by the Aburahi Laboratories. The micacocidin structure was determined by single crystal X-ray crystallographic analysis of its Zn(II) complex, which indicated the presence of an aliphatic side chain on the aromatic ring and a methyl substituent in the nitrogen atom in the thiazolidine ring. This metabolite is also produced by the economically relevant plant infecting bacterium \( \text{Ralstonia solanacearum} \) (which produces staphyloferrin B as main siderophore), and shows strong activity against \( \text{Mycoplasma pneumoniae} \), a pathogen responsible for community-acquired pneumonia.

Total synthesis of micacocidin was performed by Ino and co-workers. There are five stereogenic carbon atoms in its structure. Cysteine was utilised as a chiral source for C-9, C-12 and C-18 centres, and for generation of the (S) secondary alcohol on C-14 by a stereoselective reduction of ketone. C-10 chirality was generated at final stage by formation of a Zn complex.

Arylthiazoline part was synthesised starting from 3-methoxy-\( N,N \)-dimethylbenzylamine 11 which was converted to intermediate 12 in 5 steps and a total yield of 70%, using the procedure described by Kamikawa. Next, condensation of 12 with \( p \)-methoxybenzyl (PMB)-protected \( \alpha \)-cysteine provided compound 13 which was cyclized using PCl\(_5\) to obtain thiazoline derivative in 95% yield. Methyl deprotection of both ether and ester using boron tribromide provided carboxylic acid 14, which was subsequently converted to Weinreb amide 15 using bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOP-Cl) coupling reagent. Following phenol protection by tert-butyldiphenylsilyl (TBDDS) group, the Weinreb amide was reduced by LiAlH\(_4\) to afford aldehyde 16, the desired segment of micacocidin (Scheme 3).

The second synthon was prepared starting from thiazolidine 18 which could be obtained from \( \alpha \)-cysteine hydrochloride 17 in a two-step route, followed by the reaction with carboxyldiimidazole (CDI) and a subsequent condensation with methyl isobutyrate, leading to keto-ester 19. Reduction of the ketone function and construction of an oxazolidinone ring provided compound 20. Condensation of 20 with 2-methyl-(S)-cysteine methyl ester hydrochloride using CDI yielded 21. Reaction with TFA in refluxing toluene resulted in cyclization of

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**Fig. 5** Structure of first generation of synthetic pyochelin analogs.\(^{20}\)

**Fig. 6** Pyochelin analogs based on the thiazole ring.\(^{21}\)

**Fig. 7** Retrosynthetic analysis of micacocidin.\(^{39} - ^{41}\)
the N-acylcysteine. Treatment with [trimethylsilyl]diazo- methane restored the methyl ester moiety which was hydrolyzed during the reaction and provided 22. Cleavage of the oxazolidinone ring was achieved in several steps and provided Boc-protected segment 23. A subsequent hydroxyl group protection and N-methylation led to intermediate 24, which was further deprotected yielding building block 25 with free hydroxyl and thiol residues (Scheme 4). Hydrolysis provided compound 26 which was condensed with the first synthon 16 as shown in Scheme 5. The TBDPS-protected aryl thiazoline fragment 16 was fairly labile, it was stored as Weinreb amide 15 which was treated with LiAlH₄ shortly prior the condensation with 16. Desilylation with TBAF afforded micacocidin methyl ester 27 as a mixture of diastereomers. Hydrolysis of the terminal ester 27 by LiOH provided the corresponded acid. Treatment with zinc chloride resulted in isomerisation at C-10 and provided the desired micacocidin 29 (Scheme 5).

To understand structure-antimicoplasma activity relationship of micacocidin, Ino and co-workers prepared several derivatives by modifying hydroxyl and carboxylic groups in the...
skeleton of the siderophore isolated from the fermentation of Pseudomonas sp. No. 57-250 (Fig. 8). MIC values were determined for three strains: Mycoplasma gallisepticum, M. pneumonialae, M. hyopneumoniae. Compounds 27 and 30g were active, while a bulky ester group PCB 30a, amide derivatives 30b–d as well as methyl or MOM derivatives at the phenolic position 30f–h, 30j–k resulted in a reduced activity. According to the authors, the lack of bulky groups and the presence of hydrogen bonds

Scheme 5 Final assembly of the two segments of micacocidin.39,41

Fig. 8 (A) Structural variations of micacocidin analogs, (B) a proposed folded conformation of micacocidin.44
are required for activity, and the active derivatives have to possess a similar spatial conformation. The relationship between configuration and activity was examined as well. Regardless of the C-9 configuration, C-10 (R) isomers presented a similar activity to micacocidin 29, while C-10 (S) isomers exhibited a reduced activity. These results supported the authors’ proposal that the potency of siderophores depends on the ability of the derivatives to adopt a folded conformation.

In an additional work,43 micacocidin analogs 31a-f were generated by exploiting precursor-directed biosynthesis approach. The series varied in alkyl side chain, thus did not induce significant changes in the spatial folding. Almost all gallium complexes showed promising activities against M. pneumoniae ATCC 29342, and comparable to the native micacocidin. Derivative 31b was an exception, and exhibited a significantly reduced activity. A minimum alkyl chain length might be important for the interaction with the biological target (Fig. 9).

Yersiniabactin was first isolated from Yersinia bacterial strain, a causative agent of a broad range of diseases such as plague, bowel infections and reactive arthritis.44 Afterwards it was found that this strong chelating agent is not limited to one particular bacteria species and can be utilized by different kinds of microbes such as Enterobacteriaceae (E. coli and S. enterica).45–49 The yersiniabactin system is the most frequently carried, genetically non-conserved siderophore system in uropathogenic E. coli.50 The siderophore contains a phenol and a thiazolidine ring, as well as two thiazoline rings. Its stereochemistry is striking for the existence of five chiral centres, with a mixture of two C-10 epimers being isolated during structure elucidation studies.37–38

Following the preparation of micacocidin, Ino and coworkers accomplished a total synthesis of yersiniabactin (Fig. 10).51

The first building block was prepared starting from condensation of Weinreb amide 32 (ref. 52) and 2-methoxybenzoyl chloride 33, which provided ester 34. Next, in a 5-step route thioamide 36 was obtained which was converted to 7 by the reaction with the Burgess reagent. Further hydroxyl group protection and reduction of Weinreb amide 7 yielded aldehyde 37 (Scheme 6).

