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ADVANCEMENTS IN THE TOTAL SYNTHESIS OF CYCLOTRIPEPTIDIC NATURAL PRODUCTS: EXPLORING THE THERAPEUTIC POTENTIAL OF MARINE-DERIVED COMPOUNDS

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ABSTRACT
The exploration of marine natural products has garnered significant interest due to their unique chemical diversity and potential therapeutic applications. This document focuses on the total synthesis of cyclotripeptidic natural products, particularly those within the aurantiomide series, which contain the piperazino[2,1-b]quinazolin-3,6-dione core structure. These compounds exhibit notable pharmacological properties, including anticancer, anti-inflammatory, and antimicrobial activities. The synthesis of these complex molecules has historically faced challenges related to their intricate structures and biosynthetic pathways. Recent advancements in synthetic methodologies, such as microwave-assisted synthesis and biomimetic oxidation, have enhanced the efficiency and selectivity of these reactions. Additionally, innovative approaches like retro-Claisen rearrangements and late-stage functionalization have provided new strategies for generating cyclotripeptides with desired bioactivities. Despite these advancements, optimizing reaction conditions and improving yields remain ongoing challenges. This document also addresses the biosynthetic pathways of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides, providing insights into the enzymatic processes that facilitate their formation. By highlighting both the synthetic strategies and the biological significance of these compounds, this work contributes to the growing body of knowledge surrounding marine natural products. Ultimately, continued exploration in this field aims to harness the therapeutic potential of marine biodiversity for future medicinal applications, paving the way for innovative drug discovery and development.

KEYWORDS: Cyclotripeptides; Marine Natural Products; Piperazino[2,1-b]quinazolin-3,6-dione; Total Synthesis; Pharmaceutical Applications; Biosynthetic Pathways; Microwave-Assisted Synthesis; Oxidative Functionalization.

INTRODUCTION
The exploration of marine natural products has gained significant momentum in recent years, driven by the unique chemical diversity and biological activities exhibited by these compounds.[1] Covering over 71% of the Earth's surface, the oceans host a remarkable array of life forms, many of which produce secondary metabolites that have profound implications for pharmaceuticals and biotechnology.[2] Marine organisms, particularly those derived from sponges and associated microorganisms, are known to produce a vast range of bioactive compounds, including alkaloids, peptides, and terpenes.[3] These compounds often possess complex structures and diverse biological activities, making them valuable resources for drug discovery.[4] Among the notable classes of marine natural products are cyclotripeptides, specifically those containing the piperazino[2,1-b]quinazolin-3,6-dione core structure.[5] This heterocyclic framework is characterized by its structural complexity and has been shown to exhibit significant pharmacological properties, including anticancer, anti-inflammatory, and antimicrobial activities.[6] The study of such compounds not only furthers our understanding of marine biodiversity but also provides insights into potential therapeutic agents that could be developed for various medical applications.[8]

Historically, the synthesis of these natural products has presented numerous challenges, particularly due to the intricacies involved in their chemical structures and the biosynthetic pathways that lead to their formation.[9] The total synthesis of cyclotripeptidic natural products, such as those from the aurantiomide series, has emerged as a

critical area of research.[10] These compounds are of particular interest due to their potential applications in treating a range of diseases, including cancer and infectious diseases.[11] Recent advancements in synthetic methodologies have enhanced the feasibility of producing these complex molecules. Techniques such as microwave-assisted synthesis and biomimetic oxidation have been integrated into synthetic strategies, allowing for more efficient and selective reactions. Additionally, the exploration of retro-Claisen rearrangements and late-stage functionalization has opened new avenues for generating cyclotripeptides with desired bioactivities.[12]

Despite these advancements, many challenges remain in optimizing reaction conditions and improving yields.[13] The synthesis of oxepine-containing cyclotripeptides, for instance, has proven difficult, necessitating innovative approaches to overcome the limitations of existing methods.[14] This document presents a comprehensive overview of the synthetic strategies employed to develop cyclotripeptidic natural products, with a focus on the aurantiomide series.[15] It discusses the chemical diversity of marine-derived compounds, the biosynthetic pathways leading to their formation, and the various methodologies utilized in their total synthesis.[16] Through a detailed examination of recent research efforts, this work aims to contribute to the growing body of knowledge surrounding marine natural products and their synthetic counterparts.[17] By addressing the challenges and breakthroughs in the synthesis of these complex molecules, this document underscores the importance of continued exploration in the field of natural product chemistry, with the ultimate goal of harnessing the therapeutic potential of marine biodiversity for future medicinal applications.[18] The journey through the synthesis of these compounds not only illuminates the intricacies of their chemical structures but also highlights the innovative approaches necessary to unlock their full potential in drug discovery and development.[19]

1. Marine natural products, and those isolated from Sponge-derived microorganisms

1.1. Marine natural products

The oceans, which cover 71% of the Earth's surface and account for 95% of the biosphere's volume, represent the largest habitat for life on our planet. Marine life is astonishingly diverse, with estimates of over 10 million species, encompassing 35 of the 36 recognized animal phyla, of which 13 are unique to marine environments. However, our comprehension of marine ecosystems remains less advanced compared to terrestrial ecosystems.[20]

Marine organisms contend with unique challenges in adapting to extreme environmental conditions, including high pressure, salinity, oligotrophy, temperature variations (from the heat of volcanic vents to the cold of polar regions), limited light, and oxygen scarcity. These environmental factors significantly influence the metabolism, survival strategies, information transfer, and adaptive mechanisms of marine species, differentiating them from terrestrial organisms. Consequently, the pathways of secondary metabolism and enzymatic reactions in marine species are largely distinct from those found in land-based organisms.[21]

The complex conditions and rich biodiversity of marine ecosystems enhance the structural and bioactive diversity of marine natural products. This diversity offers a vast array of potential resources for pharmaceutical research, leading to the discovery of novel compounds for various medical applications. In contrast to the extensive historical investigation of drugs derived from terrestrial plants, the exploration and development of pharmaceuticals from marine organisms is a relatively recent endeavor.[22]

Notably, as early as 1922, researchers in Japan isolated an insecticidal toxin known as nereistoxin from the marine organism Lumbriconeris heteropoda, found in shallow sediments.[23] Despite its relatively simple structure, this toxin exhibited remarkable toxicity. This discovery paved the way for the development of several insecticides, such as padan, with nereistoxin serving as the foundational compound. These insecticides demonstrated efficacy against pests through contact and ingestion, as well as systemic and ovicidal effects figure 1.

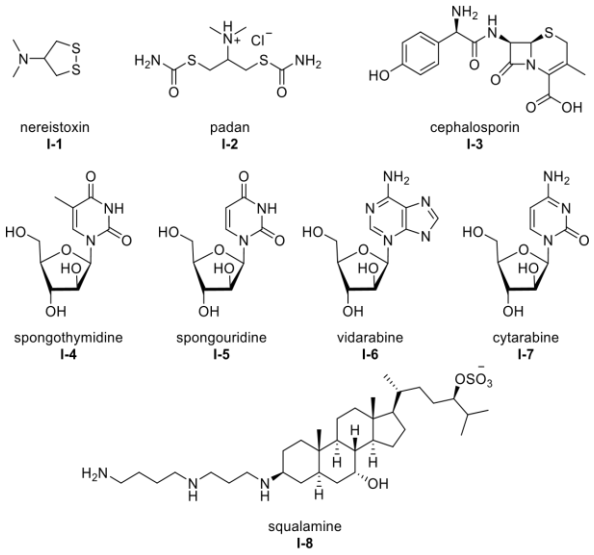

Figure 1. Marine natural products and their derivatives.

The well-known cephalosporin antibiotics, derived from the marine fungus *Cephalosporium acremonium*, play a crucial role in the treatment of bacterial infections. Thymidine analogs, such as spongothymidine and spongouridine, isolated from the sponge *Cryptheca crypta*, have served as foundational compounds for the development of significant antiviral and anticancer medications, specifically vidarabine and cytarabine, respectively.[24]

Squalamine, a polyamine with a steroid-like structure, was extracted from the liver tissue of the black-margined spiny shark, *Centrophorus atromarginatus*. Pharmacological investigations have demonstrated that squalamine inhibits angiogenesis, positioning it as a potential candidate for anticancer drug development. Further research has revealed its antiviral properties, showing efficacy against pathogens such as the yellow fever virus, equine encephalitis virus, and cytomegalovirus.[25]

In the field of marine natural products, it is clear that secondary metabolites derived from marine sponges and microorganisms frequently exhibit unique structures and significant biological activities. This phenomenon is largely due to the rich diversity of microorganisms that coexist with sponges, resulting in a wealth of bioactive secondary metabolites that enhance the symbiotic relationships among these organisms. Consequently, the study of sponges and their associated microorganisms has become an increasingly important area of research in recent years.[26]

1.2. Natural products from Sponge and Sponge-derived microorganisms

The evolutionary adaptations of sponges, as sessile organisms, have led to the development of sophisticated chemical defenses that allow them to thrive in the marine environment. This has resulted in a vast array of secondary metabolites, characterized by structural complexity that reflects their intricate biosynthetic pathways and diverse bioactivities. Sponges are known to harbor over 5,300 distinct isolated compounds, with ongoing research uncovering hundreds of new compounds annually.[27]

In addition to the previously mentioned unusual nucleosides, sponges have been found to produce bioactive terpenes, sterols, cyclic peptides, alkaloids, fatty acids, peroxides, and amino acid derivatives. A notable compound is halichondrin B, a 60-carbon macrocyclic polyether with cis-fused boat pyran rings, isolated from the Japanese black sponge *Halichondria okadai*. Halichondrin B demonstrates potent cytotoxicity against melanoma B16 cells (IC50 = 0.093 ng/mL), which has led to the development of the metastatic breast cancer drug eribulin (Halaven®), an industry-produced analog of halichondrin B synthesized through a complex process involving 60 steps, including a longest linear sequence of 20 steps.[28]

Furthermore, latrunculin B, an actin polymerization inhibitor with potential applications in modulating the electrophysiological characteristics of pulmonary veins, has also been isolated from marine sponges, specifically *Negombata* (formerly *Latrunculia*). Recent advancements in our laboratories have successfully achieved the total synthesis of latrunculin B figure2.

