Bacterial Siderophores Containing a Thiazoline Ring

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Abstract: Bacteria have adapted in environments where free iron is severely limited, secreting small iron chelating molecules. One group of these siderophores contains a thiazoline ring in its structure. These compounds isolated from bacteria will be presented and different aspects of their chemistry including synthesis will be presented.

Keywords: Siderophores, iron metabolism, thiazoline ring.

1. INTRODUCTION

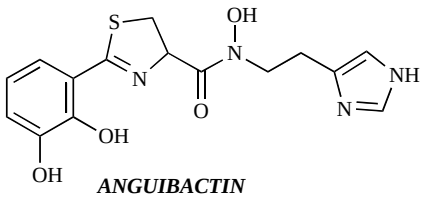
Iron is an essential element for nearly all living systems. However, iron is not a freely available nutrient but exists in the oxidized ferric form (Fe^{3+}) at neutral pH (around 7) under aerobic conditions and forms various insoluble minerals. In response to this deficiency of iron, the microorganisms produce iron-binding siderophores that bind iron and transport it into the cell.

2. SIDEROPHORES CONTAINING A THIAZOLINE RING

The siderophores that contain a thiazoline ring in their structure are: anguibactin (**1**), pyochelin (**2**), yersiniabactin (**3**) and desferrithiocin (**4**) (Fig. **1**).

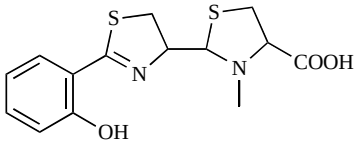
a. Anguibactin

Anguibactin (**1**), identified as ω-*N*-hydroxy-ω-*N*{[2´-(2´,3´-dihydroxyphenyl)-thiazolin-4´-yl]carboxyl} histamine, is a siderophore isolated from *Vibrio anguillarum* [8]. *Vibrio anguillarum*, a Gram-negative, polarly flagellated, comma-shaped rod bacterium, causes a highly fatal hemorrhagic septicemia in salmonids and other fish and has a highly efficient iron uptake system which allows it to survive in the iron-deficient host environment. The production and biological activity of anguibactin (**1**) and the virulence of the bacteria are linked to the presence of a 65 kb plasmid, designated pJM1, in the organism [9]. The biosynthesis of anguibactin (**1**) per se is, like that of other peptide-containing siderophores, via a nonribosomal peptide synthetase [10].



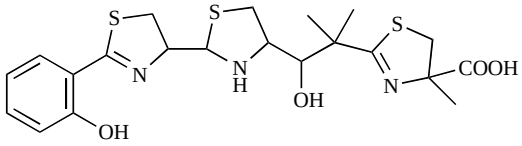
ANGUIBACTIN

1



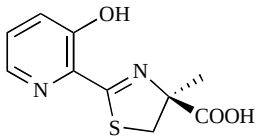
PYOCHELIN

2



YERSINIABACTIN

3



DESFERRITHIOCIN

4

Fig. (1). Structures of siderophores containing a thiazoline ring.

A siderophore (Greek for iron carrier) is a small iron chelating compound secreted by many but not all microorganisms. Thus, siderophores act as extracellular solubilizing agents for iron from minerals or organic compounds under conditions of iron limitation. There are three main types of iron coordinating functional groups in siderophores. First, there are the *N*-hydroxy amino acid side chains. Second, there are the adjacent hydroxyls of catechol rings. Third, the nitrogen atoms of five-membered thiazoline and oxazoline rings can also coordinate Fe^{3+}.

The study of different siderophores produced by microorganisms is extensive as it can be seen through the numerous reviews appeared about these compounds, that emphasize the genetics and microbiology of the many bacteria producing siderophores [1-7]. In this review we focus in the bacterial siderophores containing a thiazoline ring and different aspects of the chemistry of these compounds including their synthesis, will be presented. In some compounds their synthesis has not been reported.

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Anguibactin (**1**) ($C_{15}H_{16}N_4O_4S$) has a thiazoline ring attached to a catechol group and is composed of one molecule of 2,3-dihydroxybenzoic acid (DHBA), one of L-cysteine, and one of *N*-hydroxy-histamine [1].

The structure of anguibactin (**1**) was achieved determining the chemical and molecular structure of one of its closely related derivatives, anhydroanguibactin (**5**) by single-crystal X-ray diffraction (Fig. **2**) [11]. The molecular structure was confirmed by X-ray structure of anguibactin-gallium complex [1, 11]. Unfortunately there is not possible to find any synthesis of anguibactin (**1**).

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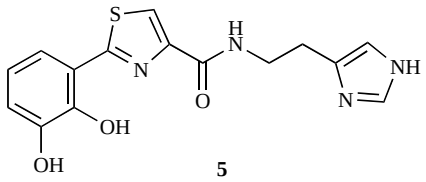

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Fig. (2). Structure of anhydroanguibactin.

b. Pyochelin

Pyochelin (**2**), identified as 2-[2-(*o*-hydroxyphenyl)-2-thiazolin-4-yl]-3-methyl-4-thiazolidinecarboxylic acid, is a siderophore isolated from *Pseudomonas aeruginosa* [12], although was shown to be produced by many strains of *Burkholderia cepacia* too [13]. *Pseudomonas aeruginosa*, is a nonfermentative, gram-negative rod considered highly pathogenic for individuals with compromised immunity. *Pseudomonas aeruginosa* is known to produce two siderophores, pyochelin (**2**) and pyoverdin. Recent reports have suggested that siderophores may be factors in the virulence of this organism. Pyochelin (**2**) was found to stimulate bacterial growth in murine infections. *P. aeruginosa* siderophores were found to be important factors in the interaction of the bacterium with transferrin, an iron-binding glycoprotein which is inhibitory to bacterial growth and is the major serum component responsible for nutritional immunity.