The second synthon for yersiniabactin was prepared according to the reaction conditions used in the total synthesis of micacocidin (Scheme 4).43 Compound 23 which was an intermediate in the synthesis of micacocidin was fully deprotected to provide derivative 38, and condensation with the first building block 37 afforded thiazolidine 39. Ester 39 hydrolysis provided the desired yersiniabactin siderophore 40 (Scheme 7).

Piscibactin, a siderophore isolated from subspecies Piscidia of Photobacterium damselae, is known as a causative agent of fish pseudotuberculosis, a malady that causes large economic losses in marine environment.53 High mortality rate and wide geographical distribution makes it a major problem in the Mediterranean fishing industry. Synthesis of piscibactin is also considered as a virulence factor in other bacteria, such as Yersinia enterocolitica responsible for severe enteric inflammation in humans.53 Piscibactin isolation was first reported in 2012 together with an additional metabolite, prepiscibactin, presumably a possible intermediate of piscibactin biosynthesis.53 The piscibactin structure was determined by Souto et al.53 and the studies performed allowed to establish the stereochemistry of piscibactin as (9R,10S,12R,13S).

A successful approach for piscibactin synthesis (close analogue of yersiniabactin) was accomplished by Jiménez et al. in 2022.54 Before, Segade and co-workers proposed a total synthesis of prepiscibactin.55,56 Retrosynthetic analysis of piscibactin was based on three synthons, and in all three cysteine was utilized as starting material (Fig. 11).
Piscibactin was prepared from two key synthons, and D- and L-cysteine were used as chiral sources for C-9 (S) and C-12 (S), respectively (Fig. 11). Applying a similar methodology as for pyochelin preparation, the first synthon was obtained through the formation of Weinreb amide, and reduction of the resulting hydroxamic ester with LiAlH4 (Scheme 2).

The second synthon, thiazoline based amino thiol was prepared utilizing multi-functionalized carboxylic acid and (S)-α-azido-methylcysteine. Synthetic route for full protected carboxylic acid was accomplished through protection of L-cysteine and a subsequent transformation in a stereoselective manner leading to final building block formation in 20% of overall yield (8 steps). For preparation of thiazoline fragment it was necessary to couple the activated acid of the protected statine with a freshly prepared thiol using EDCl. In the Staudinger reduction and a subsequent intramolecular aza-Wittig reaction, thioester was transformed into the thiazoline in good yield. Further deprotection of amino thiol led to the second building block in 42% yield. Condensation of thiazolinic aldehyde with thiazoline in dichloromethane afforded an epimeric mixture of methyl esters of piscibactin which were hydrolyzed and submitted without purification to complexation with gallium using Ga(acac)₃.

Final HPLC separation gave piscibactin Ga³⁺ complex and its 9S epimer in ratio 2 : 1 and 10% yield (Scheme 8).

2.1.3 Anguibactin. Anguibactin was first isolated in 1986 from marine bacterial strain Vibrio anguillarum by Actis et al. It is a common fish pathogen responsible for vibriosis, a deadly haemorrhagic septicaemic disease affecting various marine and freshwater fish. The disease has high morbidity and mortality rates and causes severe economical loses in the fish industry. This siderophore was of particular interest for scientists for one more reason. Its structure resembles very closely another iron carrier compound, namely the oxazoline...
derived acinetobactin (vide infra) utilized by multidrug-resistant 
Acinetobacter baumannii, an opportunistic pathogen responsible 
for many lethal hospital-acquired infections.\textsuperscript{60} Acinetobactin 
was found to be unstable and readily converted to its iso-
xazolidinone form while anguibactin was proven to be resistant 
to isomerization.

The structure of anguibactin can be described as being built 
of two planar sections, one containing the phenyl-thiazole 
system with its substituents and another with the imidazole 
ring. It was first elucidated in 1986,\textsuperscript{58} and the initial suggestion 
was later confirmed by van der Helm et al. solving an X-ray 
structure in 1989.\textsuperscript{61}

The total synthesis of angiubactin was carried out using 
a convergent approach.\textsuperscript{60} It was initiated by preparation of the 
phenylthiazole core in a similar synthetic pathway as for pyo-
chelin,\textsuperscript{56} by condensation of l-cysteine and aryl nitrile \textsuperscript{5a} (Scheme 2). The imidazole fragment \textsuperscript{49a} was prepared in two 
ways. In 2010 Takeuchi et al.\textsuperscript{62} proposed its synthesis through 
histamine dihydrochloride \textsuperscript{48} transformations into 4-(2-chlor-
oethyl)imidazole hydrochloride \textsuperscript{49} using SOCl\textsubscript{2} and a subse-
quently coupling reaction with \textit{N}-tert-butoxycarbonyl (Boc)-O-
benzyloxyamine \textsuperscript{50},\textsuperscript{63} followed by deprotection,\textsuperscript{64} yielding \textit{O} 
benzyloxyhistamine \textsuperscript{51a} in 66\% total yield (Scheme 9, part A). In 
the second approach proposed in 2015 by Kim et al.,\textsuperscript{65}
a terminal olefin 52a was first synthesized from \(N\)-Boc-O-benzyloxyamine 50 and 4-bromobut-1-ene. Dihydroxylation under Ujoh conditions afforded diol 53 which was transformed into \(\alpha\)-hydroxyketone 54 through the selective oxidation of the secondary hydroxyl group with NaBrO3/NaHSO3. In the final step, the Cu(II)-promoted imidazole formation with ammonia and formaldehyde was performed followed by deprotection with TFA which resulted in desired histamine \(N\)-oxide derivative 51a in 40% overall yield (Scheme 9, part B).

A stereoselective coupling of the intermediate 57 to a free amine of \(N,O\)-imidazole 58 mediated by HATU in dichloromethane provided product 59 (er = 98 : 2). The use of tetrabutylammonium iodide (TBAI) and boron trichloride (BCl3) led to a clean removal of both benzyl and methyl groups and successfully generated compound 61. Along with 61, its 3-deoxy derivative 62 was also prepared in an analogous manner (Scheme 10).

2.1.4 Ulbactin. Ulbactin is a natural siderophore which was isolated in two epimeric forms (ulbactin F and G, in the ratio 17 : 1, respectively) from marine bacterial genus of \textit{Brevibacillus} extracted from an unidentified sponge found near Iwate, Japan. Although \textit{Brevibacillus} sp. is not considered to be a dangerous microbe, the structures of identified compounds are captivating because its core is also shared by \textit{Pseudomonas aeruginosa} siderophore pyochelin, though a peculiar tricyclic ring system is present.