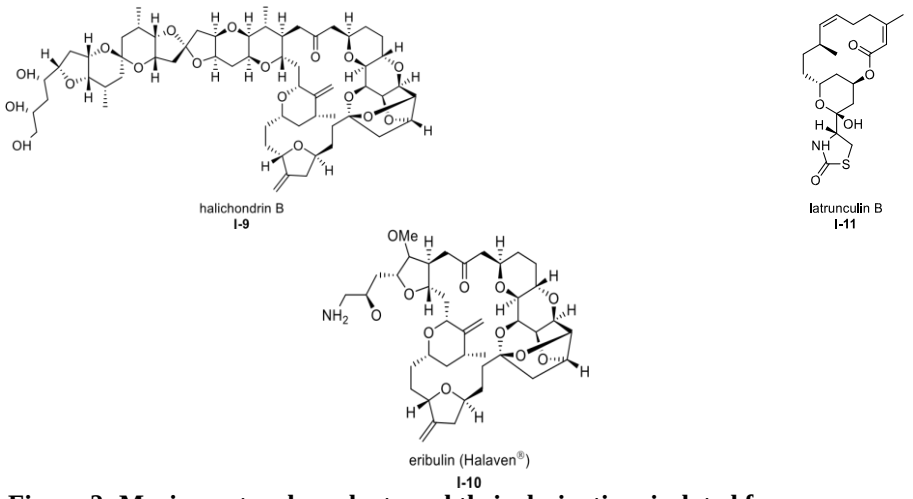

Figure 2: Marine natural products and their derivatives isolated from sponges.

In addition to the secondary metabolites directly produced by sponges, their loose and porous structures support a diverse community of bacteria and fungi that inhabit them for extended periods. These microorganisms contribute significantly to the overall biomass of the sponge. Over the past few decades, more than 800 new marine natural products derived from sponge-associated microorganisms have been documented. Many of these compounds exhibit notable biological activities, including antibacterial, anticancer, antifungal, anti-HIV, anti-inflammatory, and antimalarial effects.[29]

The compounds with unique structures, such as quinazolinopiperazine, macrocyclic polyketides, chromopeptides, and phenylspirodrimanes, have been identified from microorganisms that maintain symbiotic relationships with sponges.[30] Each of these compounds not only possesses novel structures but also demonstrates significant biological activity. One such natural product, anacine, characterized by its piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure, was isolated from the sponge-derived fungus *Penicillium aurantiogriseum* associated with *Mycale plumose*. Anacine exhibited chitinase inhibitory activity against

hexosaminidase OfHex1 (chitinolytic β-N-acetyl-D-hexosaminidase from *Ostrinia furnacalis*) and chitinase OfChi-h, as well as cytotoxic effects against various cancer cell lines, including A549 (human lung carcinoma), HGC-27 (metastatic lymph node of gastric cancer), UMUC-3 (urinary bladder cancer), HL-60 (peripheral blood leukocytes), P388 (lymphoma), and BEL-7402 (human liver cancer) figure3.

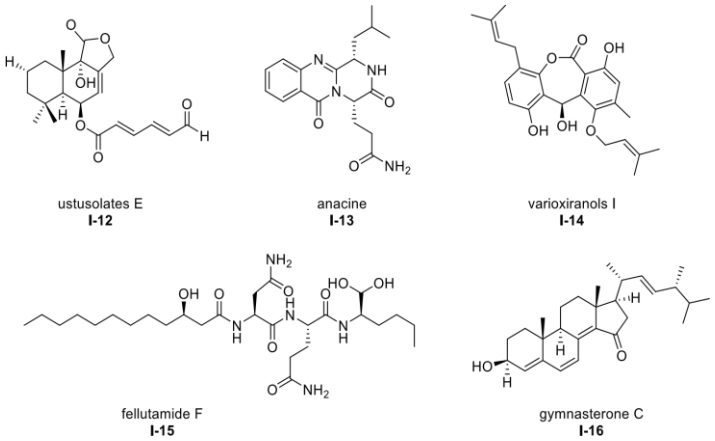

Figure 3: Marine natural products isolated from sponge-derived microorganisms.

Research has demonstrated that compounds containing the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure, primarily derived from *Penicillium* species, exhibit a wide range of biological activities. Additionally, the tricyclic piperazino[2,1-b]quinazolin-3,6-dione core features the 4(3H)-quinazolinone bicyclic heterocycle. Derivatives of quinazoline and quinazolinone are of considerable interest in pharmaceutical research. Consequently, prior to initiating our synthetic studies on natural products featuring the piperazino[2,1-b]quinazolin-3,6-dione structure, it is essential to develop a comprehensive understanding of the quinazolinone framework and to review relevant synthetic methodologies applicable to this research.[31]

2. GENERALITIES ON THE CHEMISTRY OF 4(3H)-QUINAZOLINONES

2.1. Quinazoline and quinazolinone products and natural products

These compounds have attracted significant attention due to their varied pharmacological properties, which include anticancer, antimalarial, anti-inflammatory, antibacterial, antidiabetic, anticonvulsant, and diuretic activities. Quinazolinones and their derivatives are predominantly found in nature, existing in two main forms: monosubstituted (including 2-substituted and 3-substituted variants) and 2,3-disubstituted forms.[32] Among these, disubstituted compounds have become a primary focus for researchers because of their increased structural complexity and the broad range of biological activities they demonstrate figure4.

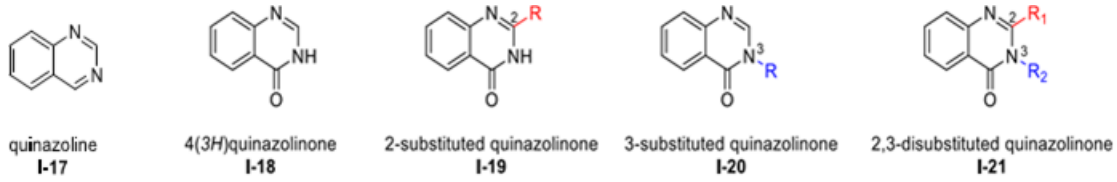

Figure 4: Quinazoline and quinazolinone structures.

Numerous natural compounds exhibit substituents on the benzene ring, commonly involving halogens or methoxy groups; however, these are not the focus of the current discussion. Among disubstituted quinazolinones, two predominant structural motifs are observed. The first motif features distinct groups substituting the 2 and 3 positions, as exemplified by methaqualone and balaglitazone. The second motif involves the fusion of a ring between the 2 and 3 positions, which can include a pyrrole, indole, pyrroloquinoline, piperidine, pyrazine, or diazepine. Notably, the 2,3-fused heterocycles are particularly abundant among natural quinazolinone alkaloids. Because these fused compounds possess a greater number of pharmacophoric elements compared to simpler quinazolinones, they exhibit a wider range of biological activities. Numerous natural compounds exhibit substituents on the benzene ring, commonly involving halogens or methoxy groups; however, these are not the focus of the current discussion. Among disubstituted quinazolinones, two predominant structural

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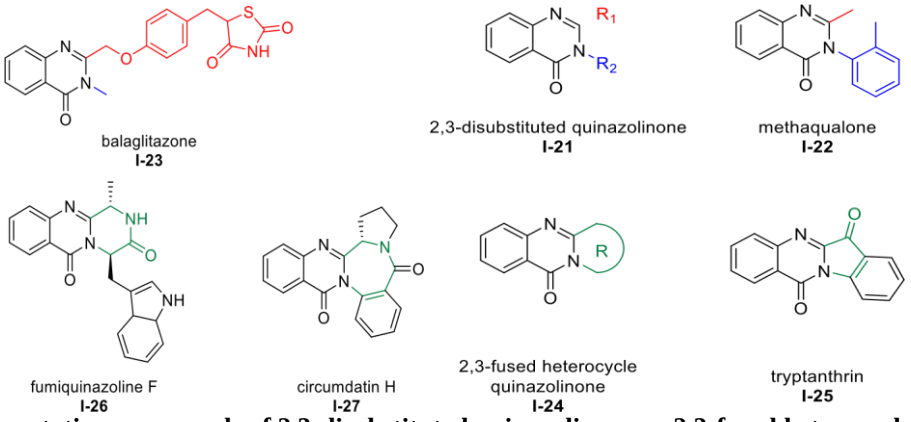

Figure 5: Representative compounds of 2,3-disubstituted quinazolinone or 2,3-fused heterocycle quinazolinone.

For instance, tryptanthrin, featuring a fused pyrrole structure, is obtained from the fungus *Candida lipolytica* and other sources, exhibiting a range of pharmacological properties, including anticancer, anti-inflammatory, antiprotozoal, antiallergic, antioxidant, and antimicrobial activities. Fumiquinazoline F, characterized by a fused piperazine structure and derived from the marine fungus *Aspergillus fumigatus*, demonstrates antibacterial, anti-insect, and cytotoxic effects. Additionally, methaqualone acts as a sedative by enhancing the activity of GABA receptors in the brain and nervous system, while balaglitazone functions as a second-generation agonist of the peroxisome proliferator-activated receptor (PPAR) gamma.[35]

2.2. General methods for the synthesis of 4(*3H*)-quinazolinones

The synthesis of 4(3H)-quinazolinone structures has been an area of extensive research for more than a century. In 1895, Niementowski successfully synthesized the 4(3H)-quinazolinone structure by condensing an amide compound with anthranilic acid at temperatures ranging from 120 to 130 °C. This reaction is referred to as the Niementowski reaction figure6.