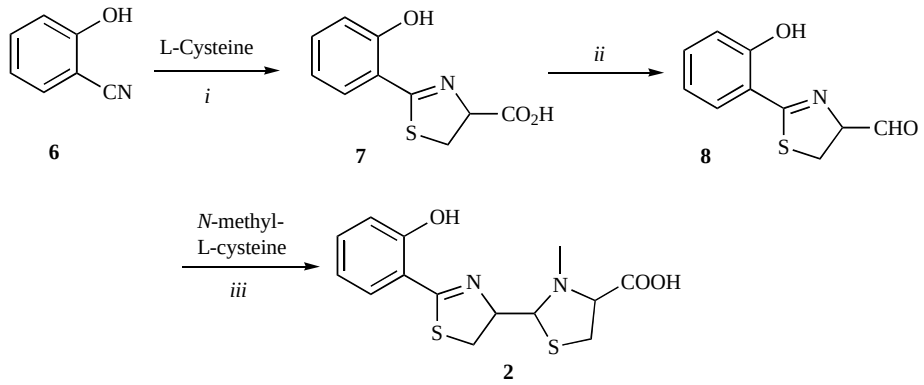
Pyochelin (**2**) is a phenolate siderophore [14, 15], in which the stoichiometry of iron binding appears to be two pyochelin molecules to one Fe(III) ion. When compared with other siderophores, pyochelin (**2**) has a very low iron-binding coefficient, 5 x 10^5. The probable reasons for this low coefficient are the iron-binding stoichiometry of two pyochelin molecules for one Fe(III) ion and the low molecular weight, 324, of pyochelin. Despite its low iron-binding coefficient, pyochelin (**2**) is extremely active in iron transport and growth stimulation in media containing transferrin and has been implicated in the pathogenicity of *P. aeruginosa*.

To investigate these contradictory phenomena, synthetic pyochelin (**2**) was made in a three-step procedure using reactions described in the literature, as shown in Scheme **1** [16].

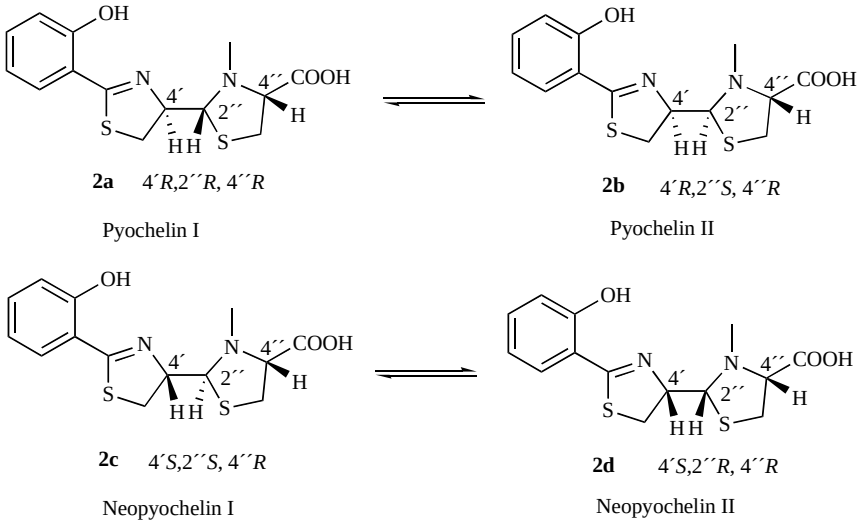
Carboxylic acid (**7**), was prepared from salicylonitrile (**6**) and L-cysteine in 92% yield [17]. Aldehyde (**8**), was obtained in 15% yield by thexylborane reduction [18] of carboxylic acid (**7**). The condensation of aldehyde (**8**) with L-*N*-Methylcysteine provided pyochelin (**2**) in 58% yield [19]. The synthetic pyochelin demonstrated chemical and biological activities identical to those of natural pyochelin [16].

An improvement in the yield of aldehyde (**8**), was obtained through a diisobutylaluminium hydride (DIBAL-H) reduction of the methyl ester of (**7**), followed by quenching with saturated solution of ammonium chloride [20]. Therefore, the overall yield of pyochelin synthesis was improved from 8% to 65% [21].

Natural pyochelin had initially been isolated from *P. aeruginosa* as a mixture of two stereoisomers, pyochelin I (**2a**) [4´*R*, 2´´*R*, 4´´*R*] and pyochelin II (**2b**) [4´*R*, 2´´*S*, 4´´*R*]. Their absolute con-



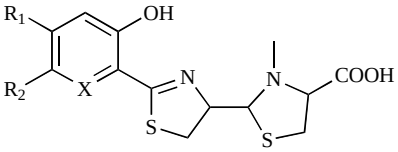
Scheme 1. Reagents and conditions. *i*) $NaHCO_3$, EtOH, reflux, 30 min; piperidine to pH 8.5, reflux, 12 h; *ii*) thexylborane in THF, -20 °C, 10 min; reflux, 40 h; *iii*) CH_3CO_2K, H_2O-EtOH (1:1), 25 °C, 1 h; 0 °C, 12 h.