The compounds possess an unusual heterocyclic structure in which two thiazolidine rings are fused to form a tricyclic ring system. After successful isolation and chromatographic purification, ulbactin F was obtained as pale yellow crystals and its structure was elucidated by Igarashi et al. A series of studies on the structure of ulbactin F allowed its identification and determination of the absolute configuration as \((4'R,3'R,6'R,9'R,9''R)\). Ulbactin G with the same molecular composition is the epimeric form of ulbactin F with absolute configuration \((4'R,3'S,6'R,9'R,9''R)\). A peculiar feature of ulbactin F and G, namely the 6,9-imino-1H,3H,5H-thiazolo[4,3-c][1,4]thiazepin-5-one tricyclic ring system containing two sulfur atoms and two nitrogen atoms makes it very intriguing. This ring system, but lacking \(N\)-methyl group, was also reported for ulbactin D.

![Scheme 9](image9.png)  
Two synthetic routes for the formation of the imidazole part 51a: (A) from histamine hydrochloride, (B) from \(N\)-Boc-O-benzyloxyamine and 4-bromobut-1-ene.

![Scheme 10](image10.png)  
Total synthesis of angiubactin 61 and its analog 62.
As ulbactin F is the major metabolite \(_{(vide~supra)}\), this diastereomer was targeted in the total synthesis.\(^{68}\) Convergent synthetic pathways were applied, with several building blocks prepared. Synthesis of the phenylthiazolidine core followed the pathway used for pyochelin, converting salicylnitril to aldehyde \(^2\).\(^{26}\) The thiazolidine synthons were prepared from protected enantiomeric cysteines. Reaction of the two fragments in ethanol/water with NaOAc, and then heating in an ethyl acetate/methanol mixture, provided the product \(^{69}\) in total yield of 12\% and its epimer, \(\text{epi-}^{69}\), as a side product (Scheme 11).

### 2.2 Aryloxazoline siderophores: origin and total synthesis

Oxazolines are a large family of heterocyclic imino ethers possessing a five-membered ring structure. Within the oxazoline family, 2-oxazolines have been most extensively studied so far and found broad applications in various fields. This is an important structural motif and pharmacophore of natural products and bioactive compounds (including siderophores, Fig. 12).\(^\text{69}\) The aryloxazoline/oxazole moiety is present in many siderophores and plays a crucial role in coordination mode and iron transport machinery in microorganisms.

#### 2.2.1 (−)-Yanglinmycin, spoxazomicins and madurastatins

In 2013, Zhang’s group isolated (−)-yanglingmycin, 2-aryl-substituted 4,5-dihydrooxazole derivative from the fermentation broth of \(\text{Streptomyces djakartensis}\).\(^\text{70}\) Though it was not clearly stated in the original paper, this compound is an (S) enantiomer of spoxazomicin C. Due to the presence of various functionalities and its biological activities, yanglingmycin has been considered as a potential component of pharmaceutical drugs, polymeric materials, insecticides and so on.\(^\text{71,72}\)

To investigate the bactericidal activities of yanglingmycin, the Zhang group\(^\text{70}\) decided to synthesize this molecule and its analogs. In order to achieve the intended goal, an efficient synthetic pathway for the preparation of 2-aryl/heteroaryl oxazolines from nitriles under metal- and catalyst-free condition was used.\(^\text{73}\) Benzonitrile and its substituted analogs \(\text{5a}–\text{c}\) were applied as the starting materials. In the initial step, a Pinner reaction was performed to afford the corresponding methyl benzimidate hydrochlorides \(\text{70a}–\text{c}\), which were then reacted with various amino acid methyl ester hydrochlorides \(\text{71–73}\).\(^\text{74}\) The final products were obtained by an
efficient reduction of esters into alcohols using LiAlH4, yielding (−)-yanglingmycin 74a and its analogs 74b–c, ent-74a–c, 75, ent-75, 76 and ent-76 in total yields of 62% and 52–65%, respectively (Scheme 12).

For a deeper exploration of the antibacterial potency, a series of hydroxyl ester rac-77a–z and hydroxyl ether rac-78a–o derivatives of the racemic (±)-yanglingmycin and its phenyl substituted analogs rac-74a–h were prepared (Schemes 13 and 14). To obtain 2-aryl-substituted 4,5-dihydrooxazole analogs rac-74a–h, arylnitriles 5a–h were reacted with serinol in the presence of sodium carbonate (Scheme 13). Hydroxyl ester derivatives of (±)-yanglingmycin rac-77a–z were synthesized through esterification reactions using a catalytic amount of EDC, and hydroxyl ether derivatives 74a–o were obtained by etherifications of the alcoholic hydroxyl group in the presence of a base. Additionally, a fluorinated analog rac-77 was afforded via (±)-yanglingmycin rac-74a treatment with DAST (68% yield) (Scheme 14). In vitro antibacterial studies against four Gram-negative and three Gram-positive bacteria strains revealed that some derivatives are more active than (±)-yanglingmycin rac-74a. Structure–activity relationship analysis clearly showed that antimicrobial activity was lost after most derivatizations of alcoholic hydroxyl group and in the absence of phenolic hydroxyl substituent. On the other hand, incorporation of a short-chain ester group, an electron-deficient ether moiety and fluorination of alcoholic hydroxyl group were found beneficial for the antibacterial potency.

In 2019 Sun et al. proposed a mild catalytic approach to 2-oxazolines via oxetane ring-opening reaction (a model substrate was synthetized by acylation of commercially available 3-amino oxetane). This synthetic protocol is a useful tool for preparation of a diverse family of natural products with 2-oxazoline unit including spoxazomycin C rac-74a and its analogs, such as spoxazomycin D 82 and madurastatin B1 81 in racemic form (Scheme 15). It is worth emphasizing that 2-aryl-substituted 4,5-dihydrooxazole derivatives are crucial building blocks in total syntheses of many natural products such as mycobactin type siderophores etc.

2.2.2 Acinetobactin, pseudomonine and fimsbactin. Acinetobactin is a siderophore which contains catechol-oxazoline moiety, hydroxamate unit and imidazole ring. It was first described as the siderophore of highly resistant human pathogen A. baumannii, and later on to be also produced by the fish pathogen Aeromonas salmonicida subsp. salmonicida (a Gram-negative γ-proteobacteria identified as the causative agent of furunculosis, a devastating disease affecting cultured and wild fish worldwide). The structure of acinetobactin was initially proposed, but further research revealed facile and spontaneous rearrangement from oxazolinyl hydroxamate into isooxazolidinone form. 