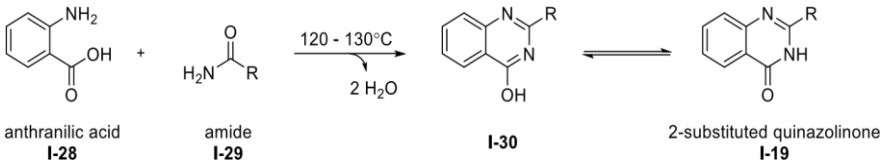

Figure 6: Niementowski reaction to the 4(*3H*)-quinazolinone structure.

The mechanism of the Niementowski reaction begins with the formation of an amidine intermediate, which subsequently undergoes cyclization through intramolecular condensation to produce a cyclic amidine intermediate.[36] This intermediate then loses a water molecule, resulting in ring closure and the formation of the 2-substituted quinazolinone figure 7.

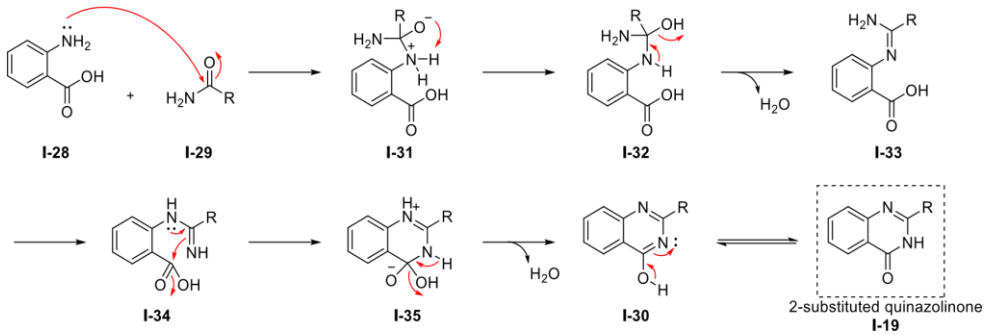

Figure 7: Mechanism of Niementowski reaction to 2-substituted quinazolinone.

Subsequently, the Niementowski reaction became a widely adopted method for synthesizing 4(3H)-quinazolinones, leading to ongoing developments and enhancements.[37] Over time, the reaction has evolved to utilize ortho-substituted anilines, such as anthranilic acid or isatoic anhydride, which are condensed with acid chlorides, imidates, or aldehydes. Additionally, it has been found that microwave irradiation can significantly improve the yields of these reactions figure 8.

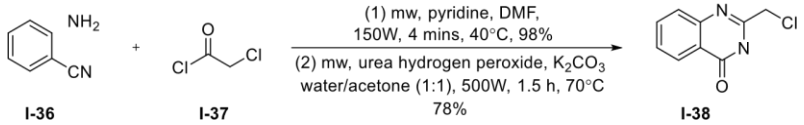

Figure 8: The preparation of 2-substituted quinazolinone under microwave irradiation.

Another frequently used method for synthesizing the 4(3H)-quinazolinone structure is the aza-Wittig reaction. This approach involves the formation of intermediate iminophosphoranes, which are prepared through the Staudinger reaction between a phosphine reagent and an aryl azide containing an ester group.[38] The iminophosphorane then reacts with an amide to generate an amidine, which subsequently undergoes cyclization to produce 2-substituted quinazolinones figure9.

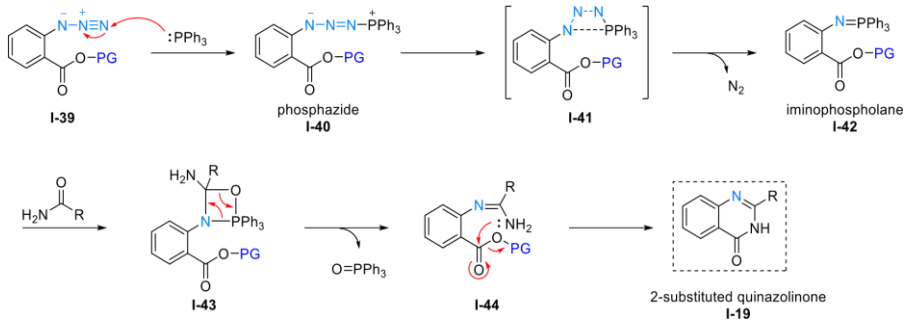

Figure 9: Mechanism of aza-Wittig reaction to 2-substituted quinazolinone.

This method is not limited to the synthesis of 2-substituted quinazolinones; it is equally applicable to 2,3-disubstituted quinazolinones. In 1989, the aza-Wittig reaction was first utilized for the synthesis of 2,3-disubstituted quinazolinones.[39] Since then, it has been further developed by various researchers into a more generalized approach. For instance, Wu's group reported a highly selective method employing the aza-Wittig reaction to synthesize 3-aminoalkyl-2-arylaminoquinazolin-4(3H)-one and 3,3'-disubstituted bis-2-arylaminoquinazolin-4(3H)-one. Additionally, the aza-Wittig reaction is often used as the final step in the ring closure for the total synthesis of 2,3-fused heterocyclic quinazolinones, particularly the piperazino[2,1-b]quinazolin-3,6-dione structure.[40] This intramolecular process will be discussed further in the context of Danishefsky's synthesis of N-acetylardeemin and Snider's synthesis of fumiquinazoline figure 10.

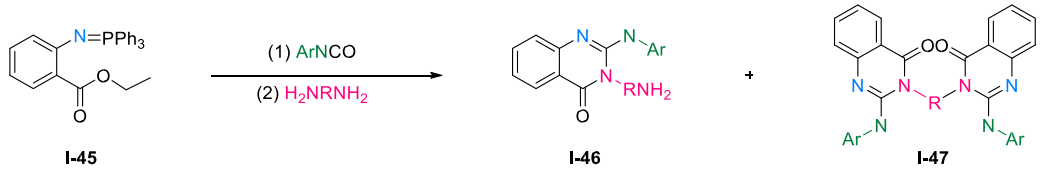

Figure 10: Aza-Wittig approach to 2,3-disubstituted quinazolinone.

In addition to the previously discussed methods, another widely adopted approach in recent decades involves the use of benzoxazinone intermediates for the synthesis of 4(3H)-quinazolinones.[41] This strategy is characterized by multi-component reactions that facilitate one-pot synthesis, with starting materials and synthetic pathways closely resembling natural biosynthetic processes. The reaction entails the condensation of anthranilic acid, ortho esters (or formic acid), and amines, leading to the formation of a benzoxazinone intermediate, which is typically utilized in the synthesis of 2,3-disubstituted quinazolinones figure 11.

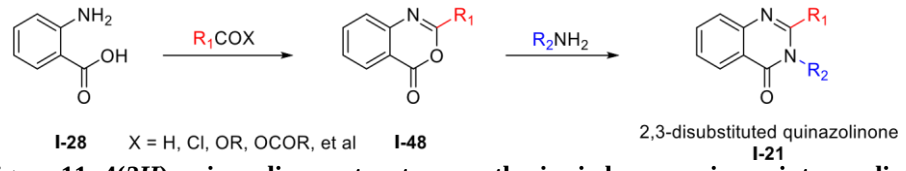

Figure 11: 4(*3H*)-quinazolinone structure synthesis via benzoxazinone intermediate.

Furthermore, the incorporation of microwave technology to accelerate reactions has made this method particularly popular for the total synthesis of 2,3-disubstituted quinazolinones.[42] This approach is especially significant in the synthesis of fumiquinazolines, where microwave-assisted methods have been extensively documented. One study described a three-component, one-pot reaction that produced piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptide, starting from anthranilic acid and various amino acids. Microwave heating facilitated this reaction, resulting in successful total syntheses of glyantrypine (R = H, 55% yield), fumiquinazoline F (R = Me from alanine, 39% yield), and fiscalin B (R = i-Pr from valine, 20% yield) figure12.

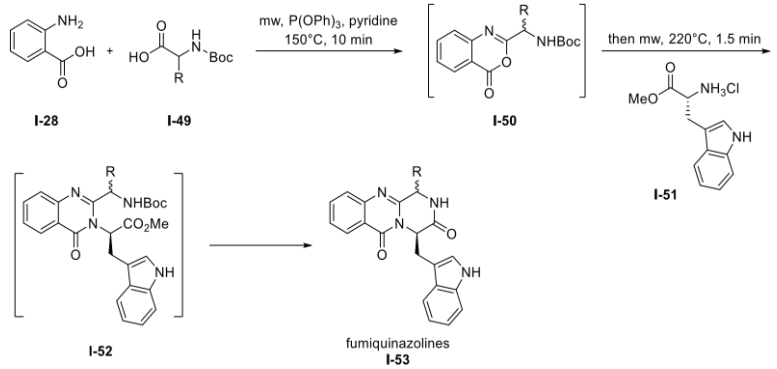

Figure 12: Microwave-promoted synthesis of fumiquinazolines via benzoxazinone intermediate.

There are several additional methods for synthesizing the 4(3H)-quinazolinone structure, including oxidative heterocyclization, transition-metal-catalyzed cyclizations, and radical cascade reactions.[43] Each of these approaches can produce the desired compound under specific conditions. However, a comprehensive discussion of these methods is beyond the scope of the current analysis figure13.