Scheme 2. Stereostructures of the four isomers of pyochelin.

figurations were stabilized based on the similarity with the NMR spectra of 4-methylpyochelin I methyl ester whose X-ray structure had been determined. The epimer (**2b**) was formed as resulting from epimerization at the C-2´´ chiral center. On the other hand, the synthesis of pyochelin provided natural pyochelin I and II and two another stereoisomers, neopyochelin I (**2c**) [4´*S*, 2´´*S*, 4´´*R*] and neopyochelin II (**2d**) [4´*S*, 2´´*R*, 4´´*R*] in an overall 65% yield. Therefore, actually there are four stereoisomers of pyochelin, resulting from its synthesis, as shown in Scheme **2** [21].

These results show that to prepare enantiopure synthetic pyochelin is a difficult work. The synthesis of pyochelin analogues has been a hard challenge and initially the only access to analogues was through the mutasynthesis. Using this technique Ankenbauer *et al*. prepared three analogues of pyochelin: 5-fluoropyochelin (**9**), 4-methylpyochelin (**10**) and 6-azapyochelin **11** [22], (Fig. **3**).



9 $R_1 = H$ $R_2 = F$ X = CH
10 $R_1 = CH_3$ $R_2 = H$ X = CH
11 $R_1 = H$ $R_2 = H$ X = N

Fig. (3). Mutasynthetic pyochelin analogues.

With the intention to design a method for total synthesis of micacocidin, an antibiotic isolated from *Pseudomonas* sp., a new analogue of pyochelin was achieved [23]. Retrosynthetic analysis of micacocidin shows two segments A and B contained in its structure, as shown in Scheme **3**.

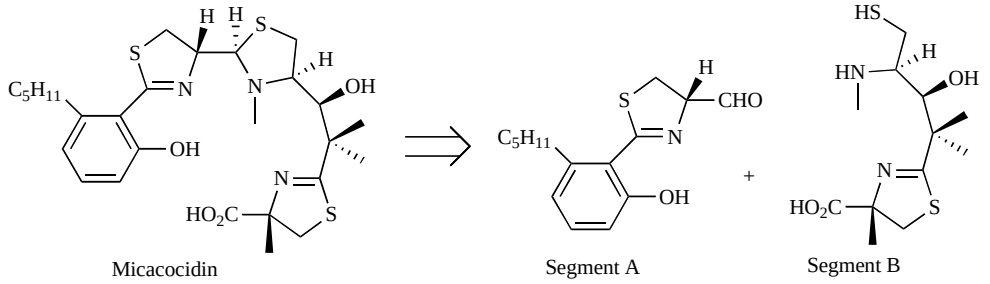
The synthesis of segment A was realized from the starting material (**12**) to give the thiazoline (**13**) in good yield preserving high enantiomerical purity (96% *ee*) and through various steps a 5-pentylpyochelin (**14**) was achieved, as shown in Scheme **4** [23].

Similarly Ino's group, realized the synthesis of yersiniabactin (**3**), which will be discussed in the next part. In the course of this synthesis they performed stereoselective synthesis of pyochelin I (**2a**) obtaining a mixture (5:1) of pyochelin I (**2a**) and neopyochelin II (**2d**) structures, in 76% yield, as shown in Scheme **5** [24].

Abdallah *et al*. introduced several modifications, as described in reagents and conditions, in the synthesis proposed by Ankenbauer [16] leading to an improved synthesis of pyochelin (**2**), as shown in Scheme **6** [25]. A mixture of four diastereoisomers of pyochelin was achieved in 70% yield.

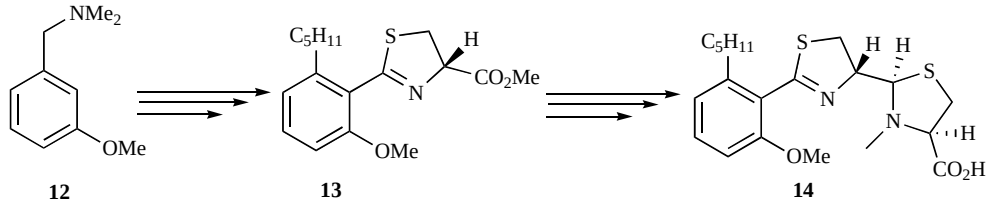
In order to measure iron transport rates of analogues bearing different functionalities in various positions, using this methodology, four analogues of pyochelin were synthesized: 3´´-nor-NH-pyochelin (**17a**), 3´´-*N*-Boc-pyochelin (**17b**), 5-*N*-Boc-pyochelin (**17c**), and neopyochelin II (**2d**), in 59%, 50%, 41% and 61% yield respectively and each of one was obtained as mixture of four diastereoisomers (Fig. **4**) [26]. The four analogues chelate iron (III) and transport it into the bacterial cells in similar way that does natural pyochelin.