Scheme 12  The synthetic route to yanglingmycin enantiomers and its analogs.76

Scheme 13  Synthesis of (±)-yanglingmycin and its phenyl-substituted analogs.77
Scheme 14  Synthesis of esterified, etherified and fluorinated analogs of (±)-yanglingmycin rac-77a–z, rac-78a–o and rac-79.77

Scheme 15  New catalytic protocol for synthesis of oxazolines from oxetanes.78
bond formation follows the intramolecular $S_{N}2$ mechanism and the oxygen of a hydroxamate intermediate attacks the $\beta$-carbon of the Thr-derived oxazoline leading to isoaxazolidinone formation. This $S_{N}2$ rearrangement reaction involves an inversion of configuration at the $\beta$-carbon of Thr side chain. Moreover, subsequent studies showed the dependence of rearrangement from oxazoline-containing form to isoaxazolidinone isomer on pH and temperature. Both isomeric forms are physiologically siderophores relevant for bacteria in processes of binding and cellular delivery of Fe(III).

Apart from acinetobactin, strains of human pathogenic A. baumannii may produce two other siderophores: baumannoin (a hydroxamate siderophore) and fimsbactin. Production of acinetobactin and baumannoin is highly conserved among clinical isolates while fimsbactin production appears to be less common. Fimsbactin is structurally related to acinetobactin because of the presence of the catechol and hydroxamate moieties together with an oxazoline ring; it possesses additionally oxazoline and 1,3- or 1,4-diaminopropane fragments.

Preacinetobactin and prepsudomonine consist of three significant structural subunits, responsible for metal chelation, namely catechol/phenol oxazoline, hydroxamate and imidazole fragments. The proposed synthetic routes for the formation of these siderophores are based on two condensations of key heterocyclic motifs, i.e. aryl oxazoline and imidazole part. The imidazole fragment was prepared in the same manner as described for anguibactin (Scheme 9). The synthesis of the second building block, aryl oxazoline moiety, was initiated with preparation of O-protected benzoic acid using p-toluenesulfonyl chloride and EWG blocking group in the aromatic part is not crucial for metal binding. Further modification shows that $N$-methylation of the imidazole ring in both $N^{1}$ and $N^{3}$ positions did not decrease the iron-binding tendency and $N^{3}$ position is a promising drug conjugation site because modifications at this site did not interfere with the iron delivery function. Additionally, all hydroxamate bridge modifications abolished iron delivery in the cellular uptake machinery. Wenewicz et al. prepared a rigid pre-acinetobactin analog via oxidation of oxazoline moiety to oxazole in order to block siderophore utilization in the pathogen growth process (Scheme 18). The strategy including rigid siderophore analogs preparation can be crucial in the synthesis of new antivirulence agents.

The stereoselective preparation of fimsbactins was proposed by Kim’s group. Their strategy for the synthesis was based on retrosynthetic analysis in which the framework construction was accomplished via amidation bond formation in condensation reaction of two building blocks, aryl oxazoline carboxylate and polyamine derivatives followed by catecholate part addition through ester formation (Fig. 13).

The preparation of the oxazoline carboxylates started from the coupling of $\alpha$-xyllyl-protected 3,4-dihydroxy benzoic acid with $\gamma$-Thre-amine methyl ester with protected acid using coupling reagents (EDC/HOBt, TBTU) and Ishihara’s dehydrative cyclization using Mo(VI) oxide catalyst followed by mild saponification using potassium trimethylsilylanolate which afforded the desired products in good yields (Scheme 19, part A). The synthesis of functionalized polyamine building blocks was accomplished by amidation bond formation between putrescine or N-monooacyl-1,3-propanediamine derivatives and $N,O$-protected $\gamma$- or $\delta$-serine via EDCl/HOBt coupling reagents (Scheme 19, part B). After derivatization of functional groups and a subsequent global deprotection, fimsbactins and derivatives were obtained in 12–22% total yield (Scheme 20).

2.2.3 Polyamine based siderophores. Three significant structural features of polyamine based aryl oxazoline chelators are of importance: the type of polyamine backbone, chelator donor groups, and the symmetry. The oxazoline ligands

Scheme 16 Structures of isomeric siderophores produced by A. baumannii and P. fluorescens. Potential iron chelating motifs are highlighted using blue background.
Scheme 17  The synthesis of preacinetobactin 86a and analogs 86b–h.66

Scheme 18  The synthesis of oxidized preacinetobactin.91
Scheme 19  Syntheses of the (A) aryloxazoline carboxylates 85a, ent-85a and 92; (B) polyamine 95a, 95b and ent-95b fragments.\textsuperscript{92,93}
possessing the spermidine moiety are represented by compounds like parabactin, agrobactin, norspermidine based – fluvibactin, vibriobactin and vulnibactin, and 1,3-diaminopropane based – serratiochelin A.

For the first time parabactin was isolated in 1975 by Tait from *Paracoccus denitrificans*. In the first approach the structure of parabactin was not well defined, because of the unstable nature of oxazoline ring. Several years later, Neilands and co-workers demonstrated that not an N-(2-hydroxybenzoyl)-L-threonyl fragment (parabactin A) but rather a (2-hydroxyphenyl)-4-carboxyl-5-methyl-2-oxazoline moiety is connected to the central nitrogen atom of the spermidine backbone in the original siderophore. Under the acidic conditions of Tait’s isolation, the oxazoline ring was opened to the threonyl derivative (acid labile oxazoline ring). Moreover, Neilands’ group showed that the hydrogen atoms of the oxazoline ring were trans to each other (Scheme 21).99

Agrobactin was isolated from iron-deficient cultures of *Agrobacterium tumefaciens*, the organism known to induce crown-gall in higher plants. *A. tumefaciens* not only produces a cancer-causing plasmid but is also interesting as a vector for incorporating foreign DNA into plants.100 Exposure of agrobactin to acid opened the oxazoline ring giving agrobactin A, in which the UV spectra undergo a characteristic redshift, same like in the case of parabactin.99

Fluvibactin was isolated and purified from *Vibrio fluvialis* in 1993. It contains only one catechol-oxazoline unit and is structurally related to agrobactin from which it differs only in its

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Scheme 20  Syntheses of fimsbactin A 97, B 99 and their stereoisomers92,93

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A stereochemically modified version of fluviibactin efficiently removed iron without increasing microbial growth.102

