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Biomimetic Synthesis and Phytochemical Analysis of Lodopyridone: Insights into 4-Pyridone Derivatives and Thiopeptide Antibiotics

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Abstract: ***This study explores the total biomimetic synthesis of lodopyridone, a rare 4-pyridone compound, and investigates the phytochemical properties of Lycopodiella cernua and Nitraria retusa. Despite the limited presence of naturally occurring 4-pyridones, a classification of 16 compounds is provided, highlighting their structural diversity and biosynthetic pathways. The work emphasizes the significance of thiopeptide antibiotics, showcasing their complex structures and antibiotic activities, which share biosynthetic similarities with lodopyridone. Proposed biosynthetic hypotheses suggest that lodopyridone may derive from a peptide precursor involving key amino acids such as glycine, cysteine, and modified tryptophan. Various synthetic methodologies, including palladocatalyzed couplings and innovative strategies for constructing nitrogenous heterocycles, are discussed in the context of thiopeptides. The findings aim to enhance understanding of lodopyridone's biosynthesis and facilitate its synthesis through biomimetic approaches, contributing valuable insights to pharmaceutical chemistry and the development of natural product-based therapeutics.***

Keywords: Lodopyridone; Biomimetic Synthesis; 4-Pyridone; Thiopeptide Antibiotics; Phytochemical Analysis; Biosynthesis; Natural Products; Pharmaceutical Chemistry

I. INTRODUCTION

Lodopyridone, a unique compound characterized by its 4-pyridone ring, presents significant interest in the realm of natural products due to its rarity and potential biological activities [1]. Despite the vast number of pyridones documented—over 250,000 in the Chemical Abstracts database—only about twenty naturally occurring 4-pyridones have been identified, highlighting the scarcity of this structural motif in nature. This study aims to explore the biomimetic synthesis of lodopyridone while also delving into the phytochemical properties of *Lycopodiella cernua* and *Nitraria retusa* [2].

The classification of naturally occurring 4-pyridones reveals that these compounds exhibit minimal structural and biosynthetic similarities, suggesting diverse origins and pathways [3]. A preliminary classification of 16 natural substances has been established, emphasizing the need for deeper understanding of their biosynthetic contexts. Among these, lodopyridone stands out, necessitating comparisons with closely related compounds such as WS75624 A and B, as well as B-90063. These comparisons indicate potential shared biosynthetic pathways, particularly those involving peptide origins [4].

In addition to our focus on lodopyridone, the study examines thiopeptide antibiotics, a family of modified high-sulfur peptides known for their complex structures and potent biological activities. These antibiotics, primarily isolated from soil and marine bacteria, share structural elements with lodopyridone, particularly the presence of pyridine and thiazole rings [5]. The exploration of thiopeptide biosynthesis offers valuable insights into the possible origins of lodopyridone's unique structure, suggesting that its biosynthesis may involve similar pathways [6].

By analyzing the biosynthetic origins and synthetic methodologies of both lodopyridone and thiopeptide antibiotics, this work aims to not only enhance the understanding of these compounds but also to provide innovative strategies for their synthesis. Ultimately, this exploration contributes to the broader field of pharmaceutical chemistry, paving the way for the development of new therapeutics derived from these fascinating natural products [7].

A. Introduction of 4-Pyridones Naturally Occurring, Classification Trial

Lodopyridone contains a 4-pyridone ring, a structural motif that is relatively rare in nature. Only a limited number of naturally occurring 4-pyridones have been identified, with approximately twenty compounds documented in the literature. In the Chemical Abstracts database, which lists over 250,000 pyridone derivatives, we have identified and reviewed 16 natural substances, as shown in Table 1. This table categorizes these compounds based on their structures, the organisms from which they are derived, and their reported biological activities. While the presence of a 4-pyridone ring is a common feature among these molecules, they exhibit minimal structural and biosynthetic similarities. However, a provisional classification can be proposed based on their hypothesized biosynthetic pathways [8].

In particular, lodopyridone (1), which is the focus of this study, can be compared to compounds WS75624 A and B (2 and 3), as well as B-90063 (4). The shared structural elements, including the 6-membered nitrogen-containing ring (either pyridine or pyridone),

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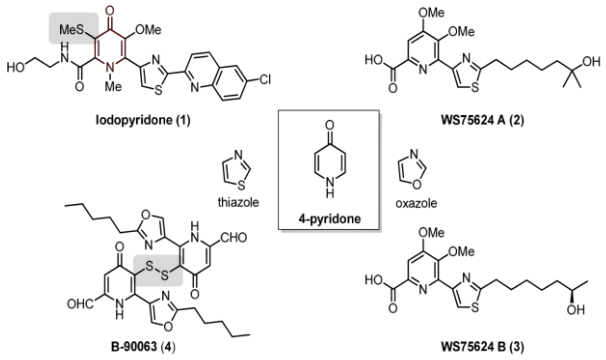
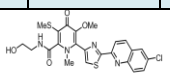
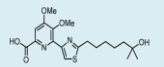
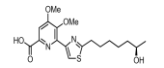
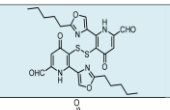
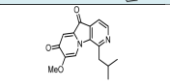
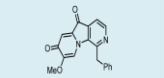
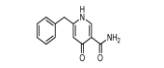
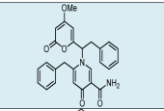
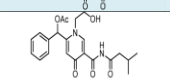
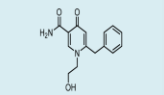
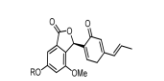
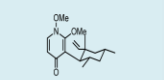
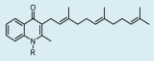
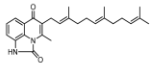
thiazole and oxazole rings, oxygenation sites, the sulfur position in B-90063 (4), and the location of carbonyl substituents, suggest that these compounds likely follow similar biosynthetic routes, possibly involving peptide-based synthesis, as illustrated in Figure 1.