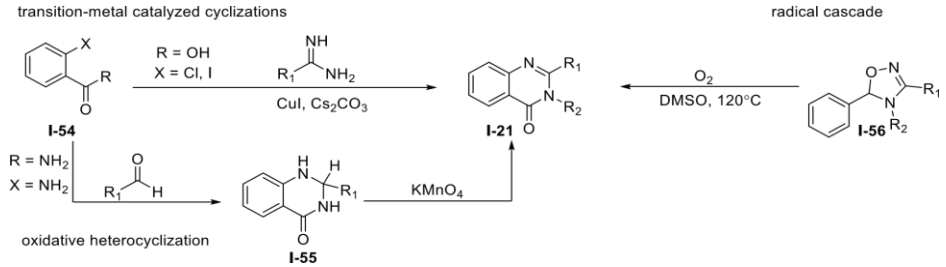

Figure 13: Different strategies to synthesize 4(*3H*)-quinazolinones.

The exploration of 4(3H)-quinazolinone synthesis primarily focuses on the development of 2,3-fused heterocyclic structures.[44] As previously mentioned in relation to anacine, fumiquinazolines, and other compounds featuring the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic framework, comprehending the methods for synthesizing these compounds is essential for advancing total synthesis efforts.[45]

3. CYCLOTRIPEPTIDE NATURAL PRODUCTS WITH A PIPERAZINO[2,1B]QUINAZOLIN-3,6-DIONE CORE

3.1. Chemical diversity and biology of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides isolated from marine fungi

In the preceding sections, we explored the classification and chemical synthesis of quinazoline and quinazolinone compounds, with a particular emphasis on 2,3-

disubstituted quinazolinones.[46] Our focus aligns with compounds such as anacine and fumiquinazoline F, which are categorized as 2,3-fused piperazine quinazolinones. The defining feature of these compounds is the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure, characterized by various substituents at the C-1 and C-4 positions. These substituents may be identical or different, depending on the amino acid precursor involved in their biosynthesis figure 14.

Notably, certain structures, such as compounds I-58 and I-59, not only exhibit substituents at the 1 and 4 positions but are also bridged or fused with another cycle, as seen in fumiquinazoline C and ardeemin. While compounds containing modifications in the benzene ring, such as the oxidized derivative oxepine I-60, are outside the primary focus of this discussion, their inclusion is justified due to their close biosynthetic relationship with piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides. Given our team's interest in this series of compounds, we will also address them in this section.[47]

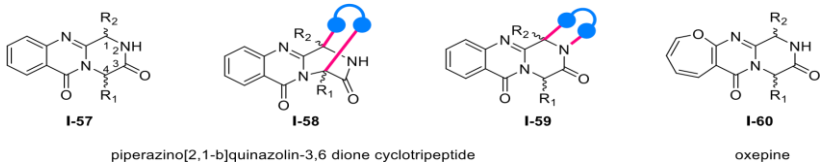

Figure 14: The piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptide and oxepine structure.

To date, more than a hundred natural products featuring the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure have been documented, with the majority originating from marine sources, particularly marine fungi.[48] Among these, fumiquinazolines are notable for their structural complexity, diversity, and abundance, with over 80 identified compounds and new discoveries reported annually. This class is characterized by the presence of a piperazino[2,1-b]quinazolin-3,6-dione core linked to an indole moiety.[49] The first secondary metabolite from the fumiquinazoline series, fumiquinazoline A, was reported in 1992 and originated from cytotoxic fungal metabolites derived from Aspergillus fumigatus, isolated from the marine fish Pseudolabrus japonicas. The structure of fumiquinazoline A differs from that of the more common fumiquinazoline F, particularly in the indole moiety, which features a more complex tricyclic imidazoindolone core.[50]

Using fumiquinazoline A and fumiquinazoline F as templates, it is evident that many natural products, such as fiscalin B, cladoquinazoline, and fumiquinazoline M, are analogs of these compounds.[51] The primary distinction among these analogs lies in the substituent groups at the C-1 and C-4 positions, with variability attributed to different substrate choices during biosynthesis and unique catalytic phases in enzyme reactions, often involving oxidation steps. In more complex structures like fumiquinazolines C, D, K, and Q, as well as N-formyllapatin A and sartorymensin, the bridging between positions 1 and 4 occurs under specific conditions, resulting in diverse spatial arrangements and three-dimensional structures.[52] Additionally, glucosidic compounds linked to β-D-glucose have also been identified. The structural diversity of fumiquinazolines and related alkaloids is associated with significant biological activity, including antimicrobial and antitumor effects, making them of considerable interest for both biosynthetic and synthetic research figure15

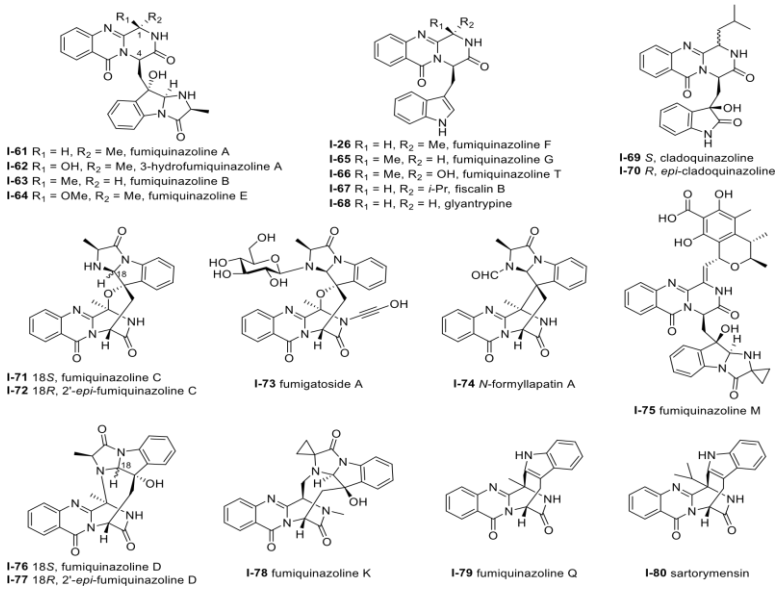

Figure 15: Fumiquinazolines and structurally related alkaloids.

In addition to the fumiquinazoline compounds that contain an indole moiety, there exists a significant group of compounds featuring the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure. This class of compounds shares similarities with fumiquinolines, primarily differing in the orientation of substituent groups at the C-1 and C-4 positions. Notable examples include versicomide A, protuboxepin K, verrucine A, and polonimide C.[53]

Compounds such as anacine exhibit a distinct three-carbon chain at the C-4 position, terminating in an amide bond (propanamide), a characteristic derived from glutamine or glutamic acid in their biosynthesis.[54] A detailed comparison of these compounds indicates that oxidation reactions can readily occur on the benzene ring and at carbon 1, leading to structural variations such as felicarnezoline A, chrysopiperazine C, 3-hydroxyprotuboxepin K, and aurantiomide A.[55] Additionally, olefinic compounds like carnequinazoline A, 3,15-dehydroprotuboxepin K, and aurantiomide C can form through dehydration following oxidation. This class of compounds demonstrates significant biological activities, including cytotoxicity and antimicrobial effects, which are largely attributed to the presence of the piperazino[2,1-b]quinazolin-3,6-dione pharmacophore figure16.

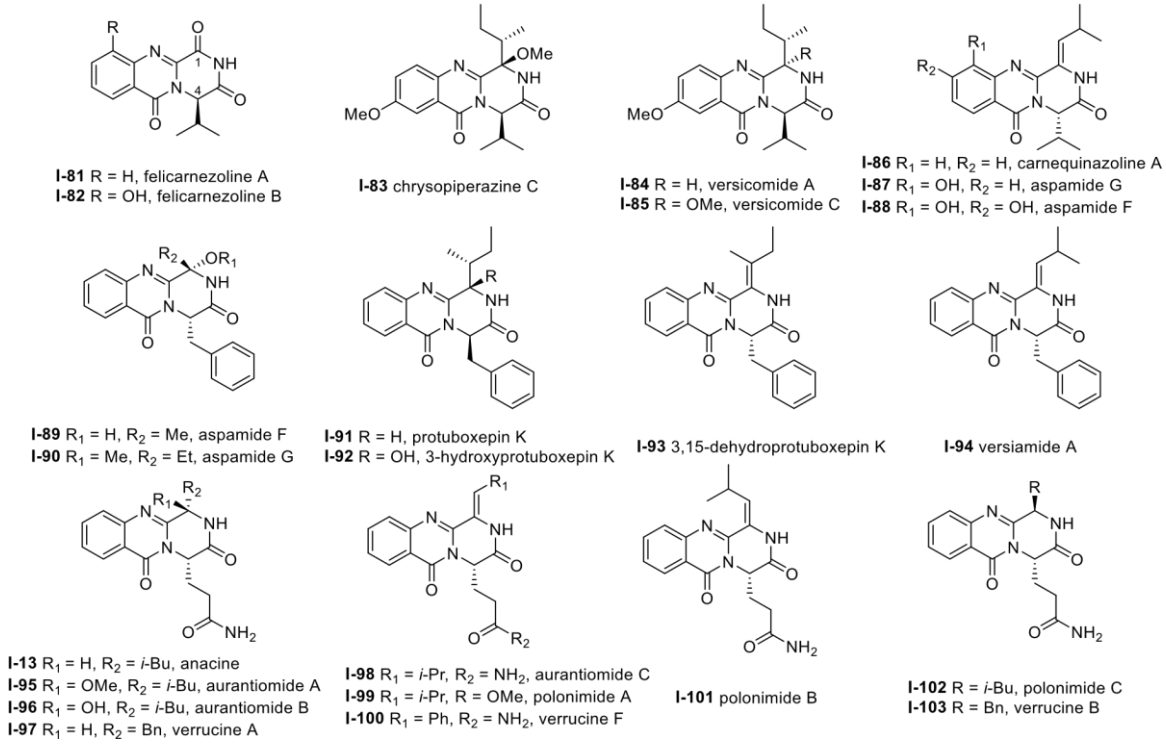

Figure 16: Natural products with piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure.