Vibriobactin (produced by *Vibrio cholerae*) is structurally highly similar to agrobactin with three minor alterations: (i) the polyamine backbone is norspermidine, (ii) it contains two L-threonines per molecule, forming two oxazoline rings, and (iii) it contains three DHB moieties as aryl caps. The discovery of the second oxazole ring in vibriobactin suggested some interesting possibilities in its metal-binding capacity.103 Although *V. cholerae* can use heme directly as an iron source, it has been shown that vibriobactin is also an important virulence factor.104

Vulnibactin, which was isolated from culture supernatants of *Vibrio vulnificus* M-2799 grown in a low-iron medium, is possessing two salicylate caps that are tethered to the oxazoline ring.105 Virulent *Vibrio vulnificus* is a halophilic estuarine bacterium that causes fatal septicemia and necrotizing wound infections in humans with high serum iron levels and vulnibactin enables it to acquire iron from highly iron saturated host proteins.106 Vulnibactin is structurally related to vibriobactin, from which it differs only in its salicyloyl moieties on two oxazoline rings, while fluviibactin contains only one oxazoline ring consisting of L-threonine and 2,3-dihydroxybenzoic acid attached to the central nitrogen of norspermidine.105

Serratiochelin A was isolated from *Serratia* sp. V4 and discovered in *S. marcescens* in 1974.107 Furthermore, in 2020 serratiochelin A was isolated from an iron-dependent co-culture of *Shewanella* sp. and the mechanism of its degradation to
serratiochelin C was proposed. Serratiochelins are bis-catecholate siderophores that could be tetra- or hexadentate, moreover, serratiochelin A and B contain a propane-1,3-diamine backbone.

So far total synthesis of six aryloxazoline iron chelators based on a polyamine backbone were described, namely the trisamines parabactin, agrobactin, \( \text{uvibactin}, \text{vibriobactin} \) and \( \text{vulnibactin} \), and the diamine – serratiochelin A. The pioneering works in polyamine-based siderophores synthesis and explorations were performed by Bergeron’s group. They proposed total syntheses of parabactin, agrobactin, \( \text{uvibactin}, \text{vibriobactin} \) and \( \text{vulnibactin} \). At the turn of years, this research field was supplemented by other scientists.

Based on performed research connected with structure exploration, in 1982 Bergeron’s group synthesized parabactin employing a stereospecific procedure under acid free conditions to preserve the oxazoline ring. A proposed synthesis employed \( N^1,N^8\)-bis(2,3-dimethoxybenzoyl) spermidine as a starting material, a unique reagent for the generation of spermidine phenolamides. In the first step, \( N\text{-Cbz-L-threonine} \) was condensed with \( N^1,N^8\)-bis(2,3-dimethoxybenzoyl)spermidine in the presence of coupling reagents such as NHS and DCC under basic conditions. Afterwards, both carbobenzoxy and methyl protecting groups were removed from threonylamide. In the last step, the most critical one, coupling of 2-hydroxybenzimidyl ethyl ester, obtained before in a Pinner reaction with the deprotected threonyl amide was involved. As a result of this synthetic route, parabactin was obtained in 18% total yield (Scheme 22).

Scheme 23  The synthesis of vulnibactin.

Scheme 24  The dehydration cyclization of \( N\text{-}(o,m\text{-dialkoxybenzoyl})\text{-L-threonine epi-84} \) via \( \text{MoO}_2\text{(TMHD)}_2 \).
Another synthetic route to parabactin 106 was proposed by Fujita in 1984. The researchers decided to attach the catechol moieties in the final step of the synthesis ("inside-out" approach) in contrast to Bergeron’s pathway. The key intermediates for parabactin formation were dihydro-1,3-oxazole derivative (obtained in 7 steps, 40% total yield) and N\textsubscript{1},N\textsubscript{10}, bis(benzyloxycarbonyl)-spermidine. In the final step, condensation of both intermediates and deprotection of terminal amine groups of the spermidine backbone followed by incorporation of the catechol fragment led to parabactin 106 in 5% total yield.

In the 1984 Bergeron’s group obtained another spermidine-based aryloxazoline chelator, agrobactin 107. Due to the structural similarity to parabactin, methodology was applied, with ethyl 2,3-dihydroxybenzimidate 105 (ref. 116) used in the stereospecific formation of the acid-sensitive trans-oxazoline ring subunit. The oxazoline-forming condensation between N-functionalized spermidine 100 and 2,3-dihydroxybenzimidate ester 105 afforded agrobactin 107 in 21% overall yield (Scheme 22).

The protocol for the synthesis of parabactin 106 (ref. 110) and agrobactin 107 (ref. 115) developed by Bergeron’s group was utilized for further synthesis of vibriobactin 124, fluviabactin 120 (ref. 118) and vulnibactin 113 (ref. 119) (shown for the latter in Scheme 23). All these siderophores contain the symmetrical spermidine analog, N-(3-aminopropyl)-1,3-diaminopropane (norspermidine) scaffold. The selective activation of norspermidine 108, its N-acylation with 2,3-dimethoxybenzoic acid 107 and then with the activated 1-threonine ester 111 was followed by threonyl fragment condensation with the ethyl imidate of mono- or dihydroxybenzoic acid 104 or 105. The target siderophores vibriobactin, fluviabactin and vulnibactin 113 were formed in 29%, 23%, 25% total yields, respectively.

A new concept of norspermidine based synthesis of oxazoline-containing siderophores was proposed by Ishihara and co-workers. The basis of this methodology lies in the oxazoline core construction at an early stage in total synthesis. Based on previously investigated approach for oxazoline and thiazoline rings formation such as Mo(\textit{V}) oxides, preparation of fluviabactin 120 and vibriobactin 124 was reported. In the synthesis, three building blocks were used: norspermidine 117, 2,3-dialkoxybenzoxa 116, and 2-(\textit{o},\textit{m}-dialkoxyphenyl)oxazoline 115 prepared from N-(\textit{o},\textit{m}-dialkoxybenzoyl)-\textit{l}-threonine \textit{epi}-82a via the Mo(\textit{V}) oxide catalyzed method. Dehydrative cyclization of N-(\textit{o},\textit{m}-dialkoxybenzoyl)-\textit{l}-threonine \textit{epi}-84a was performed using MoO\textsubscript{2}(TMHD\textsubscript{2}) (Scheme 24). Afterwards, a selective amide formation was conducted using Sb(\textit{m}) alkoxide-catalyzed amide transformation of primary amine groups in norspermidine 117. The amidation of the secondary amine group in products 118 and 122 was achieved using the respective carboxylic acid 115 and EDC, HOAt coupling reagents in the presence of base. In the course of this transformation fluviabactin 120 and vibriobactin 124 were obtained in overall yields of 65% and 50%, respectively (Scheme 25). This improved methodology eliminates the most inefficient step in the Bergeron methodology involving 2,3-dihydroxybenzimidate formation for oxazoline scaffold construction.