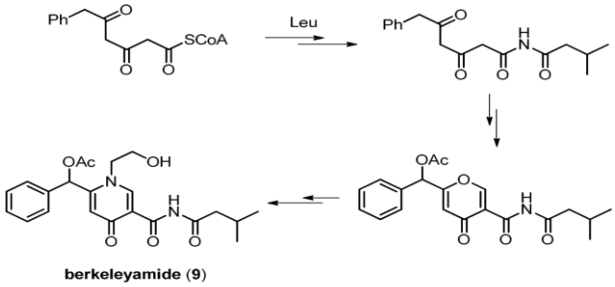


[Fig.1: Structure of Iodopyridone (1), and WS75624 A and B (2,3), and B-90063 [4]]

Table 1: Literature Review on Naturally Occurring 4-Pyridones

Name	Structure	Spring	Year of Isolation	Biological Activities
Lodopyridone (1)		*Saccharomonospora* sp. CNQ490 Actinomycète	2009[3]	cytotoxique CI_{50}=3.6 µM sur cellules HCT-116
WS75624 A (2)		*Saccharothrix* sp.75624 Actinomycète	1995[3]	
WS75624 B (3)		*Saccharothrix* sp.75624 Actinomycète	1995[3]	
B-90063 (4)		α-Protéobactérie	1998[4]	
Piérocelline A (5)		*Pterocella vesiculosa* bryozoaire marin	2003[5]	Cytotoxique sur cellules murines P388 CI_{50} = 477 nM et sur cellules simiesques BSC-1 (CI_{50} non précisée). Antifongique sur *Tricophyton mentagrophytes*
Piérocelline B (6)		*Pterocella vesiculosa* bryozoaire marin	2003[5,7]	Cytotoxique sur cellules murines P388 CI_{50} = 323 nM/mL et sur cellules simiesques BSC-1 CI_{50} non précisée. Antibactérien sur *Bacillus subtilis*. Antifongique sur *Tricophyton mentagrophytes*
Aspernigrine A (7)		*Aspergillus niger* Eurotiomycètes	2004[8]	Cytotoxique sur cellules JURKAT CI_{50} = 50 µM.
Aspernigrine B (8)		*Aspergillus niger* Eurotiomycètes	2004[8]	Cytotoxique sur cellules JURKAT CI_{50} = 50 µM. Activité neuroprotective.
Berkeleyamide C (9)		*Penicillium rubrum* Eurotiomycètes	2008[9]	Inhibition du signal de transduction des enzymes métalloprotéinase-3 (MMP-3) et caspase-1. CI_{50} non précisées.
Pestalamide C (10)		*Pestalotiopsistheae* Actinomycète	2008[10]	Antifongique sur *Aspergillus fumigatus*. Inhibition de la réplication HIV-1 dans les cellules C8166.
Pénicidone A (R=Me) : 11 Pénicidone B (R=H) : 12		*Penicillium* sp. IFB-E022 Eurotiomycète	2007[11]	Cytotoxique sur cellules SW1116, K562, KB et HELA pour la pénicidones A : SW1116(60,1 µM), K562 (54,0 µM), KB (46.5 µM), HELA (41.5 µM) et pour la pénicidone B : SW1116 (54,2 µM), K562(21,1 µM), KB (29,6 µM), HELA (35,1 µM).
13		OS-F61800 Souche fongique non caractérisée	1999[12]	
L-Mimosine (14)		*Leucaena* sp. Fabaceae	1937[13]	Antimitotique, inhibition de la synthèse de l'ADN chez les animaux. Inhibition de la croissance et de la synthèse des protéines.
Aurachine C (R=OH) : 15 Aurachine D (R=H) : 16		*Stigmatella aurantica* Cystobacteraceae	2008[14]	Activité anti bactérienne sur les cocci et bacilles à Gram positif. Aurachine C : antipaludique *in vitro* sur cellules W-2 clone CI_{50} = 26 ng/mL et sur cellules D-6 CI_{50} = 0,90 ng/mL. Aurachine D : antipaludique *in vitro* sur cellules W-2-clone CI_{50} = 370 ng/mL et sur cellules D-6 CI_{50} = 250 ng/mL.
Aurachine E (17)		*Stigmatella aurantica* Cystobacteraceae	2008[14]	Activité anti bactérienne sur les cocci et bacilles à Gram positif. Antipaludique *in vitro* sur cellules W-2 CI_{50} = 13 ng/mL et sur cellules D-6 CI_{50} =0,4 ng/mL. Faible cytotoxicité : CI_{50} = 25 µg /mL.
Cladobotryal (18)		*Caldobotrium varium* champignon	2003[15]	Antibactérien. Antifongique.

The second group includes penicidones A and B (5 and 6), aspernigrins A and B (7 and 8), as well as berkeleyamide C (9), all of which are likely to have biosynthetic origins from the polyacetate pathway, as depicted in Figure 2.



[Fig.2: Biosynthesis of Berkeleyamide C [9]]

The final group consists of compounds that do not belong to either of the first two groups.

Through this comparison of naturally occurring 4-pyridones, it becomes clear that this chemical structure does not arise from a single biosynthetic pathway. The compounds listed in Table 1 do not share a common biosynthetic origin. To better understand the biosynthetic context of lodopyridone (1), a comparison with thiopeptide antibiotics offers more definitive insights into its potential biosynthetic pathway [9].

II. THIOPEPTIDE ANTIBIOTICS

Thiopeptide antibiotics, aptly named due to their distinctive structures, form a family of highly modified sulfur-rich peptides that includes over a hundred compounds (Figure 3). Most of these antibiotics have been isolated from bacteria sourced from terrestrial soils, with some also derived from marine environments [10]. The defining structural feature of this family is the presence of a pyridine ring, which undergoes varying degrees of oxidation and is substituted with thiazole rings. These thiazole rings are integral to the formation of the modified peptide macrocycles. The pyridine ring plays a crucial role in the folding of the peptide backbone through head-to-tail electrocyclization. Additional recurring structural elements in these macrocycles include multiple sulfur atoms in the thiazole rings, the presence of dehydroamino acids, and often, oxazole rings. Among the many members of this family, three key compounds stand out: i) micrococcine (20), isolated in 1948 from Oxford sewage,

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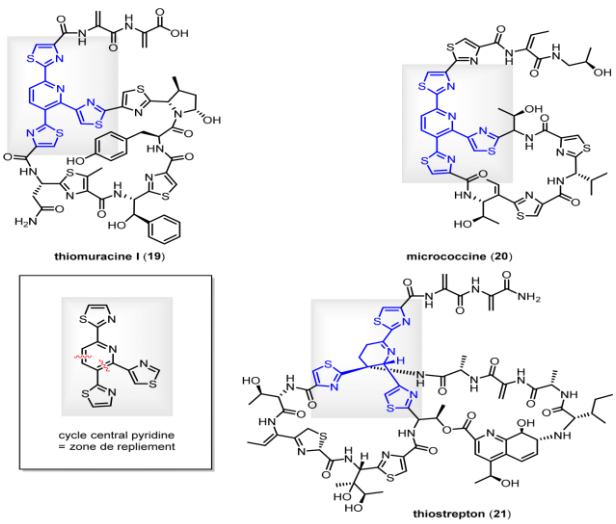
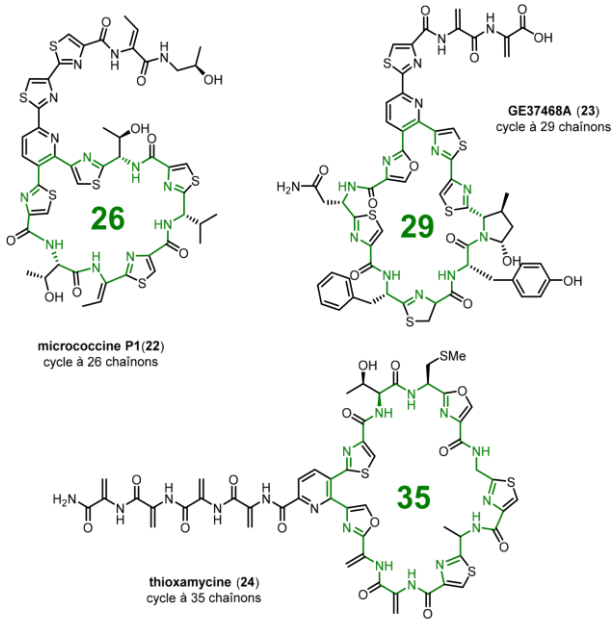
representing the historical member of the group; ii) thiomuproot I (19), which helped elucidate the biosynthetic origins of the family; and iii) thiostrepton (21), a strikingly complex structure that exemplifies the challenges involved in the total synthesis of thiopeptides [11].