The Weinreb amide (**7b**) was used as starting material to prepare new thiazole analogues of pyochelin (**19**) and (**20**), both in



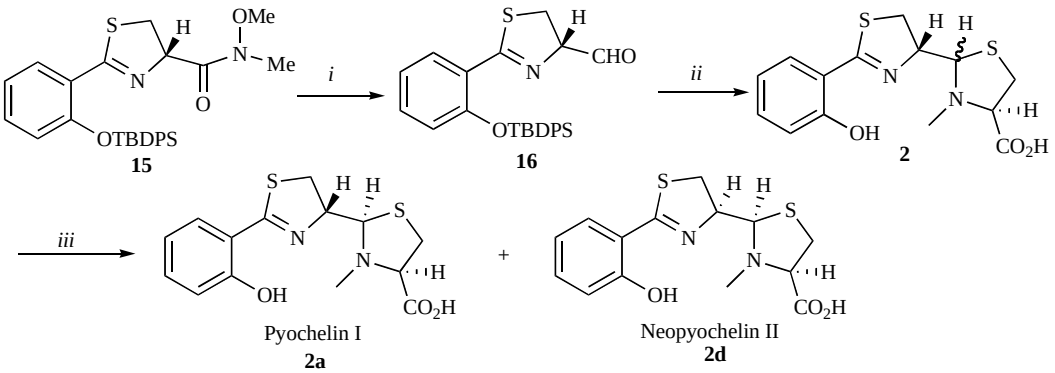
Micacocidin Segment A Segment B

Scheme 3. Retrosynthetic analysis of micacocidin.



12 **13** **14**

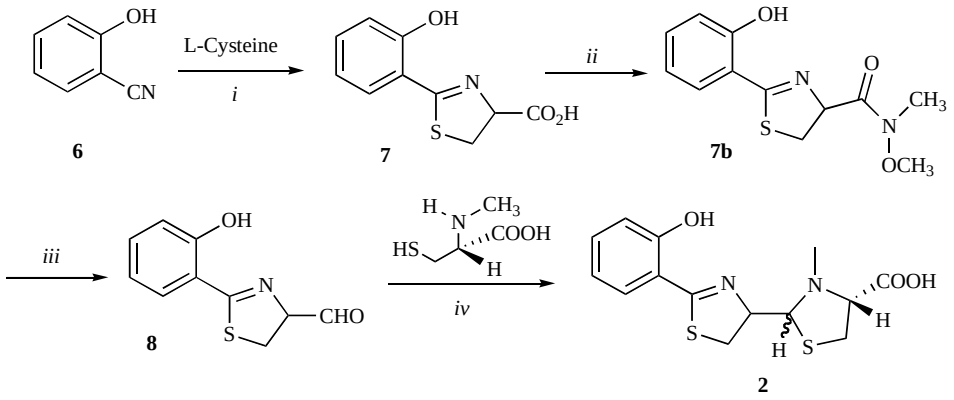
Scheme 4. Synthesis of 5-pentylpyochelin (**14**).



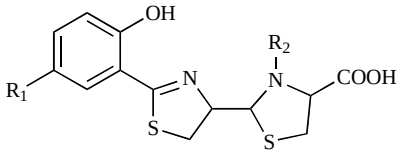
15 **16** **2**

Pyochelin I **2a** Neopyochelin II **2d**

Scheme 5. Reagents and conditions. *i*) $LiAlH_4$, 0 °C 30 min; *ii*) N-Me-L-cysteine-HCl, CH_3COOK, r.t., overnight, TBAF, r.t. 30 min; *iii*) $ZnCl_2$, H_3O^+.



Scheme 6. *i*) Phosphate buffer, 0.1M pH 6.4/MeOH 1:1, 50 °C, 4 days; *ii*) DECP/DMF, MeNH-OMeHCl/TEA; *iii*) LAH (3 equiv.) in THF at -20 °C for 20 min; *iv*) CH_3COOK, $EtOH/H_2O$ 4:1.



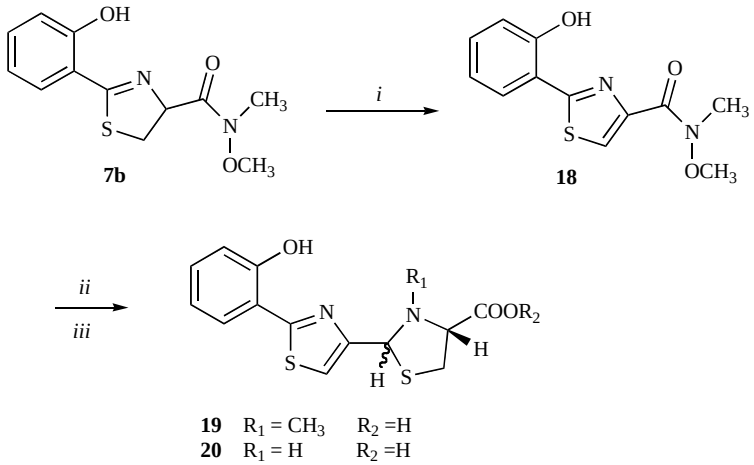
2d R_1 = H R_2 = CH_3
17a R_1 = H R_2 = H
17b R_1 = H R_2 = Boc
17c R_1 = NHBoc R_2 = CH_3

Fig. (4). Pyochelin analogues.