The most recent synthesis of fluviabactin 120 and vibriobactin 124 was described in 2013 by Raymond’s group. In their approach, 2-mercaptothiazoline was used to prepare a building block necessary to install the catechol-amide units in all siderophores. The 1,3-thiazolodine-2-thione functionality reacted with the primary amine group in norspermidine 117 in a very selective way. The central amine group in norspermidine 117 due to low reactivity was functionalized using HATU as a coupling reagent followed by benzyloxycarbonyl-N-Cbz-L-threonine treatment. In the final step, a catechol-oxazoline building block obtained via Bergeron’s methodology\cite{110,115} was used leading to the desired siderophores in total yields of 20% (compound 120) and 15% (compound 124).

In the group of synthesized polyamine siderophores, equipped with oxazoline moieties, serratiochelin A 129 was achieved using the respective carboxylic acid 115 and EDC, HOAt coupling reagents in the presence of base. In the course of this transformation fluviabactin 120 and vibriobactin 124 were obtained in overall yields of 65% and 50%, respectively (Scheme 25). This improved methodology eliminates the most inefficient step in the Bergeron methodology involving 2,3-dihydroxybenzimidate formation for oxazoline scaffold construction.
containing the 1,3-diaminopropane chain is also found. The synthetic route reported by Ehlert et al. for serratiochelin A129 was based on Bergeron’s procedure described for agrobactin. In the initial stage, the catechol-amide fragment of 126 was formed through N-(3-aminopropyl)benzylamide coupling with 2,3-dimethoxybenzoic acid. Subsequently, benzyl protection from the terminal amine group was removed, followed by N-(L-N-t-butoxycarbonylthreonyloxy) succinimide incorporation. At the end all protecting groups were removed and the oxazoline core was formed using ethyl imidate of 2,3-dihydroxybenzoic acid in total yield 10% (8 steps) (Scheme 26).

Many research groups have been interested in the synthesis of analogs of naturally occurring polyamine-based siderophores. The main goal for this trend is to investigate the relationship between structure and iron transporting ability. Moreover, there is an increased interest in developing new antibiotic treatments by linking antibiotics to siderophore moieties (Trojan horse strategy). Many efforts were put into the structural modifications of spermidine-containing catehol-type siderophore, parabactin and its natural analog agrobactin. All modifications of these siderophores had to be performed in such a way as to preserve the ability for iron binding and microbial growth under conditions of limited iron access. The aryloxazoline part directly linked to the central

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**Scheme 26** The synthetic route for serratiochelin 129 synthesis.107

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**Fig. 14** Examples of parabactin analogs 130a–p.124,125
amino group in the polyamine chain was mainly modified (Fig. 14). The performed research showed that the original structure of polyamine siderophore is still favoured as compared to analogs in coordination and iron transport system study.

In the previously cited work of Bergeron et al. on the synthesis of D-fluvibactin 120, the synthesis of unnatural enantiomer α-fluvibactin ent-120 and L-homofluvibactin 145 were also presented (Scheme 27). This research revealed that modifications of the polyamine chain of the fluvibactin 120 (L-homofluvibactin 145) do not affect bacterial growth and iron uptake machinery of P. denitrificans. However, an inversion of the configuration of two carbon atoms in the oxazoline ring (α-fluvibactin, ent-120) inhibits microbial growth. D-Fluvibactin ent-120 still functions as deferration agent with iron clearing efficiency similar to L-fluvibactin 120, but due to the stereochemistry of the created ferric complex it cannot be utilized by the microorganisms.

### 2.2.4 Mycobactin-type siderophores.
Mycobacterium tuberculosis, a species responsible for tuberculosis, serves as a source of siderophores that play a crucial role in the pathogenesis of the disease. These siderophores are produced by the bacteria to scavenge iron from the host environment, which is essential for bacterial growth and survival. The mycobactin-type siderophores exhibit high affinity for iron(III) ions and are capable of transport across the bacterial membrane. They can be classified into two main groups: mycobactins and mycobactin derivatives.

![Scheme 27](image)

**Scheme 27** Synthesis of L-fluvibactin 120 and its unnatural analogs.

![Fig. 15](image)

**Fig. 15** A general structure of mycobactin type siderophores. Fragments engaged in iron coordination marked blue, amide and ester linkages shown in red. Possible chiral centres indicated by asterisks.
of various lipopeptidic siderophores called mycobactins.\textsuperscript{126} Also strains of genus \textit{Nocardia} produce similar lipid-soluble intracellular iron-binding compounds (nocobactins, formylobactins, brasilibactins, amamistatins and others).\textsuperscript{127} Their common features include the presence of two amide and one ester connections, a seven-membered caprolactam ring at one end, and 2-aryloxazole or 2-aryloxazoline at the opposite end (Fig. 15).

The mycobactins are now quite well-known siderophores since mycobactin P was first isolated from \textit{Mycobacterium phlei} in 1949.\textsuperscript{128} Due to the position of the hydrophobic alkyl tail (R\textsubscript{5} or R\textsubscript{6}), mycobactins are classified into two types: P-type (after mycobactin P) or M-type (after mycobactin M), respectively.\textsuperscript{129} Mycobactin J is one of the P-type mycobactins and is produced by \textit{M. avium} ssp. \textit{paratuberculosis} which is the causative agent of Johne’s disease in cattle.\textsuperscript{130} The carboxymycobactins are structurally related to the mycobactins except that their R\textsubscript{5} or R\textsubscript{6} alkyl side chain (Fig. 15) is shorter and terminates in a carboxylic acid, resulting in much greater hydrophilicity.\textsuperscript{131} Pathogenic mycobacteria strains like \textit{M. tuberculosis} and \textit{M. bovis} express carboxymycobactins as the sole extracellular siderophores.\textsuperscript{132,133}