[Fig.3: Examples of Antibiotic Thiopeptidic]

A. Antibiotic Activities of Thiopeptides

The thiopeptide family has garnered significant attention due to its diverse biological activities, particularly its antibiotic properties [12]. Thiostrepton, for example, is used topically in veterinary medicine under the brand name Panalog [13]. Among the various thiopeptides, the antibiotic activities have been the most extensively studied. A common feature of this class of natural products is their inhibition of protein synthesis at the ribosomal level, although the specific mechanisms of action can vary depending on the size of the thiopeptide macrocycle [14]. Thiopeptides are categorized based on the number of ring links they contain, with typical macrocycles consisting of 26, 29, or 35 members, depending on the number of amino acid residues involved (Figure 4).



[Fig.4: Aantibiotic Thiopeptidic Presented of Macrocycles (26,29,35)]

26-membered macrocycles, like micrococcine P1 (22), are known to interact with the GTPase domain of the ribosome in complex with the L11 protein. This interaction obstructs the binding site for Elongation Factor G, thereby inhibiting the translocation of the elongated peptide-tRNA complex into the ribosome [15].

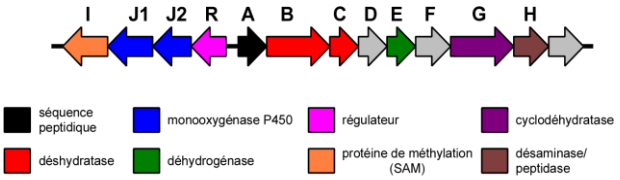
For thiopeptides with a 29-membered macrocycle, such as GE37468A (23), the antibiotic binds to the elongation factor EF-Tu, thereby blocking the active site of the tRNA-aminoacyl complex and preventing its transfer to the elongating peptide chain (Art. 22) [16]. In the case of thiopeptides with a 35-membered macrocycle, like thioxamycin (24), the exact mechanism of action remains unclear. These antibiotic activities likely serve as a defense mechanism for the microorganisms that produce them, reflecting their role in chemical ecology [17].

B. Biosynthesis of Antibiotic Thiopeptides

Antibiotic thiopeptides share certain structural features with lodopyridone, the target molecule of this study [18]. While their overall structures differ, the biosynthetic pathways of thiopeptides provide valuable insights into the potential biosynthetic origins of lodopyridone [19]. Focusing on the biosynthesis of thiomurain I (19), the biosynthetic pathway can be outlined as shown in Figure 2.

As suggested by their name, antibiotic thiopeptides are derived from genetically encoded peptide chains, which are synthesized on the ribosome (Figure 5) [20]. The gene responsible for the biosynthesis of the precursor peptide is translated into a peptide (25) consisting of two distinct domains:

1. The first domain contains 12 to 17 amino acid residues, corresponding to the final thiopeptide sequence.
2. The second domain consists of 34 to 55 residues and is linked to the N-terminal of the first domain. This second domain is later truncated during biosynthesis (figure 5, process A). In some thiopeptides, the native peptide sequence also includes one or two residues at the C-terminal end, which are similarly truncated during the biosynthetic process.



[Fig.5: Gene Cluster Conducing the Biosynthesis of Thiomuracin I [19]]

It has been demonstrated that the genes responsible for encoding the enzymes required for modifying the precursor peptide are clustered around the gene encoding the peptide itself, forming a gene cluster (Figure 5) (Art. 19) [21].

Regarding the sequence of modifications, the formation of thiazole and oxazole rings occurs first, through a series of cyclizations, dehydrations, and oxidations involving cysteine and serine residues (figure 2, processes B and C). Next, the serine residues undergo phosphorylation and dehydration, leading to the

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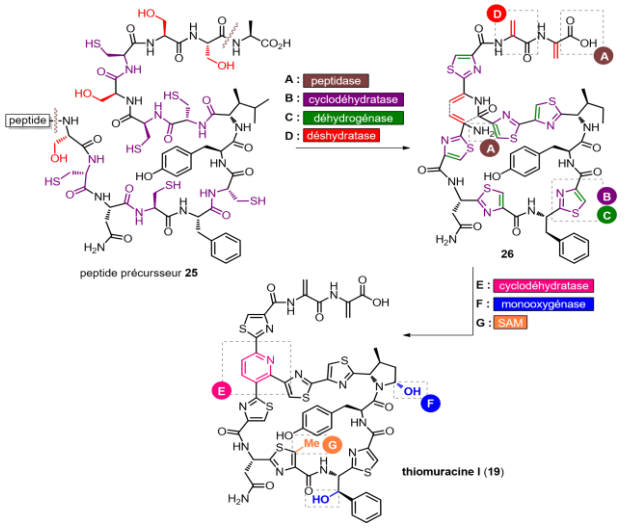
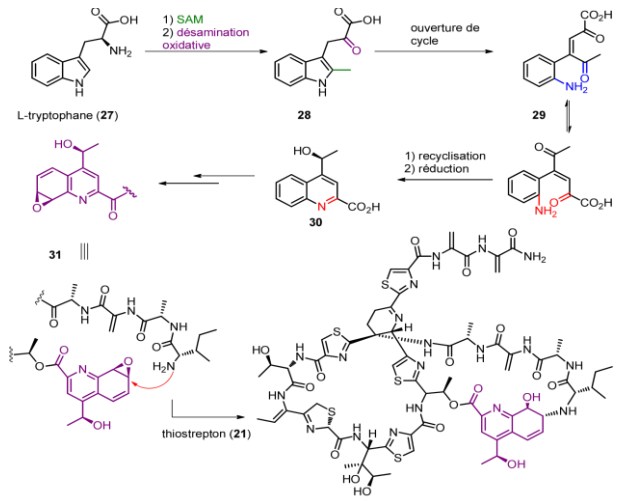
formation of dehydroalanines (figure 2, process D) [22]. Finally, the peptide chain undergoes folding, where distant residues in a head-to-tail orientation interact, likely through a process resembling an aza-Diels-Alder reaction, followed by dehydrogenation to form the central nitrogen ring (Figure 6, process E) [23]. Later modifications of antibiotic thiopeptides include oxidation, methylation, and the incorporation of quinoline moieties—one of the more distinctive features of these compounds (see below) [24].