Compounds that feature a connection to a nitrogen atom at the 2-position include notable examples such as ardeemin and N-acetylardeemin.[56] These compounds were isolated from the fermentation broth of a strain of Aspergillus fischeri and have demonstrated cytotoxic activity against multidrug-resistant human tumor cells figure 17.

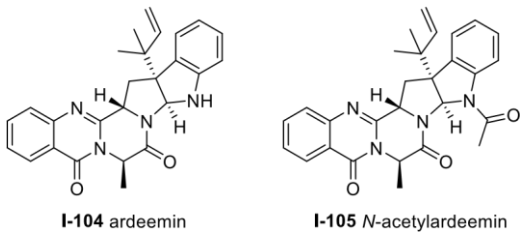

Figure 17: Natural products ardeemin and *N*-acetylardeemin.

The oxepine analogs are structurally related to the previously discussed compounds featuring the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure. Specifically, compounds such as chrysopiperazines A and C, chrysopiperazine B, versicomide C, cinereain, and carnequinazoline A differ primarily by the presence of an oxepin or a benzene ring figure 18.

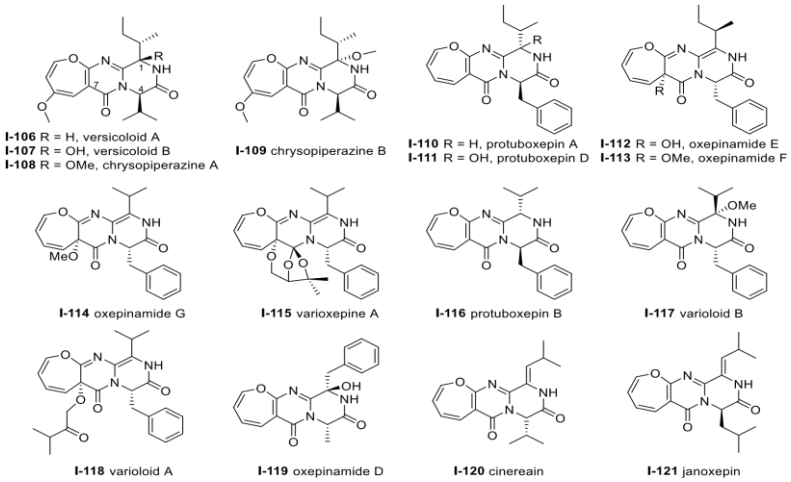

Figure 18: Natural products with an oxepine structure.

During the isolation of these compounds, researchers in natural products often find them alongside the previously mentioned piperazino[2,1-b]quinazolin-3,6-dione, indicating a shared biosynthetic origin. Variations among the compounds are likely due to different stages of oxidation mediated by enzymes. Notably, oxidation readily occurs at the C-1 position as well as at the 7-position on the aromatic ring, as demonstrated by oxepinamides F and G. These processes can lead to the formation of more complex structures, such as varioxepine A and varioloid A. The oxepin structures and their biosynthetic pathways have garnered significant interest in our lab, with detailed synthetic studies conducted by colleagues. Dr. Wei Zhang focused on biomimetic oxidation of quinazolinone derivatives and the development of an alternative retro-Claisen rearrangement for total synthesis, while Dr. Quentin Ronzon worked on the total synthesis of cinereain and janoxepin. Further details on these works will be provided later.[57]

3.2. Biosynthesis of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides

3.2.1. The biosynthetic pathway of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides

In the past decade, the biosynthetic pathways leading to the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure have been explored, with a primary focus on the enzymatic processes that contribute to the fungal fumiquinazoline family of peptidyl alkaloids. The initial stage involves trimodular non-ribosomal peptide synthetases (NRPSs) that incorporate anthranilic acid and various amino acids to form a linear tripeptide. This tripeptide then undergoes cyclization to produce cyclotripeptides figure 19.

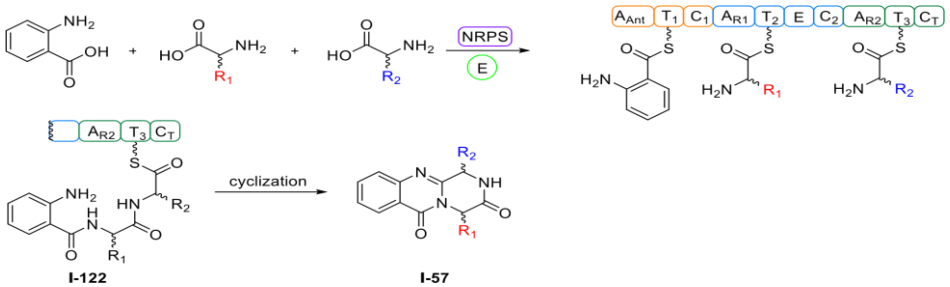

Figure 19: Proposed biosynthetic route to piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides.

In the research on fumiquinazoline biosynthesis, the cyclization of tripeptide I-123 into fumiquinazoline F involves a two-step condensation reaction that produces different intermediates based on two possible mechanisms. In pathway A, the amino group of anthranilic acid condenses with the thioester group to form a macrocyclic intermediate, which subsequently undergoes intramolecular cyclization to yield fumiquinazoline F. In pathway B, the amide group of the first condensed amino acid reacts with the thioester group of the second amino acid to form a diketopiperazine intermediate. This intermediate then cyclizes and dehydrates, resulting in the formation of the cyclotripeptide fumiquinazoline F figure 20.

For compounds such as fumiquinazolines A, which feature a tricyclic imidazoindolone structure, as well as more complex compounds like fumiquinazolines C and D that possess functional groups at the C-1 and C-4 positions, these structures can be derived from fumiquinazoline F through the action of three tailoring enzymes: the monomodular NRPS Af12050, the flavoenzyme oxygenase Af12060, and the monocovalent flavoprotein Af12070.[58]

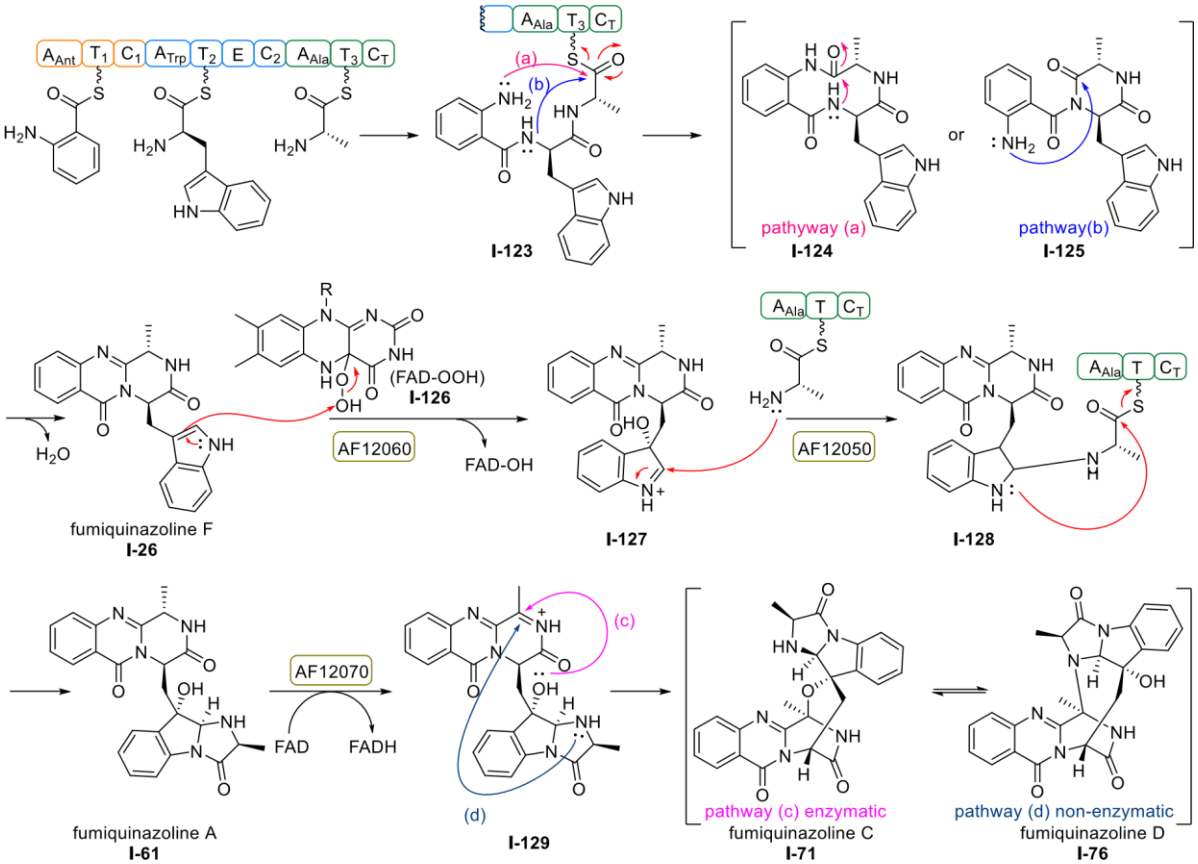

Figure 20: Proposed biosynthetic route to fumiquinazolines A, C, D, and F.