90% yield and as a mixture of two diastereoisomers in equimolar proportion, as shown in Scheme **7** [27].

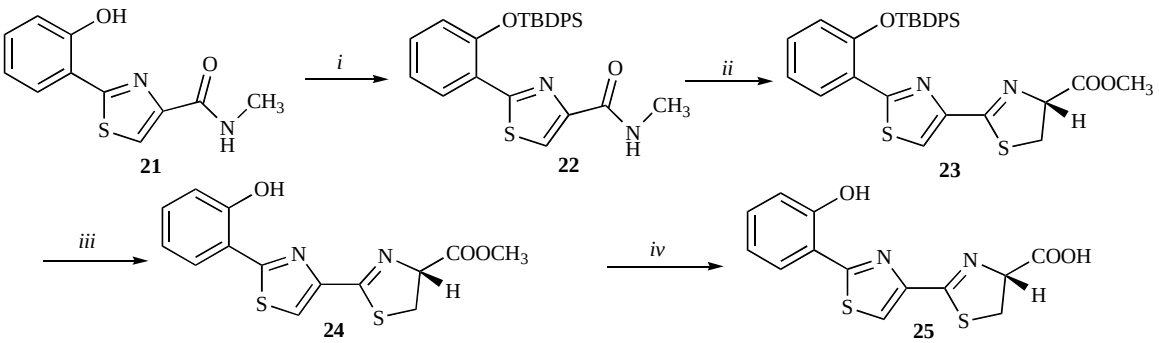
They report a new conversion procedure of thiazolines into thiazoles which applied to the synthesis of (**25**) as shown in Scheme **8**. This compound (**25**), achieved in 91% yield, is a thiazolic analogue of pyochelin, called HPTT-COOH, that was previously isolated and described as an oxidized form of an hydrolytic intermediate in the nonribosomal biosynthesis of pyochelin (**2**) and yersiniabactin (**3**), [27].

Some antibiotics have been coupled to siderophores and transported across the bacterial membranes via the iron uptake pathways [6]. In view of the use of pyochelin as versatile antibiotic vector, it was functionalized in order to be further connected to the selected antibiotics. The synthesis of three analogues was carried out starting from amino substituted 2-hydroxybenzonitriles (**26**-**28**), which were converted into the thiazolines (**29**-**31**), when treated with *R*-

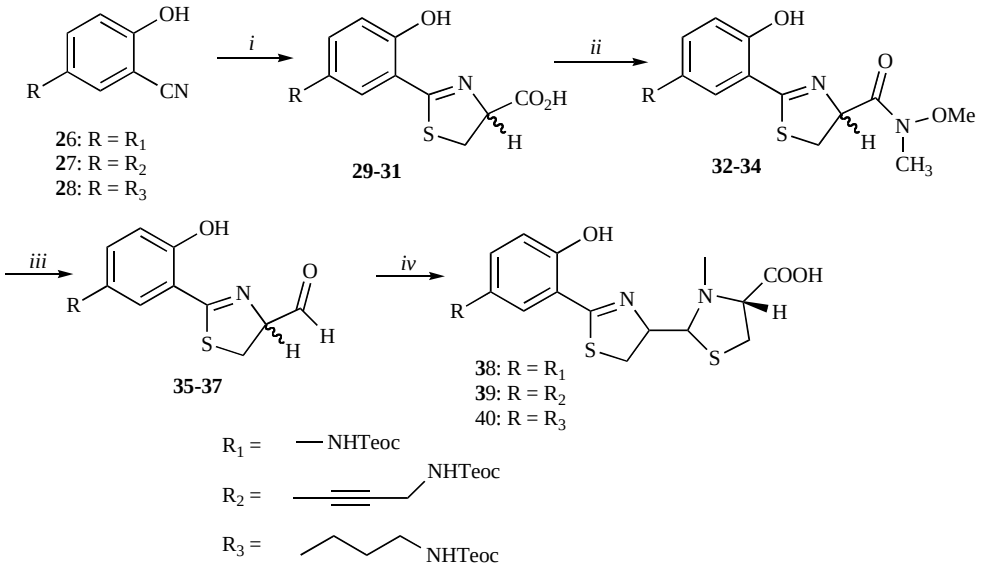


19 R_1 = CH_3 R_2 = H
20 R_1 = H R_2 = H

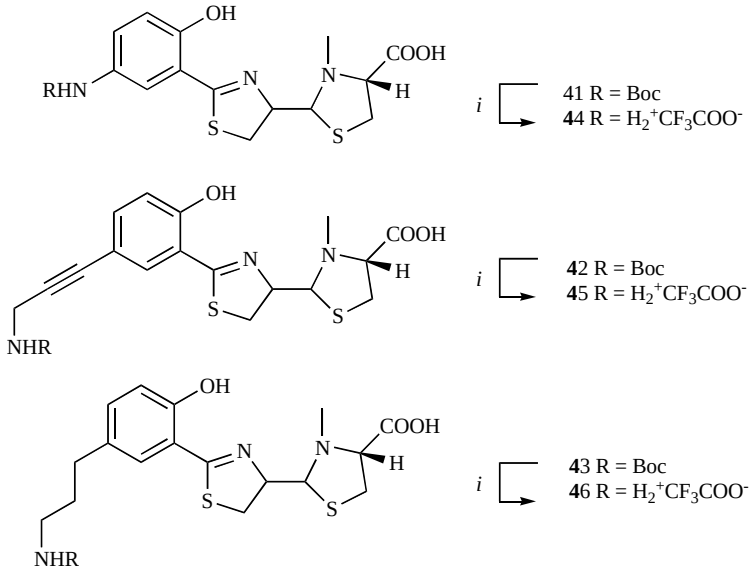
Scheme 7. *i*) DBU, $CBrCl_3$, CH_2Cl_2, 20 °C; *ii*) $LiAlH_4$, THF, -40 to -20 °C; *iii*) (*R*)-cysteine or (*R*)-N-methylcysteine·HCl, AcOK, $EtOH/H_2O$, 20 °C.