[Fig.6: Biosynthesis of Thiomuracin I [19]]

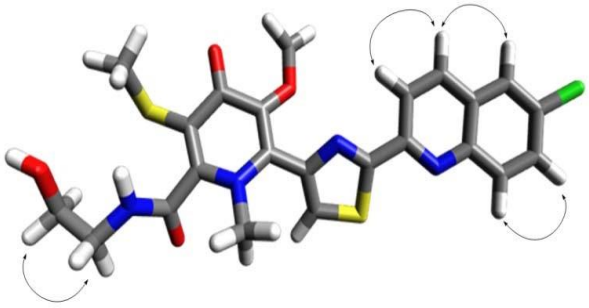
Regarding late-stage modifications (Figure 7), nitrogen-containing heterocycles, such as the dihydroquinoline found in thiostrepton (21), are believed to arise from modifications to tryptophan (27) [25]. The most unexpected biosynthetic step involves the formation of the quinoline structure. This process begins with the methylation of tryptophan, followed by deamination to yield pyruvate (28). The indole ring is then opened and subsequently re-closed, completing the reorganization of the heterocycle (30) [26]. Further modifications, including ketone reduction and epoxidation, are required before the quinaldehyde fragment (31) is incorporated into thiostrepton. It is important to note that the epoxy group plays a crucial role in the formation of the second macrocycle of thiostrepton (21) [27].



[Fig.7: Organic Biosynthesis of Dihydroquinoleine of Thiostrepton]

III. OUR HYPOTHESES FOR LODOPYRIDONE BIOSYNTHESIS

Lodopyridone (1, structure shown in Figure 8) exhibits a highly distinctive structure for a natural product [28]. Based on our hypotheses, its polyheterocyclic biosynthetic sequence is most likely derived from a peptide precursor (33), which consists of glycine, two cysteine residues, and a modified tryptophan.



[Fig.8: Structure of Lodopyridone 1 and HMBC Correlations]

Inspired by the biosynthetic pathways of antibiotic thiopeptides, the formation of various heterocycles in lodopyridone biosynthesis can be proposed as follows:

- The chlorinated quinoline structure (32) is likely derived from tryptophan (27). It is widely accepted that the indole ring of tryptophan can undergo oxidation, which facilitates the extension of the ring to form a quinoline derivative [29].
- The thiazole ring (intermediate 34) is thought to result from the cyclization of cysteine. One well-established biosynthetic route for thiazoles involves the condensation of cysteine, which participates in peptide bond formation. A similar biosynthetic process can lead to the formation of oxazole from serine [30].
- Finally, the 4-pyridone ring may arise from the condensation of a modified peptide (38) of the aza-diene type. This peptide likely contains dehydrocysteine and a three-carbon unit derived from malonyl-CoA (36) or dehydroalanine (37). The condensation would be followed by cycloaddition, decarboxylation, oxygenation, and methylation steps to complete the biosynthesis of lodopyridone (1). The exact mechanism behind the formation of 4-pyridone remains unclear, and it is likely that a specific enzyme catalyzes this transformation as part of the biosynthetic pathway. The importance of the C2 unit in this process should also be highlighted [31].

Streamlining biosynthesis plays a crucial role in the retrobiosynthetic analysis of lodopyridone.

The key components of our proposed hypothesis are summarized in the figure below (Figure 9).

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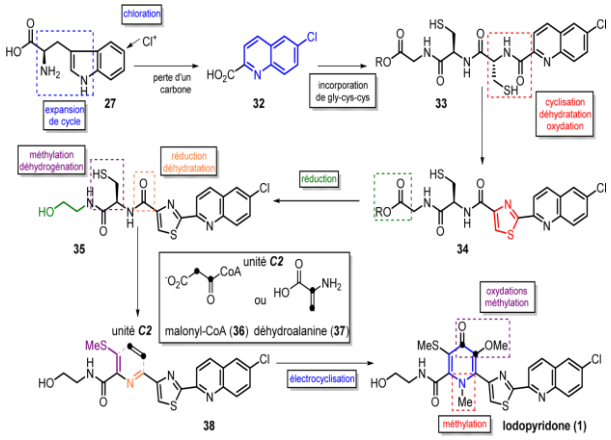
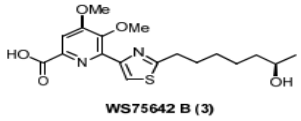


[Fig.9: Biosynthesis of Iodopyridone Hypothesis]

Lodopyridone was isolated from the culture medium of an actinomycete, yielding 4 mg from 40 liters of medium. To enhance the production of lodopyridone, W [32]. Fenical and colleagues supplemented the culture medium with glycine, cysteine, and tryptophan. This strategy was inspired by the work of M. Okuhuara et al. on the WS75624 B molecule (3, Figure 10), which is structurally similar to lodopyridone and was isolated from *Saccharothrix* sp. However, no increase in lodopyridone production was observed in *Saccharomonospora* sp. The unique formation of the pyridone ring prompted our efforts toward its total synthesis, guided by a biomimetic approach [33].



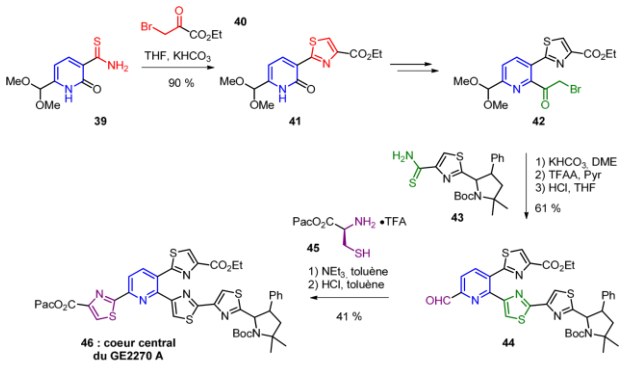
[Fig.10: Structure of WS75624 B (3) Isolated Saccharothrixsp]

IV. SYNTHETIC APPROACHES TO THE NITROGENOUS CORE OF ANTIBIOTIC TIOPETIDES

While numerous methods for synthesizing 6-membered nitrogen-containing heterocycles are discussed in the literature, this section will specifically focus on those used for constructing the nitrogenous core of antibiotic thiopeptides. Special emphasis will be placed on techniques that enable the full assembly of the heterocyclic structure [34].