The flavin adenine dinucleotide (FAD)-dependent enzyme Af12060 facilitates the transfer of an oxygen atom to the 3-position of the indole. Subsequently, the alanine-activating NRPS module Af12050 adds L-alanine to the iminium intermediate I-127, resulting in the formation of the tricyclic imidazolindolone ring system characteristic of fumiquinazoline A. Finally, the flavoprotein Af12070 catalyzes the oxidation of fumiquinazoline A to generate an imine intermediate within the piperazine ring, leading to the production of fumiquinazoline C. In contrast, fumiquinazoline D is primarily formed from fumiquinazoline C under non-enzymatic conditions or through a minor pathway.[59]

3.2.2. Other biosynthetic pathways towards piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides

An alternative pathway for the synthesis of quinazolinones was discovered through the activity of the Fe^{2+}/α-ketoglutarate-dependent dioxygenase on benzo[1,4]diazepine-2,5-dione substrates. Specifically, when the substrate contains substituents where n equals 0 or 2, the enzyme facilitates the formation of quinazolinones. Conversely, when the substituent is altered to n equals 1, the enzyme catalyzes the rearrangement of the substrate to form 2-quinolone. This observation indicates a novel enzymatic route for the production of quinazolinone derivatives figure 21.

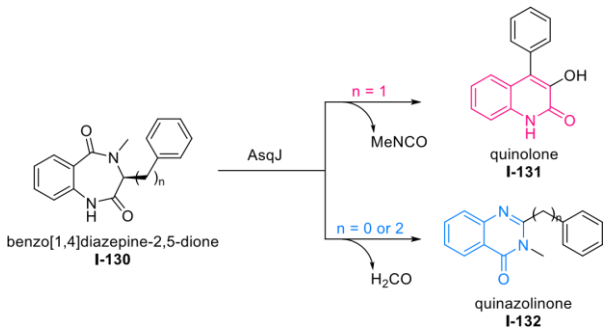

Figure 21: Synthesis of quinolone and quinazolinone alkaloids catalyzed by substrate-directed dioxygenase AsqJ.

Recent discoveries have revealed an unexpected assembly mechanism for 4(3H)-quinazolinones through the biochemical analysis of the chrysogine pathway. This process is mediated by a three-module non-ribosomal peptide synthetase, ftChyA, which features an atypical terminal condensation domain that facilitates the formation of tripeptides. Additionally, an unusual α-ketoglutarate-dependent dioxygenase, ftChyM, is involved in catalyzing the oxidative cleavage of the C-N bond in a tripeptide, leading to the production of 4(3H)-quinazolinone. This biosynthetic pathway, transitioning from tripeptides to dipeptides, represents a novel route distinct from previously known methods for synthesizing 4(3H)-quinazolinones figure 22.

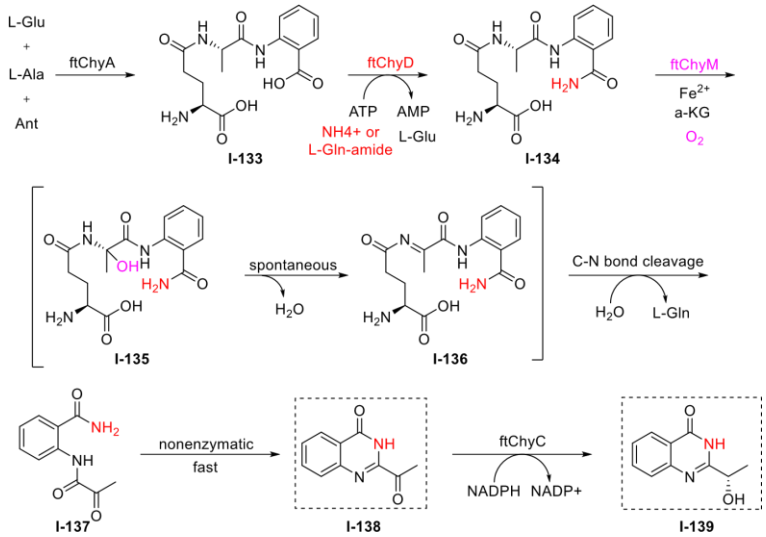

Figure 22: Primary pathway of unexpected assembly machinery for 4(*3H*)-quinazolinone scaffold synthesis.

3.2.3. The biosynthesis of oxepine products

The cyclotripeptide piperazino[2,1-b]quinazolin-3,6-dione, produced through gene deletion, heterologous expression, and feeding experiments, can undergo oxidation on its aromatic ring to form an oxepin ring, facilitated by cytochrome P450 enzymes. Additionally, this process permits over-oxidation at various sites, leading to the formation of protuboxepin A (I-110) and oxepinamides D (I-119) and F (I-113) figure 23.

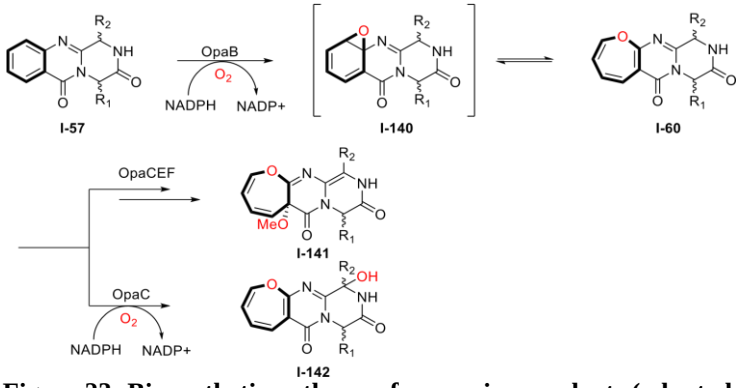

Figure 23: Biosynthetic pathways for oxepine products (adapted.

The exploration of biosynthetic pathways has provided significant insights that can inform chemical strategies for synthesizing these compounds. Consequently, biomimetic approaches have been employed to accomplish the total synthesis of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides and their oxidized derivatives. Furthermore, several alternative methods have been documented. The subsequent discussion will present the chemical synthesis of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides, organized according to the classification of the compounds. [60-66]

3.3. Synthesis methods of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides

The Niementowski method, the aza-Wittig method, and the condensation method using a benzoxazinone intermediate were previously introduced as general strategies for synthesizing 4(3H)-quinazolinones. In the synthesis of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides, the Niementowski method was not utilized, as it is primarily applicable to 2-substituted quinazolinones and is not suitable for this class of disubstituted compounds. As a result, the most commonly used methods for synthesizing piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides in recent decades have included the aza-Wittig method and the condensation method, along with techniques such as one-pot reactions and microwave-accelerated condensation in specific contexts figure 24.

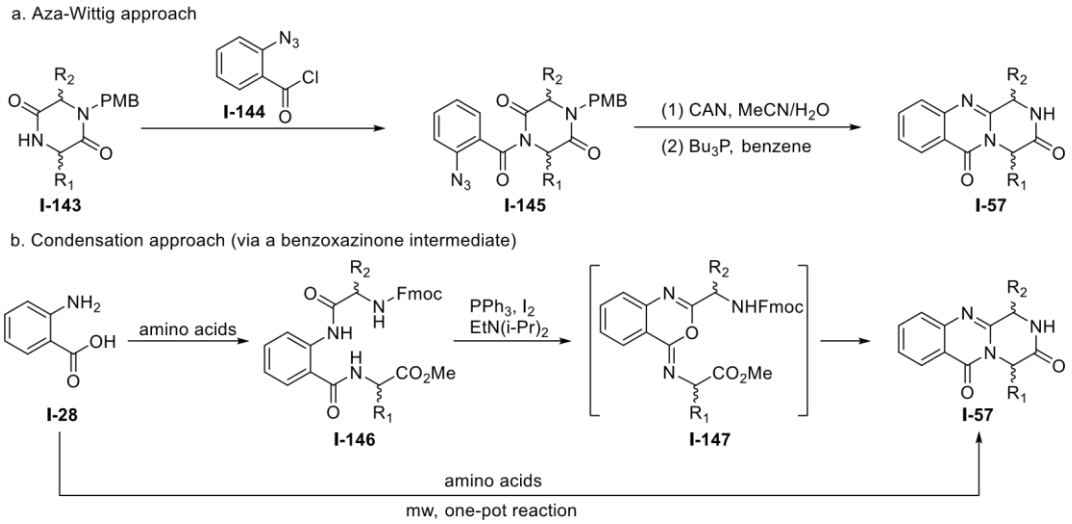

Figure 24: Two commonly used methods to synthesize piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides.

3.3.1. Recent research on the total synthesis of fumiquinazolines

The first synthetic study of fumiquinazolines was conducted in 1997, employing the aza-Wittig method to synthesize (+)-fumiquinazoline G and (+)-dehydrofumiquinazoline G. This synthetic approach, based on a procedure by Eguchi, began with the preparation of pyruvamide from Cbz-L-Trp and dimethoxybenzylamine. The synthesis involved a sequence of steps that included reduction and acylation with o-azidobenzoyl chloride, leading to the formation of an intermediate. Subsequent reactions included the Staudinger reaction, deprotection, and cyclization, culminating in the natural product (+)-fumiquinazoline G after 12 steps with an overall yield of 11%. The final oxidation step produced (+)-dehydrofumiquinazoline G with an 80% yield figure 25.