Nocobactins NA1 and NA2 were isolated from \textit{Nocardia asteroides} grown under conditions of iron deficiency. They are related in their structure to the mycobactins what was described by Ratledge and Snow in 1974.\textsuperscript{134} Amamistatin B (isolated from the actinomycete \textit{Nocardia – Nocardia asteroides})\textsuperscript{135} is also structurally related to mycobactins siderophore as it contains lysine-derived \textit{N}-formyl hydroxylamine. Amamistatin A has anti-proliferative, but not cell-killing, effects against several kinds of human tumor cell lines.\textsuperscript{135} Amamistatin’s anti-cancer activity is probably due to histone deacetylase enzymes inhibition mediated by the \textit{N}-formyl hydroxylamine ligand.\textsuperscript{136} Brasilibactin A, a siderophore found in \textit{Nocardia brasilienis}\textsuperscript{137} contains oxazoline moiety and a pentadecyl substituent. Brasilibactin A is a membrane-bound siderophore with structural similarity to the mycobactin class of siderophore in mycobacteria and possesses a nearly identical molecular nucleus, which includes a hydroxamic acid, an \textit{N}-hydroxyformamide, and a 2-(2-hydroxyphenyl)-\textit{Δ}²-1,3-oxazoline.\textsuperscript{138} Nocardichelins A and B were isolated from the \textit{Nocardia} sp. \textit{Acta} 3026 and the structural characterization of the compounds was performed by mass spectrometry and NMR spectroscopy. The chemical structures of these siderophores are closely related to mycobactin siderophores. In contrast, comparison of nocardichelins A and B to brasilibactin A reveals that only the 4,5-dihydro-2-(2-hydroxyphenyl)-4-oxazolecarboxylic acid moiety is identical.\textsuperscript{139}

Scheme 28 Preparation of oxazoline derivative 148 as a part of synthesis of mycobactin S.\textsuperscript{143}

Scheme 29 The use of \textit{l}-lysine for the preparation of two building blocks 150, and cobactin T 153 in mycobactin S synthesis.\textsuperscript{145}
Scheme 31  Preparation of amamistatin B 164 by Miller and co-workers.\textsuperscript{127}
Nocardimicins A, B, C, D, E and F members of the family of siderophores isolated from *Nocardia* sp. TP-A0674 (ref. 140) bear an undecyl chain and oxazole moiety. Nocardimicins are the first example of siderophores that have demonstrated inhibition activity to the muscarinic M3 receptor.\(^{140}\) Nocardimicins G, H and I were isolated from *Nocardia nova* JCM 6044 and their chemical structures were determined by spectroscopic analysis using NMR and MS.\(^{141}\)

First preparations of mycobactin type siderophores were described by Miller and coworkers.\(^ {142,143}\) They prepared mycobactin S2, an analog of mycobactin S with a long alkyl chain of the mycobactin acid residue replaced by a methyl group.\(^ {142}\) However, the modification resulted in lowered lipid solubility which was found essential for the siderophore activity in mycobacteria.\(^ {143}\) A total synthesis of mycobactin S was thus designed using a similar strategy: coupling of cobactin T and mycobactic acid derivative, *i.e.* two compounds formed in the
saponification process of mycobactins. The first component was prepared from two building blocks, one containing 2-aryloxazoline residue which was constructed from methyl salicylate and L-serine benzyl ester, using Burgess’ reagent to induce cyclization (Scheme 28). It was connected with L-lysine derivative containing hydroxamic acid moiety and a pentadecane chain (Schemes 29 and 30). Cobactin T component was also based on the blocked L-lysine as a starting material, converted to the corresponding hydroxylamine which underwent cyclization to yield a seven-membered ring (caprolactam derivative) with a preserved configuration of a stereogenic centre. Coupling with (R)-3-hydroxybutanoic acid and deprotection gave cobactin T (Scheme 30). Its reaction with mycobactic acid followed by treatment with TFA afforded mycobactin S (27% yield of the last stages). As it could be seen, L-amino acids and 3-hydroxybutanoic acid were used as sources of chirality.

Eleven years later, Miller’s group accomplished the synthesis of amamistatin B, one of siderophores isolated from a strain of Nocardia. Using methods previously developed in Miller’s laboratory, they prepared 2-aryl-oxazole and L-lysine-derived hydroxamic acid; a third component, (S)-3-hydroxy-2,2-dimethyldecanoic acid was also obtained following the procedure introduced by Yokokawa et al. The last building block, a cyclic hydroxamic acid, was synthesized by a modified route from Cbz-L-lysine in 19% overall yield (Scheme 31); its configuration was preserved in the caprolactam derivative formed in the cyclization step. This component was then reacted with hydroxydecanoic acid, and the product esterified using a linear hydroxamate. Two enantiomers of the latter were used (one is shown in Scheme 31), which allowed preparation (after deprotection and reaction with oxazole part) of amamistatin B and its epimer. A similar protocol was applied in the synthesis of an analog lacking two hydroxyl groups, however, only the original siderophore was (moderately) active against M. tuberculosis.

A similar synthetic approach was used earlier by Yokokawa, Shioiri, and co-workers who prepared amamistatin A, which differs only by the presence of a methoxy substituent from B form. In the paper describing the synthesis, a stereoselective
preparation of \((S)-3\text{-hydroxy-2,2-dimethyldecanoic acid}\) \(158\) was presented utilizing aldol reaction of octanal \(166\) and methyl trimethylsilyl dimethylketene acetal \(165\) in the presence of stoichiometric amounts of a chiral oxazaborolidinone \(167\) obtained from \(\delta\)-valine; hydrolysis of the resulting ester \(168\) afforded the desired acid \(158\) in 50% overall yield (Scheme 32). The oxazole component \(171\) was prepared starting from 5-methoxysalicylic acid \(169\), and ring closure of \(170\) was achieved through a Wipf’s variant of Robinson–Gabriel synthesis (oxidation with Dess–Martin reagent followed by dehydration of the intermediate ketoamides, Scheme 32). Amamistatin A \(175\) was constructed by a stepwise addition of subsequent building blocks to the caprolactam derivative \(152\) (Scheme 33; this compound \(152\) and a linear hydroxamate \(173\) were prepared by previously described methods\(^{143}\)), and the overall yield of the seven steps was ca. 7.5% (part of the unreacted intermediates, however, could be recovered).