A. Synthesis of the Heterocyclic Core of GE2270 A

Extensive research has been conducted on the synthesis of antibiotic thiopeptides. In many instances, the construction of the central core involves the functionalization of a preexisting pyridine or another 6-membered nitrogen-containing heterocycle [35]. For instance, Bach and his team employed a strategy that involved functionalizing an ortho-pyridone to synthesize the central core of GE2270 A (46, figure 11).

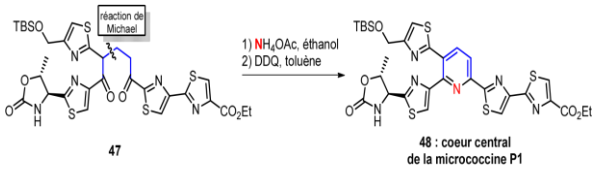


[Fig.11: Key Steps in the Synthesis of the Central Core of GE2270]

The central core of GE2270 A (46) features a pyridine ring substituted with three thiazole groups [36]. In this synthetic approach, the thiazole rings were constructed around a pre-existing pyridine. The first thiazole ring was synthesized via a Hantzsch reaction, which involved the condensation of thioamide 39 with α-bromo-ketone 40 [37]. The second thiazole ring was formed in a similar manner, through a reaction between fragments 42 and 43 [38]. The third thiazole in compound 45 was generated through a biomimetic condensation reaction, where a modified cysteine (44) reacted with aldehyde 43, followed by oxidation. Additionally, thiazole rings can be introduced onto a pyridine scaffold through palladium-catalyzed coupling reactions, a commonly used strategy for synthesizing molecules in this chemical family [39]. This approach will be further discussed in section 1.7 , where the synthesis of WS75624 A and B (2 and 3) is detailed. For the purposes of this work, we will now focus on synthesis methods specifically aimed at constructing the nitrogenous heterocycle within the central core of antibiotic thiopeptides [40].

B. Synthesis of the Heterocyclic Core of Micrococcine P1

To synthesize the central core 48 of micrococcine P1 (22, figure 12), Ciufolini's team employed an azotation reaction on diketone 47. The diketone 47 was synthesized through a Michael addition reaction between a ketone and an enone. Subsequently, the azotation reaction using ammonium acetate, followed by oxidation with DDQ, facilitated the formation of the central pyridine ring in a single step, thereby completing the synthesis of the central core 48 [41]. This method was also applied by the same team in the total synthesis of thiocillin I [42].



[Fig.12: Key Steps in the Synthesis of the Central Core of Micrococcine P1]

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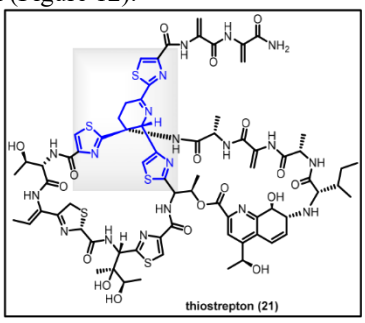
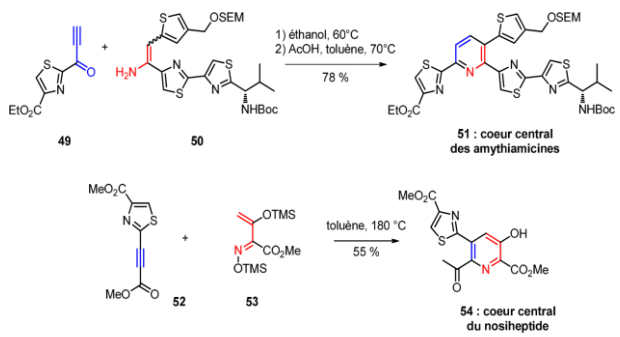
C. Synthesis of the Heterocyclic Core of Amythiamicins and Nosiheptide

Among this family of molecules, thiostrepton (21) is undoubtedly the most structurally complex member, consisting of two folds of the peptide chain that create two macrocycles. During its total synthesis, Nicolaou's team constructed the central nitrogen-containing heterocycle (compound 58) via a biomimetic cycloaddition [43]. This reaction, independently discovered by Wulff and Gilchrist in the early 1990s, was later demonstrated by Nicolaou to be involved in the biosynthesis of thiostrepton. The reaction begins with the condensation of amine 55 and aldehyde 56, forming a transient imine, which is then stabilized in situ as a thiazolidine 57, corresponding to a cyclic thioaminal [44]. Under basic conditions (using silver carbonate and DBU), the open form of the imine can be regenerated, and the cysteine residue is transformed into dehydroalanine through the elimination of an equivalent of H_2S in a process akin to crotonization (Figure 12).



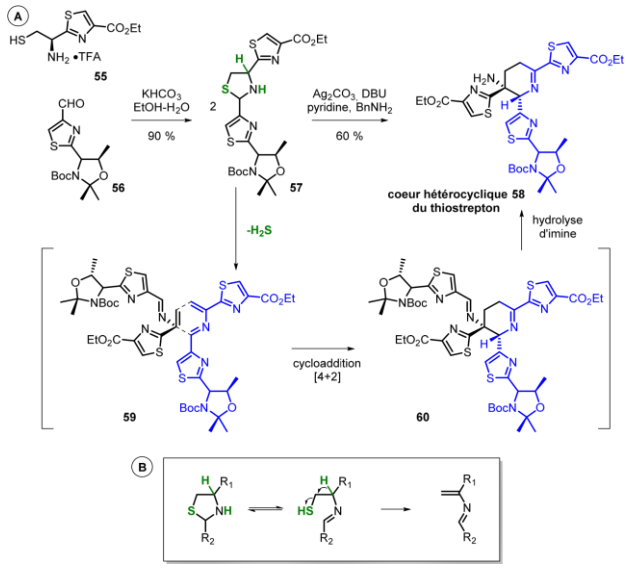
This elimination reaction yields aza-diene 59, a highly reactive intermediate that cannot be isolated. It undergoes spontaneous self-addition via a [4+2] cycloaddition to form the central core of thiostrepton (compound 60) [45]. The presence of benzylamine in the reaction medium promotes the hydrolysis of the residual imine, completing the synthesis of the complex fragment 58 with an excellent yield of 60% after this impressive cascade of reactions. The mechanistic steps of this [4+2] cycloaddition are conceptually similar to those in our strategy for synthesizing the pyridone ring of lodopyridone [46]. However, to preserve the sulfur substituent on the amino acid in our case, we needed to develop a novel methodology to synthesize dehydrocysteine rather than dehydroalanine [47].