Scheme 8. *i*) TBDPSCl, NEt_3, CH_2Cl_2, 20 °C; *ii*) (a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, -30 to 20 °C. (b) *O*-methylcysteine·HCl, pyridine, -30 to 20 °C; *iii*) TBAF, THF, 20 °C; *iv*) $LiOH·H_2O$, THF/H_2O, 25 °C.



Scheme 9. *i*) *R*-cysteine, phosphate buffer 0.1 M, pH 6.4, MeOH, 60 °C; *ii*) $CH_3NHOCH_3 \cdot HCl$, DIPEA, EDCI, CH_2Cl_2, 0-20 °C; *iii*) $LiAlH_4$, THF, -40 °C to -10 °C; *iv*) *R-N*-methylcysteine·HCl, AcOK, EtOH/H_2O, 20 °C.



Scheme 10. *i*) TFA, CH_2Cl_2, 20 °C.

cysteine. Thiazolines were used to synthesize the corresponding Weinreb amides (**32**-**34**). The Weinreb amides were then reduced to the corresponding aldehydes (**35**-**37**). Condensation of these aldehydes with *N*-methylcysteine furnished the expected functionalized pyochelins (**38**), (**39**) and (**40**) in 72%, 75% and 65% yield respectively over the last two steps, and each of one as a mixture of four diastereoisomers, as shown in Scheme **9** [28].

To connect the synthetic pyochelins to an antibiotic fitted with a spacer arm, the next step was thus the deprotection of the three pyochelin analogues (**38**-**40**). Unfortunately, the Teoc group removal was unsuccessful and three new pyochelin analogues (**41**-**43**) had to be synthesized with a new protecting group (Boc) which removal was much easier to produce the corresponding ammonium salts (**44**-**46**), as shown in Scheme **10** [29]. The compounds (**45**) and (**46**) were coupled to norfloxacin antibiotic, a fluoroquinolone active against *P. aeruginosa* [29]. The preliminary biological tests against a wild-type strain of *Pseudomonas aeruginosa* show a bactericidal activity for two of these four conjugates. It was not possible to isolate the conjugates derived from the pyochelin analogue (**44**).

Recently some studies about the coordination of the Fe(III) complexes of pyochelin were carried out, demonstrating that the coordination in the case of the 2:1 complexes of pyochelin-Fe(III) was asymmetrical, with one molecule of pyochelin tetradentately coordinated (O1, N1, N2 and O3) to the Fe(III), and the second molecule bound bidentately (O1, N1 or N2, O3), to complete the octahedral geometry, (Fig. **5**) [30].

c. Yersiniabactin

Yersiniabactin (or yersiniophore redundantly called) (**3**) is a siderophore that was initially isolated from *Yersinia* spp. in 1975 [31], as a virulence factor during iron starvation, and was confirmed by other groups [32-34]. The *Yersinia* spp. includes *Yersinia pestis* the agent of bubonic plague and *Y. enterocolitica* that causes a

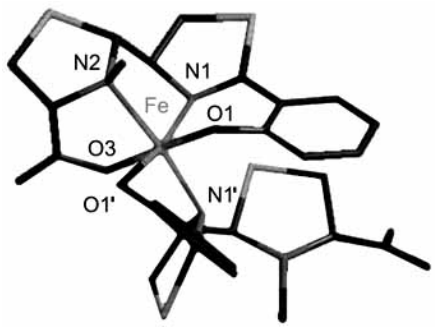


Fig. (5). Stick presentation view of the most stable pyochelin–Fe (III) model, reported by Tseng *et al.* [30].

broad range of diseases ranging from acute bowel disease to extraintestinal manifestations such as reactive arthritis and uveitis.

coordinated as a 1:1 complex by three nitrogen electron pairs and three negatively charged oxygen atoms with a distorted octahedral coordination, (Fig. **7**) [41].

d. Desferrithiocin

Desferrithiocin (**4**), identified as 2-(3-hydroxypiridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxylic acid, is a siderophore isolated from *Streptomyces antibioticus* in 1980 [42]. It forms 2 to 1 complexes with iron-(III) using the thiazoline nitrogen, the phenol oxygen, and a carboxylate oxygen as donor sites [43].

Iron accumulation eventually produces many diseases and treatment with a chelating agent capable of sequestering iron and permitting its excretion from the body is then the only therapeutic approach available. One of these chelating agents that are now in use is desferrithiocin.