Among other compounds from the mycobactin family, a total synthesis of J form \(191\) was described by Kapur and co-workers in 2018.\(^{145}\) The specific component of this compound,
a long-chain carboxylic acid **178** with a double C=C bond with (Z) configuration, was prepared in 48% overall yield via oxidation of 1-tetradecanol **176** to tetradecanal, its Corey–Fuchs conversion to alkyne, its esterification with chloroformate, and hydrolysis (Scheme 34). Thus obtained acid **177** with a carbon–carbon triple bond was stereospecifically hydrogenated over Lindlar catalyst to give (Z)-pentadec-2-enoic acid **178**. It was attached to a mycobactenic acid fragment which in turn was constructed from salicylic acid **179**, L-threonine methyl ester, and a fragment derived from Cbz-L-lysine **184**; oxazoline **181** formation was achieved by molybdate-mediated cyclization with a retention of configuration (Schemes 35 and 36). The second synthon also required L-lysine which was converted to a cyclic amide using HATU; coupling with (2S,3R)-3-hydroxy-2-methylpentanoic acid **189** (a source of two stereogenic centres in the final molecule) resulted in the cobactin fragment **190**. However, in contrast to Miller’s preparations,142,143 the attempts of esterification to yield mycobactin J were unsuccessful.

Scheme 38  Solid-phase synthesis of carboxymycobactin T **203**.

Scheme 39  Preparation of two diastereomers of hydroxyacid-caparolactam part of brasilibactin A **208**.
Instead, a chiral pentanoic acid derivative 189 was first connected to mycobactic acid 188, and a cyclic hydroxamic acid 186 was added in a subsequent step yielding the desired final product 191 (21% yield over three steps).

Carboxymycobactin T 203 and its three analogs were prepared by Slomczynska and co-workers using a solid-phase approach. L-Norleucine 192 derivative was reacted with nosyl-activated hydroxylamine bound to Wang resin 194; PyAOP-induced cyclization afforded an immobilized

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**Scheme 40** Synthesis of brasilibactin 208 by Mitchell and Show.\(^\text{147}\)

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**Scheme 41** Preparation of four diastereomers of hydroxyacid part of brasilibactin A by Ying and Hong.\(^\text{138}\)
caprolactam derivative 197 (Scheme 37) to which subsequent fragments were connected (Scheme 38): (S)-3-hydroxybutyric acid 198, another L-norleucine-derived component 200, and 2-(2-hydroxyphenyl)oxazoline-4-carboxylic acid 181 which preparation was described by Miller’s group.143 To the obtained skeleton, a monomethyl ester of heptane-1,7-dioic acid 202 was attached as a side chain and the carboxymycobactin T 203 was removed from the resin. Its epimer with the opposite configuration of carbon atom bearing methyl group was prepared by the same route with (R)-3-hydroxybutyric acid ent-198 as one of components; in case of two analogs bearing amide instead of ester linkage, separation of diastereomeric mixture appeared necessary due to unexpected epimerization.

In 2007, two research groups reported on a synthesis of brasilibactin A. In a paper of Mitchell and Shaw, preparation of two diastereomers differing in the configuration of the β-hydroxyacid component allowed the assignment of absolute configuration of the naturally occurring form.147 This fragment was prepared using the titanium-mediated aldol reaction of chiral thiazolidinethione auxiliary 204 with hexadecanal which led to syn products 205 and dia-205 with the absolute configuration dependent on the amount of (+)-sparteine added (45% yield and diastereomeric ratio >95:5 were noted in both cases, Scheme 39). Coupling with caprolactam-based amine 186 released the auxiliary and resulted in the respective diastereomeric products 206 and dia-206. Their subsequent reactions with the known building blocks derived from L-lysine 173 and, finally, oxazoline fragment 181 prepared from L-serine followed the previously reported procedures and led to brasilibactin A 208 (found to be a 17R,18S isomer; Scheme 40) and its (17S,18R)-analog. Independently, Ying and Hong prepared four diastereomers differing by configurations of these two stereocentres.138 The four hydroxyacid components 213, ent-213, dia-213 and did-213 were prepared by diastereoselective aldol reactions from N-propanoyloxazolidinones (syn isomers) and O-propanoylnorephedrines (anti selectivity, Scheme 41). The

Scheme 42  Preparation of three components 219, 224 and 229 of nocoardimicin B.148
The overall synthetic strategy was similar to the one of Mitchell and Shaw, and the stereochemical assignment of natural brasiliactin A was identical.

Banks and Moody prepared nocardimicin B from four usual components, though they modified the synthesis of particular building blocks. The 2-aryloxazole part was obtained by rhodium-catalyzed reaction of 2-benzoyl-2-benzonitrile with dimethyl diazomalonate; removal of the methoxy group and hydrolysis gave the 2-aryloxazole-4-carboxylic acid in 67% yield (Scheme 42). The linear hydroxamic acid component was prepared by a previously established method, while for the α-hydroxycarboxylic acid, an anti-selective aldol reaction was applied between a lactate-derived ketone and dodecanal under Patterson conditions. Standard four-step manipulation provided the desired hydroxyacid in 25% overall yield. The cyclic hydroxamic acid was prepared using ring-closing metathesis (RCM) as a key step. -Benzyl-N-Boc-hydroxylamine was converted into N-allyl derivative which in turn reacted with L-Boc-allylglycine to give the respective amide. RCM employing Grubbs’ catalyst yielded a seven-membered caprolactam derivative with a double bond (59% yield from hydroxylamine derivative, Scheme 42). Starting from this building block, all fragments were connected subsequently, and the final step involved a hydrogenative deprotection, but also reduction of the C=C bond, and yielded the expected siderophore (Scheme 43).

Concluding this part, siderophores containing an oxazole or oxazoline ring exhibit a significant similarity of four main chiral synthons which can be appropriately assembled. Part of these fragments inherit chirality of the starting amino acid residues, however, others are prepared in stereoselective reactions (for example, 3-hydroxycarboxylic acid in aldol reaction). Though a total synthesis of all known members of the family has not been accomplished yet (as exemplified by other mycobactins, nocardin, and formobactin), the general procedure for their preparation should not differ much from their analogs obtained in the laboratories.

3 Conclusions

In this comprehensive review we presented the total synthesis of naturally occurring siderophores bearing arylthiazoline and arylxanole subunits. During the years a development of synthetic strategies has been observed to find the optimal approach for synthons used for many siderophores. The progress of characterization techniques allowed to determine configurations of all stereogenic centres and to correctly describe all stereoisomers. The yield of the total synthesis and enantiomeric purity of prepared compounds have been greatly improved which is important from the application point of view. Amounts of siderophores required in biomedical studies are typically in the range of hundred milligrams, two orders of magnitude more than typically isolated from natural sources.

Conflicts of interest

There are no conflicts to declare.

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