[Fig.13: Construction of Heterocycles by Electrocyclization]

D. Synthesis of the Heterocyclic Heart of Thiostepton

In the thiostrepton family of molecules, thiostrepton (21) stands out as the most intricate member due to its structural complexity, which results from two folds of the peptide chain, leading to the formation of two macrocyclic rings [47]. During the total synthesis of thiostrepton, Nicolaou and his team synthesized the central nitrogen heterocycle (compound 58) via a biomimetic cycloaddition . This reaction, initially discovered by Wulff and Gilchrist in the early 1990s, was later incorporated into a biosynthetic pathway by Nicolaou during the synthesis of thiostrepton [48]. The process begins with the reaction of amine-55 and aldehyde-56 to form a transient imine, which is then stabilized in situ as a thiazolidine (compound 57), formally corresponding to a cyclic thioaminal [49]. Under basic conditions (silver carbonate and DBU), the open-chain form of the thiazolidine can be regenerated, and the cysteine residue is converted into dehydroalanine by the elimination of H_2S, similar to the crotonization process . This elimination results in the formation of aza-diene 59, a highly reactive intermediate that cannot be isolated. The aza-diene undergoes a spontaneous [4+2] cycloaddition, yielding the central core of thiostrepton (compound 60) figure 14. The presence of benzylamine in the reaction medium facilitates the hydrolysis of the residual imine, completing the synthesis of the complex fragment 58 with a notable yield of 60% following this remarkable cascade of reactions. The disconnections involved in this [4+2] cycloaddition are analogous to those used in our synthesis strategy for the pyridone ring in lodopyridone. However, to preserve the sulfur substituent on the amino acid, we developed a novel methodology to synthesize dehydrocysteine, rather than dehydroalanine [50].



[Fig.14: Biomimetic Synthesis of the Central Core 58 of Thiostrepton [21]]

V. METHODS OF OBTAINING DEHYDROAMINO-ACIDS

Many peptides contain dehydroamino acid residues, yet the methods for their laboratory preparation are limited, typically involving crotonization reactions of serine or cysteine

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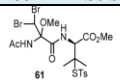
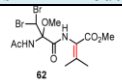
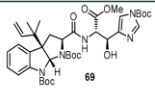
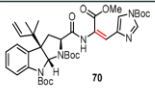
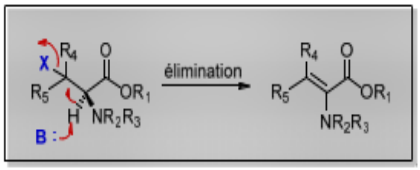
derivatives. Recent advancements have introduced new preparation techniques, often utilizing organometallic couplings catalyzed by palladium or copper [51]. To contextualize our synthesis of the dehydrocysteine fragment, we will review some representative methods. Serine, threonine, and cysteine are essential amino acids that are biosynthesized through aldol transferases. Serine and threonine can be considered aldols, while cysteine is a thioaldol. The reactivity observed in aldol reactions is transferable to these amino acids and their derivatives. Consequently, the crotonization reaction applied to these substrates leads to the formation of dehydroamino acids under basic conditions through the elimination of a leaving group figure15. Several examples are provided in Table 2 to illustrate this approach. Notably, the formation of dehydroalanine from cysteine (Table 2, entry 3) offers a point of comparison to Nicolaou's biomimetic strategy used in the total synthesis of thiostrepton [52].

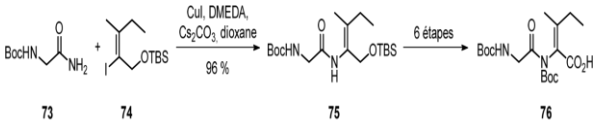
Table 2: Formation of Dehydroamino-Acids by Crotonization

Entrance	Substrate	Conditions	Product	Yield
1[36]		triétylamine		30 %
2[37]		DBU, CH_2Cl_2		90 %
3[38]		K_2CO_3, DMF, 1,5-diiodopentane		93 %
4[39]		EDC, $Cu(OTf)_2$, THF		73 %
5[40]		EDC, $CuCl_2$, toluène		81 %
6[41]		1) *i*-PrCHO, *t*-BuOK, *t*-BuOH-DMF 2) PhCHO, *t*-BuOK, *t*-BuOH-DMF		48 %



[Fig.15: Formation of Dehydroamino-Acid by Elimination]

The formation of dehydroamino acids through group elimination is a highly effective and widely used approach, as evidenced by numerous examples in the literature (Figure 16). However, for the synthesis of lodopyridone, the need for a dehydrocysteine residue made this method unsuitable, as it could compromise the sulfur functionality [53]. A more recent strategy for synthesizing dehydroamino acids, such as compound 76, involves coupling an amide (73) with an allyl iodide (74) under copper(I) iodide catalysis in the presence of a diamine (e.g., DMEDA). This approach represents an innovative technique for the preparation of such compounds. However, the sequence to convert the coupling product (75) into the desired carboxylic acid (76) is lengthy, requiring six additional steps. Notably, we had already considered and begun implementing a similar coupling strategy prior to the publication of this method [54].

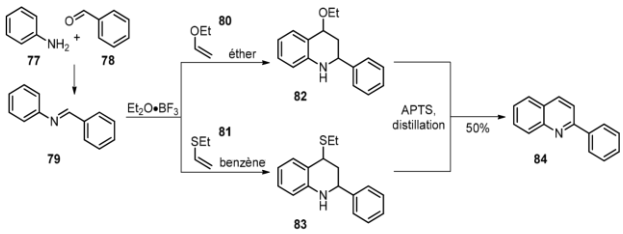


73 74 75 76

[Fig.16: Formation of Dehydroamino-Acid by Organometallic Coupling]

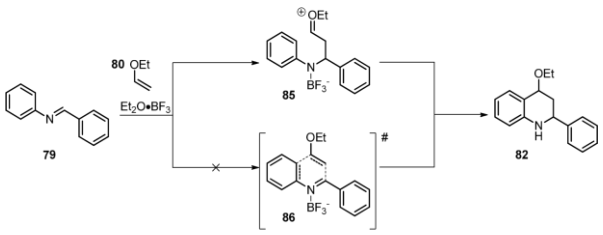
VI. POVAROV'S REACTION

The Povarov reaction will play a central role in our synthetic strategy. This reaction is an aza-Diels-Alder process that involves a multicomponent assembly between an aniline, an aldehyde, and an enol ether [55]. It enables the efficient synthesis of substituted quinolines from simple building blocks. The reaction was first described by Povarov in 1963 (Figure 17) in a series of papers, where he outlined the cycloaddition of a vinyl ether (80) or a vinyl thioether (81) with an aromatic imine (79) in the presence of $Et_2O{\bullet}BF_3$. The cycloaddition products (82 or 83) undergo further treatment in an acidic medium to form aryl-quinoline derivatives [56].