Desferrithiocin was found to be orally active compound. The desferrithiocin aromatic hydroxyl and the thiazoline ring carboxyl

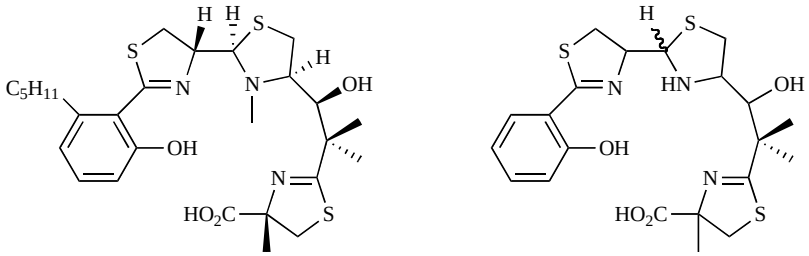
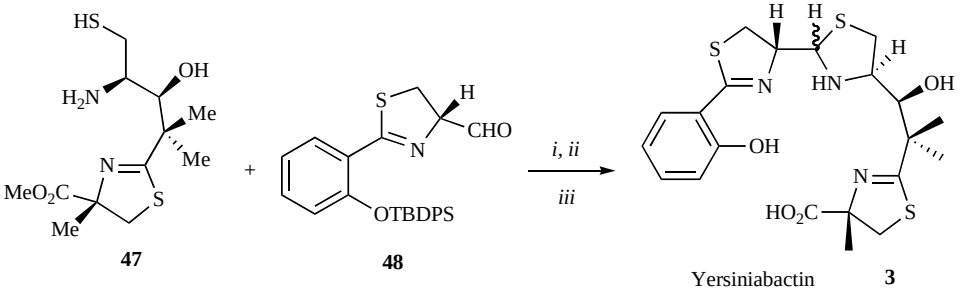


Fig. (6). Structures of micacocidin and yersiniabactin.



Scheme 11. *i*) AcOK, CH_2Cl_2, r.t. for 18 h; *ii*) TBAF, r.t. for 20 min; *iii*) $LiOH.H_2O$, r.t. for 2.5 h.

The structure of yersiniabactin (**3**) was determined independently by two groups [35, 36] and contains a phenolic group (derived from salicylate) and three five-membered heterocycles of the thiazole group (derived from cysteine), two at the dihydro oxidation state (thiazoline) and one at the tetrahydro oxidation state (thiazolidine), as potential high-affinity iron ligands. Many studies have been carried out about the biosynthesis and the genes involved in this [37-40] but in this review we are focused in some chemical and synthetic aspects of this siderophore.

As it has been described above, Ino's group [24] achieved a synthesis of yersiniabactin (**3**), due to its similarity with micacocidin structure, which they were synthesizing (Fig. **6**).

For the synthesis of yersiniabactin (**3**), condensation of two segments, which were synthesized in different steps, was achieved. Condensation reaction of (**47**) with (**48**) gave yersiniabactin methyl ester in 43% yield and after alkaline hydrolysis afforded (**3**) as mixture of two diastereomers, as shown in Scheme **11** [24].

Recently yersiniabactin (**3**), has been crystallized in the ferric complex form. The crystal structure showed that the ferric ion was

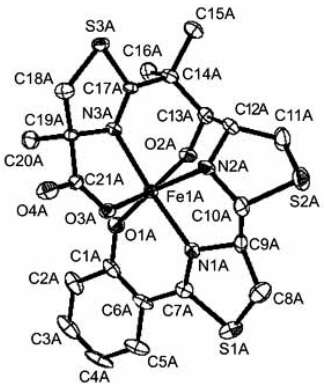


Fig. (7). Crystal structure of ferric-yersiniabactin complex.

group were shown to be central to desferrithiocin's activity. The ligand's methyl and the aromatic nitrogen played little role in the