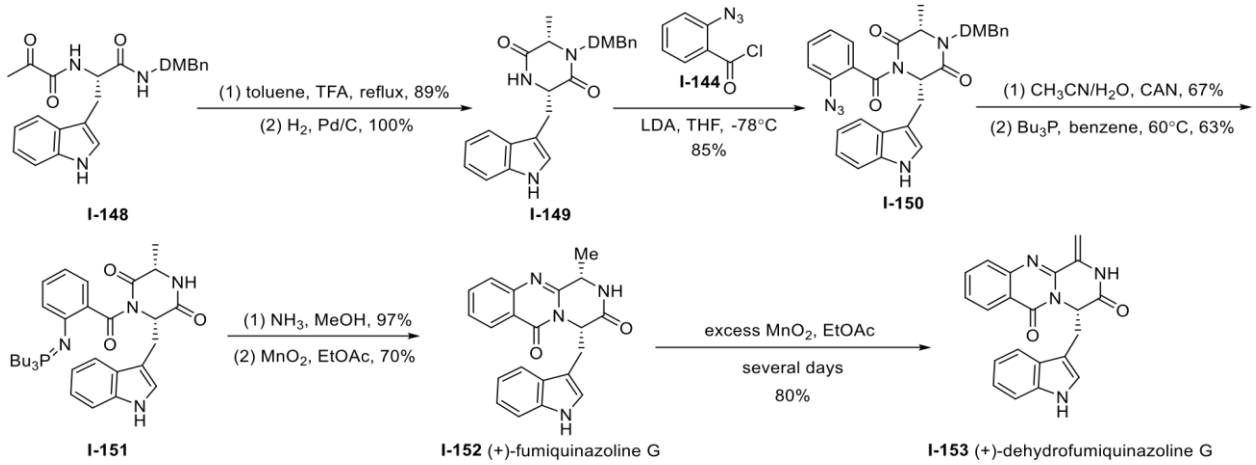

Figure 25: Total synthesis of (+)-fumiquinazoline G and (+)-dehydrofumiquinazoline G.

Although the synthesis of the natural products (+)-fumiquinazoline G and (+)-dehydrofumiquinazoline G was successful using this strategy, certain limitations were identified due to the harsh reaction conditions required for deprotecting the dimethoxybenzyl (DMB) moiety and for preparing diketopiperazine through the condensation of pyruvamide. These factors restricted the broader applicability of the method. In response, efforts were made to refine this strategy into a more general synthesis route. This modification was inspired by the work of others who employed a similar approach to synthesize glyantrypine and ent-glyantrypine, based on the double cyclization of open-chain tripeptides. Consequently, a more versatile method was developed for synthesizing (+)-fumiquinazoline G, also referred to as ent-fumiquinazoline G. This revised approach utilized a 2-nitrobenzyl group as a light-sensitive protecting group and began with amino acids to form diketopiperazine. The synthesis was completed using the aza-Wittig reaction to yield the target compound. Notably, the 2-nitrobenzyl protecting group could be efficiently removed upon UV irradiation in methanol at 254 nm using Pyrex glass figure 26.

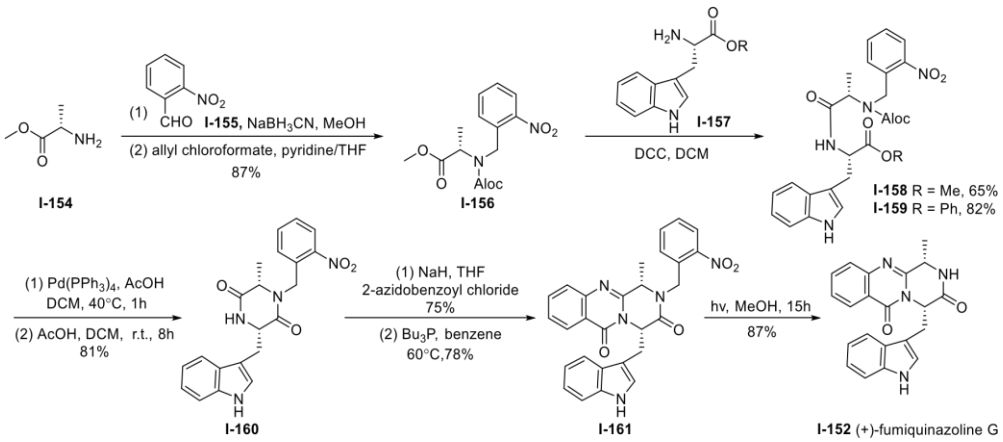

Figure 26: Total synthesis of (+)-fumiquinazoline G commenced with amino acids.

During a benzylation step, it was observed that diketopiperazine adopted a boat-shaped conformation, as determined through NOESY experiments and corroborated by proton NMR data. The shielding of the N-3 position due to this conformational effect favored the formation of product I-163 over I-164 or I-165 in subsequent reactions. Building on this finding, a four-step total synthesis was developed for fumiquinolines F and G, fiscalin B, and glyantrypine. Furthermore, a regio- and diastereoselective alkylation at the C-4 position was identified as an effective method for generating fiscalin B figure 27.

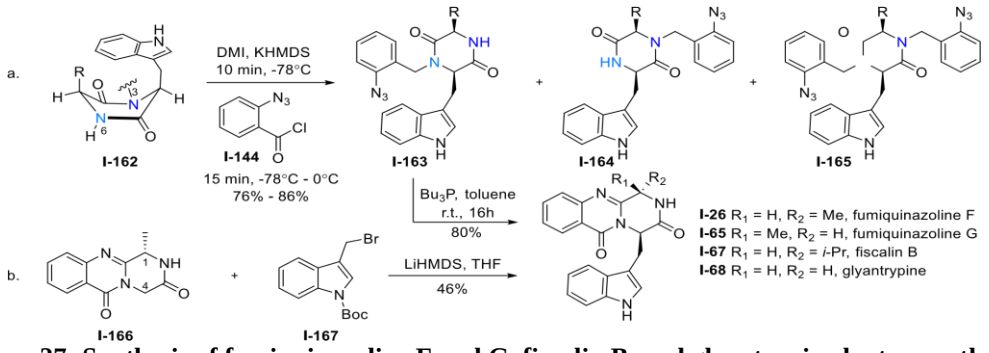

Figure 27: Synthesis of fumiquinazoline F and G, fiscalin B, and glyantrypine by two methods.

While exploring the aza-Wittig method for synthesizing fumiquinazolines, an alternative and efficient biomimetic approach was concurrently developed for the synthesis of these alkaloids, including fumiquinazoline G and fiscalin B. A key step in this synthesis involves the formation of an anthranylamide residue within a linear tripeptide.[67-69] This residue is then dehydrated to create a benzoxazine, which subsequently undergoes rearrangement to yield the natural products via an amidine intermediate. This methodology was applied to synthesize a variety of fumiquinazolines, both on solid support and in solution. In solid-phase studies, the total synthesis of glyantrypine was successfully achieved. In solution-phase studies, glyantrypine, along with fumiquinazolines F and G, as well as fiscalin B, were synthesized in four steps starting from tryptophan methyl ester figure 28.

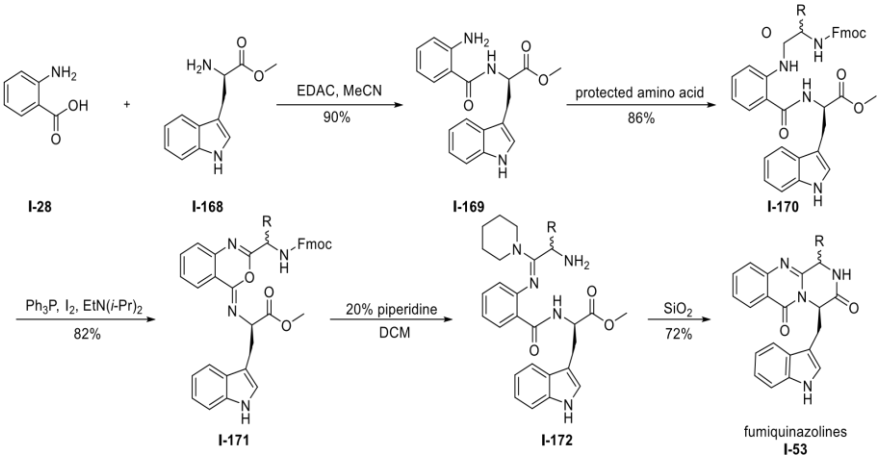

Figure 28: Condensation method via dehydrative oxazine intermediateapproach to fumiquinazolines.

While Snider was the first to synthesize fumiquinazolines using the aza-Wittig method, he subsequently adapted his approach after reviewing the work of Ganesan et al., who employed the condensation method. Snider then reported the synthesis of fumiquinazolines A, B, C, E, H, and I using this strategy. The synthesis commenced with compound I-173, derived from protected D-tryptophan. A two-step acylation process was conducted to produce compound I-175, after which conditions similar to those used by Ganesan (Ph3P, Br2, and Et3N in DCM) were applied to form fumiquinazoline I (I-176). Another pathway led to the formation of an iminobenzoxazine intermediate (such as I-177), which, when treated with pyridine, resulted in an amino amidine intermediate (similar to I-178). The final target product, fumiquinazoline H (I-180), was obtained by refluxing this intermediate in acetonitrile **Figure 29**.