[Fig.17: Historic Example of Povarov Reaction]

Regarding the reaction mechanism (Figure 18), it is proposed that the process involves the formation of intermediate cationic species (compound 85) rather than a concerted mechanism with a transition state (86). Initially, a Lewis acid would activate imine 79, which then reacts with olefin 80, substituted with an electron-donating group. This results in the formation of the cationic intermediate (85), which subsequently undergoes an intramolecular electrophilic substitution reaction on the aromatic ring of the original aniline [57].



[Fig.18: Mechanism of Povarov Reaction]

The Povarov reaction demonstrates significant flexibility in terms of substrate diversity and catalyst selection. While it is traditionally catalyzed by $Et_2O{\bullet}BF_3$, other catalysts, such as rare earth salts or Brønsted

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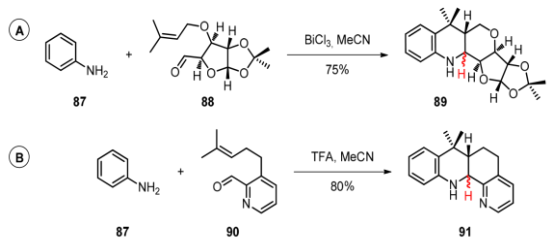
acids, can also be employed (Figure 19) [58]. Despite its widespread use in synthetic organic chemistry, the Povarov reaction has not been proposed as a key step in the biosynthetic pathways of specialized metabolites [59].

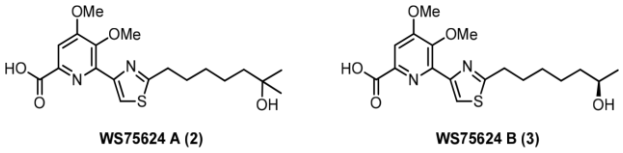


[Fig.19: Povarov Reaction Catalysis by A: Lewis Acid, B: Bronsted Acid]

VII.PREVIOUS SYNTHESES OF A/B WS75624 AND LODOPYRIDONE

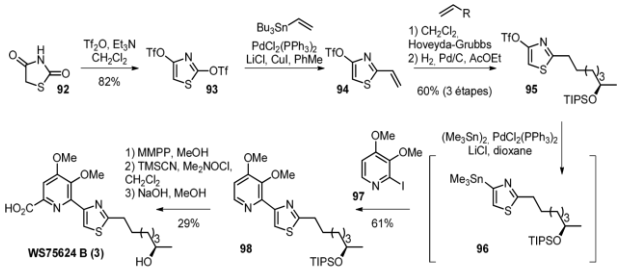
A. Summaries of WS75624 A and B

WS75624 A and B (compounds 2 and 3, Figure 20) are molecules that were isolated in 1995 from the actinomycete *Saccharothrix* sp. They contain a pyridine ring and a thiazole substituted with an aliphatic side chain. These compounds are considered the closest structural analogs of lodopyridone (1), and their biosynthesis likely follows a pathway similar to that of lodopyridone. The most recent synthesis of these molecules was reported in 2011 by Stellios Arseniyadis and Janine Cossy, who presented a rapid and elegant synthetic approach.



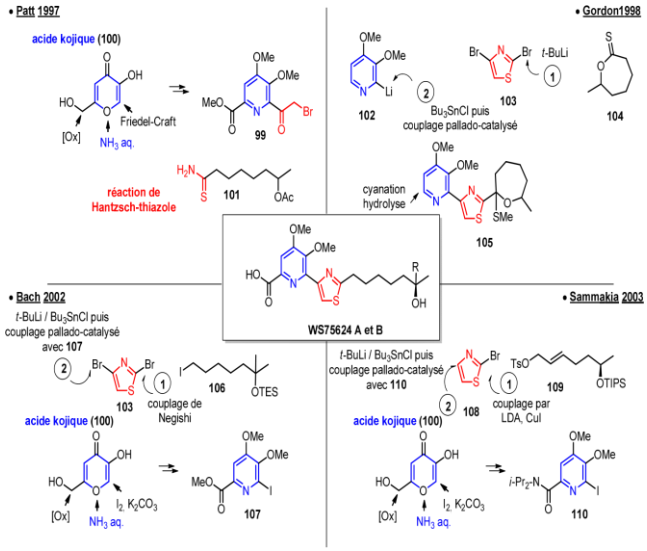
[Fig.20: Structure of WS75624 A and B 2and 3 Isolated of Saccharothrix sp]

In their approach (Figure 21), an aliphatic chain primer was attached to the thiazole ring through a Stille coupling reaction between an allyl stannane and thiazole triflate 93. The remainder of the side chain was assembled via cross-metathesis on intermediate 94, followed by hydrogenation. The residual triflate group on intermediate 95 was then stannylated, and another Stille coupling was employed to anchor the stannylated thiazole (96) to iodo-pyridine 97.



[Fig.21: Synthesis of WS75624 B (3) by Arseniyadisand Cossy]

The synthesis developed by Arseniyadis and Cossy represents the fifth synthetic approach for WS75624 A and B (compounds 2 and 3). These five approaches share similar disconnections (Figure 22) and can collectively be described as "heterocyclic block assembly syntheses." All these strategies involve the functionalization of a pre-existing pyridine, achieved through the azotation of kojic acid (100) in the syntheses by Patt, Bach, and Sammakia. In each case, the pyridine and the side chain are coupled to the thiazole via lithiation/stannylation of one of the heterocycles, followed by a metallocatalyzed coupling. The Patt strategy is distinct in that it forms the thiazole using a Hantzsch-thiazole reaction. The primary innovation across these synthetic approaches lies in how the aliphatic side chain is constructed; however, none of them introduces a new method for the construction of the pyridine ring itself.



[Fig.22: Comparison of WS75624 A and B Synthesis]

B. Synthesis of Koert's Lodopyridone

The first total synthesis of lodopyridone was reported in 2012 by Koert. This approach heavily relies on methodologies previously developed for the synthesis of WS75624 A and B, utilizing palladocatalyzed couplings to assemble heterocyclic blocks.

The synthesis began with kojic acid (100), to which the ethanolamine chain (112) was introduced via a peptide coupling, following hydroxymethylation and Jones oxidation (figure 23). The pyranone ring (113) was subsequently nitrogenated using methylamine, followed by bromination with NBS to yield pyridone 114. A key step in this synthesis was the introduction of the S-methyl group, which was efficiently achieved through a copper iodide-catalyzed coupling between bromo-pyridone 114 and sodium thiomethylate. The final step in the synthesis of fragment 116 involved the introduction of an iodine atom, which was necessary for the subsequent attachment of the thiazole

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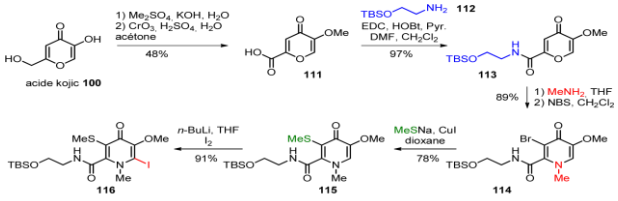
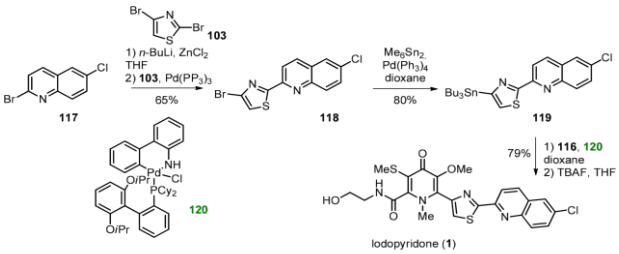
ring.