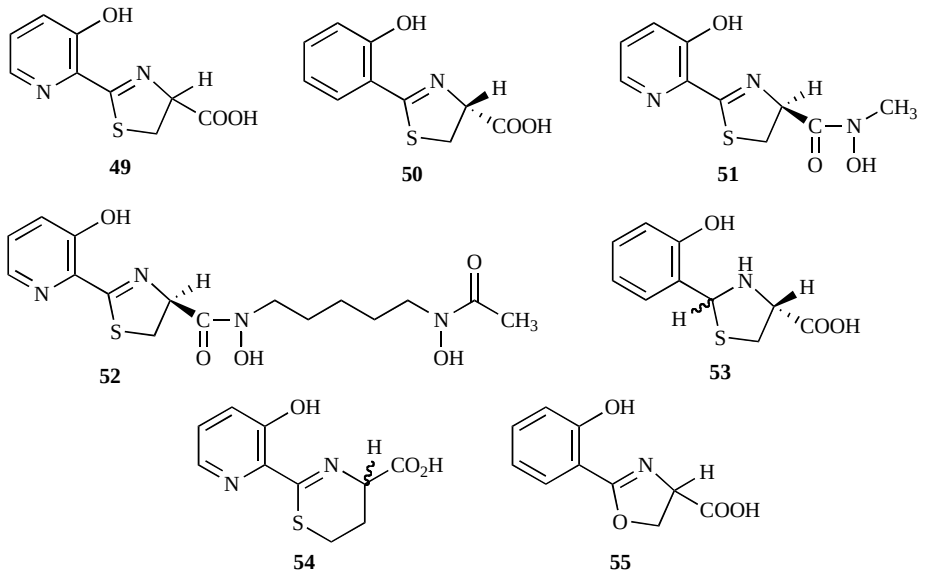
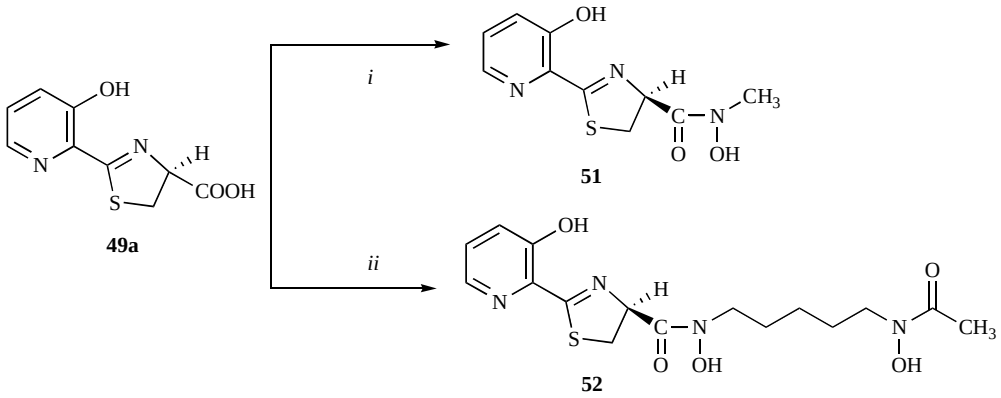
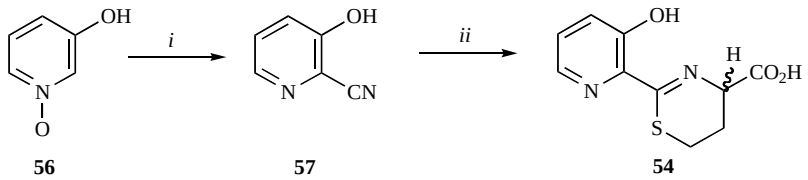


Fig. (8). Structures of desferrithiocin analogues.



Scheme 12. *i*) $CH_3NHOH \cdot HCl$, BOP/*i*-Pr_2NEt/DMF; *ii*) $AcNOH(CH_2)_5NHOH \cdot TFA$ BOP/*i*-Pr_2NEt/DMF.



Scheme 13. *i*) TMS-CN, NEt_3, CH_3CN; *ii*) DL-homocysteine, phosphate buffer (pH 5.95), CH_3OH.

compound's efficacy [44]. This high oral activity of desferrithiocin made this chemical backbone a promising scaffold warranting further structural investigations.

Many analogues of desferrithiocin, such as, Desmethyldesferrithiocin (**49**), (*R*)-desazadesmethyl desferrithiocin (**50**), (*S*)-desmethyldesferrithiocin-*N*-methylhydroxamate (**51**), (*S*)-desmethyldesferrithiocin-*N*-[5-(acetylhydroxyamino)pentyl] hydroxamate (**52**), 2-(2'-hydroxyphenyl)-4(*R*)-thiazolidinecarboxylic acid (**53**), DL- 2-(3´-hydroxypyrid-2´-yl)-4H-5,6-dihydro-1,3-thiazine-4-carboxylic acid (**54**) and 2-(2'-hydroxyphenyl)-4-oxazoline carboxylic acid (**55**) (Fig. **8**) have been synthesized to identify which structural components of the siderophore are required for iron clearance after oral administration [45].

The compounds (**51**) and (**52**) were synthesized in 47% and 60% yields respectively, as shown in Scheme **12**.

Condensation of 3-hydroxy-2-cyanopyridine (**57**) with DL-homocysteine afforded compound (**54**) in 71% yield as a mixture of two enantiomers, as shown in Scheme **13**.

Studies realized by Bergeron *et al*. demonstrated that of the nonchelating functionalities, the aromatic nitrogen and the thiazoline methyl of desferrithiocin were not necessary while the sulfur atom was required. Of the chelating functionalities, the aromatic hydroxyl and thiazoline nitrogen were critical for activity, while the carboxyl group can be altered [45].

A major drawback of this siderophore was that it exhibited severe nephrotoxicity [46]. Due to this nephrotoxicity, structure-activity relationship studies have been performed to develop less toxic derivatives of this pharmacophore. In these studies it has been examined the effect of thiazoline ring alterations such as, oxidation to an thiazole, reduction to a thiazolidine, expansion by a methylene

group and substitution of the thiazoline sulfur with oxygen, nitrogen or a methylene group. All of them resulted in a loss of iron clearing activity. It can be concluded that the thiazoline ring must remain intact for iron clearing activity. The stereochemistry and alterations on distances between donating centers have been also examined resulting in a loss of iron clearing activity [47-49].

3. CONCLUDING REMARKS

The progress realized in the iron transport field and in the study of many siderophores has been hazardous in many fields. In this review we have focused in the thiazoline ring containing siderophores, in their chemistry, in their synthesis and how the need for the continued development of new iron-chelating agents, that are either more effective than currently available therapies or can selectively remove iron from organs and tissues especially vulnerable to iron-induced toxicity, has lead to the synthesis of new analogues. Our knowledge of finding new structures and their mode of action should aid in future research to design new chelating agents.

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