[Fig.23: Iodopyridone Synthesis by Koert]

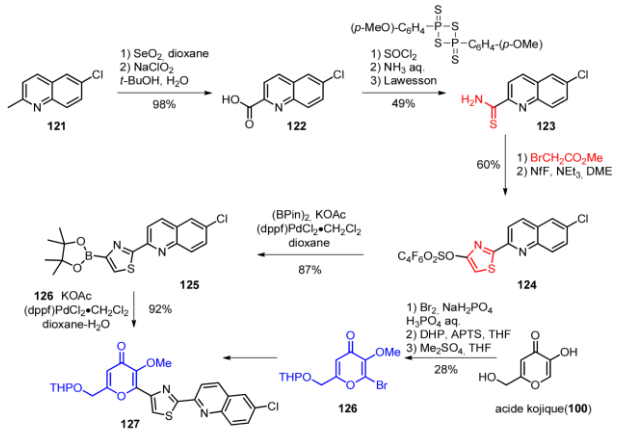
The second fragment, 118 (Figure 24), which contains both quinoline and thiazole, was synthesized via a Negishi coupling between bromo-quinoline 117 and dibromothiazole 103. This intermediate was then converted into stannane 119. To complete the total synthesis of lodopyridone, the polyheterocyclic backbone was finalized by a palladocatalyzed coupling between stannane 119 and iodo-pyridone 116, followed by deprotection of the alcohol group on the amine ethanol chain. This final coupling step mirrors the one used by Bach in his synthesis of WS75624 A.



[Fig.24: Iodopyridone Synthesis by Koert]

C. Synthesis of Moody's Lodopyridone

The second synthesis of lodopyridone by Moody (Figure24) closely resembles Koert's approach, utilizing the same disconnections but in a different sequence. Starting with quinoline 121, a thioamide group (123) was introduced, facilitating the construction of the thiazole ring through a "Hantzsch-thiazole" reaction. This step represents the key distinction from Koert's synthesis. After making some functional modifications to the thiazole ring, a borane group was incorporated (compound 125), enabling a palladium-catalyzed coupling with pyranone 126, which was synthesized from kojic acid 100. Whereas Koert opted to convert pyranone into pyridone and introduce the S-methyl group early in the process before linking to the thiazole, Moody chose to perform these steps after constructing the polycyclic system 127.



[Fig.25: Iodopyridone Synthesis by Moody]

The ethanolamine 112 chain was introduced to compound 127 under oxidative conditions (Figure 25). Subsequently, the pyranone ring of compound 128 was converted into pyridone 129 using methylamine. It is important to highlight that the yield of this reaction, when performed at this late stage of synthesis, is significantly lower compared to the Koert synthesis method. In the next step, the introduction of the S-methyl group was achieved through a bromination of the pyridine ring, followed by nucleophilic substitution of the bromine atom. This reaction, conducted without the use of copper salts, was notably less efficient than in earlier steps of the synthesis. To complete the total synthesis of lodopyridone (1), the alcohol functional group was deprotected.

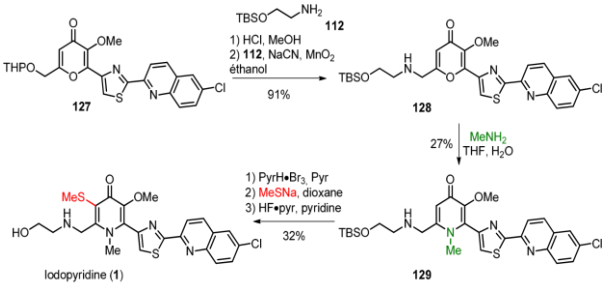


Schéma 18 : Synthèse de la lodopyridone par Moody.

[Fig.26: Iodopyridone Synthesis by Moody]

The various synthetic routes to lodopyridone and WS75624 A and B are all highly elegant and efficient. However, the strategies that rely on metallo-catalyzed couplings to form the different cycles, as well as the frequent use of kojic acid as a precursor for pyridone, make these approaches somewhat repetitive. To differentiate our synthesis, we have conceived a novel strategy based on the construction of pyridone, using biomimetic-inspired disconnections informed by the biosynthetic hypotheses we previously proposed.

VIII. CONCLUSION

This study successfully advances the understanding of lodopyridone and its biosynthetic pathways, contributing significantly to the field of natural product chemistry. Through a comprehensive exploration of the biomimetic synthesis of lodopyridone, we have elucidated potential biosynthetic routes that involve key amino acids, underscoring the compound's complex structure and its relationship to thiopeptide antibiotics. The classification of 4-pyridone derivatives revealed a rich diversity among these compounds, while the comparative analysis with thiopeptide antibiotics highlighted crucial structural and biosynthetic similarities.

The innovative synthetic strategies discussed, including palladocatalyzed couplings and the construction of nitrogenous heterocycles, pave the way for more efficient and targeted approaches to the synthesis of lodopyridone. By integrating insights from both natural biosynthetic pathways and synthetic methodologies, this research presents a promising framework for the development of novel

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therapeutics derived from these unique natural products.

Moreover, the phytochemical analysis of *Lycopodiella cernua* and *Nitraria retusa* offers valuable data that may further elucidate the ecological roles and potential applications of these species. The findings from this study not only enhance our comprehension of lodopyridone's biosynthesis but also set the stage for future research aimed at discovering new compounds with significant pharmaceutical potential. As the field continues to evolve, the integration of biomimetic strategies with traditional synthetic approaches will undoubtedly yield exciting advancements in the development of natural product-based therapeutics.

DECLARATION STATEMENT

I must verify the accuracy of the following information as the article's author.

- **Conflicts of Interest/ Competing Interests:** Based on my understanding, this article has no conflicts of interest.
- **Funding Support:** This article has not been sponsored or funded by any organization or agency. The independence of this research is a crucial factor in affirming its impartiality, as it has been conducted without any external sway.
- **Ethical Approval and Consent to Participate:** The data provided in this article is exempt from the requirement for ethical approval or participant consent.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Authors Contributions:** The authorship of this article is contributed solely.

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