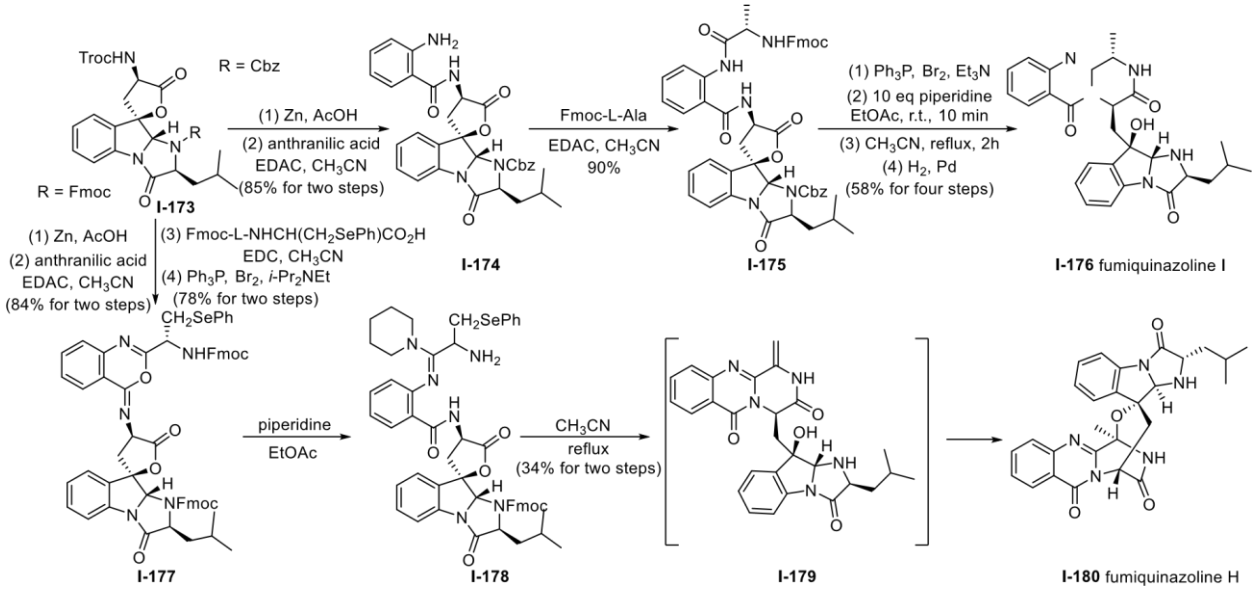

Figure 29: Total synthesis of fumiquinazoline H and I by condensation via dehydrative oxazine intermediate approach.

In addition to the previously mentioned syntheses, this methodology has been widely applied in the total syntheses of various fumiquinazolines. Researchers utilized this approach to synthesize ent-alantrypinone and serantrypinone.[70-73] Additionally, the same methodology was employed by other scientists to synthesize the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic structure. They subsequently used a Diels-Alder reaction for the total synthesis of alantrypinone, which was achieved in eight steps with an overall yield of 13.5%, and lapatin B, synthesized in five steps with an overall yield of 8% **Figure 30**.

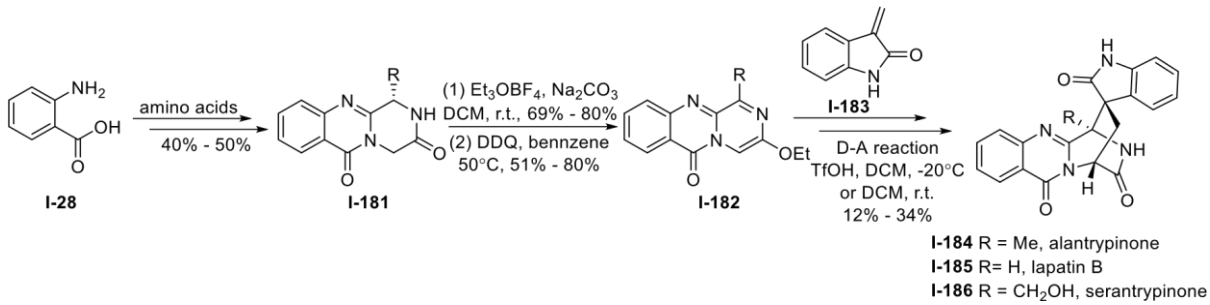

Figure 30: Total synthesis of alantrypinone and lapatin B by Diels-Alder reaction and structure of serantrypinone.

Additionally, a three-component, one-pot reaction was developed to synthesize glyantrypine, fumiquinazoline F, and fiscalin B.[72-77] This process began with the condensation of anthranilic acid with various amino acids, and microwave irradiation was employed to facilitate the reaction. In a separate study, another team introduced a microwave-assisted synthesis using $Zn(OTf)_2$, which enabled a double cyclocondensation process **Figure 31**.

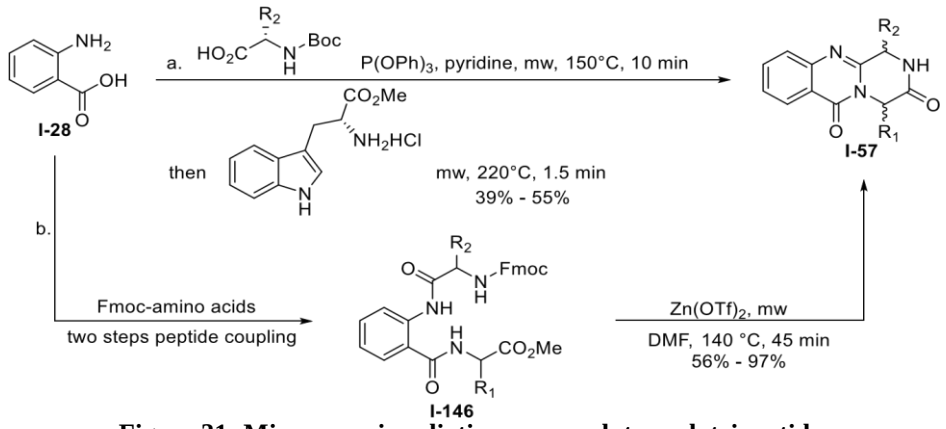

Figure 31: Microwave irradiation approach to cyclotripeptide.

3.3.2. Recent research on the total synthesis of anacine and its derivatives

For compounds related to fumiquinazolines that lack an indole moiety, with the exception of anacine and verrucines A and B—discovered prior to 2000—most have been reported primarily in the last decade or even in the past two years. Consequently, their synthesis has not been extensively researched. Notably, only one study utilized a solid-phase method similar to that of others to achieve the first total synthesis of anacine, verrucines A, and B. This synthesis required seven steps, yielding anacine, verrucines A, and B with overall yields of 9%, 14%, and 15%, respectively.[76-79]

In this synthetic route, the starting materials included anthranilic acid and glutamine, which were bound to a solid phase and had three protecting groups that needed to be removed in subsequent steps. The synthesis involved five steps to transition from these starting materials to the cyclic tripeptide, including a dehydrative step on the oxazine intermediate, leading to the final cyclization. However, this multistep process could potentially be streamlined into a single step using microwave-assisted reactions, as previously discussed **Figure 32**.

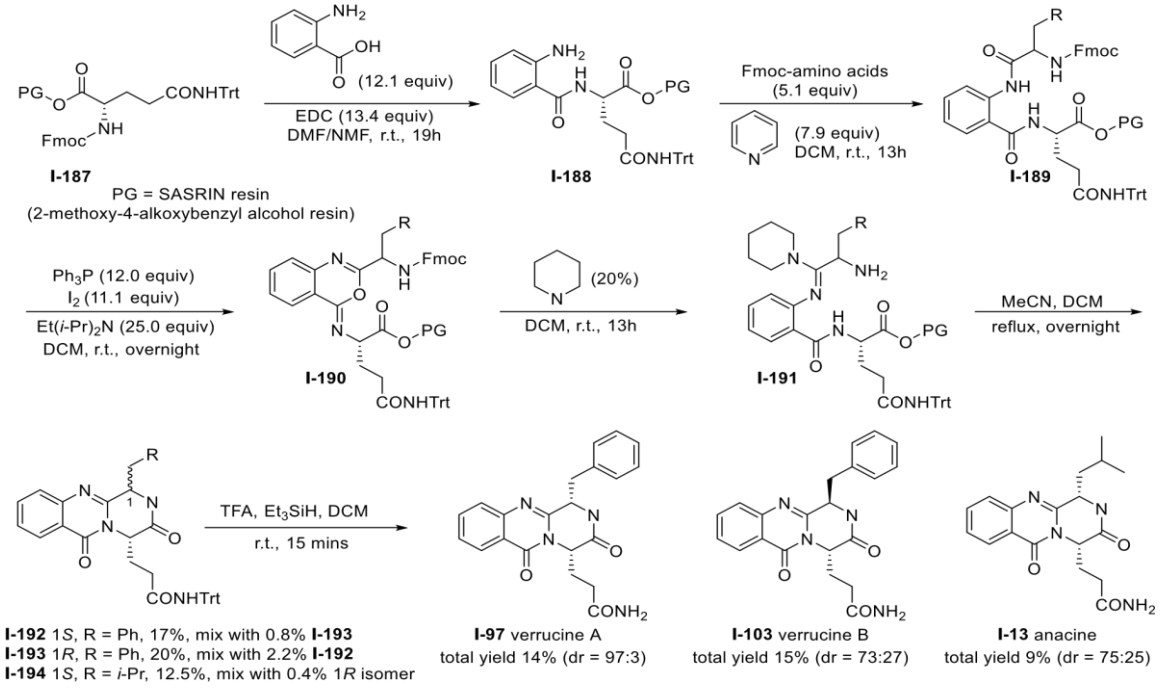

Figure 32: Total synthesis of anacine, and verrucines A and B.

Epimerization at the C-1 position is an unavoidable consequence of the strongly acidic conditions used during the reaction. Previous discussions have indicated that fumiquinazolines can epimerize at both the C-1 and C-4 positions under strongly basic conditions; however, under strongly acidic conditions, epimerization occurs primarily at the C-1 position. The cyclopeptide structure features a highly conjugated unsaturated ketone-like system, where the interconversion between ketone and enol forms acts as the driving force for the epimerization at the C-1 position **Figure 33**.

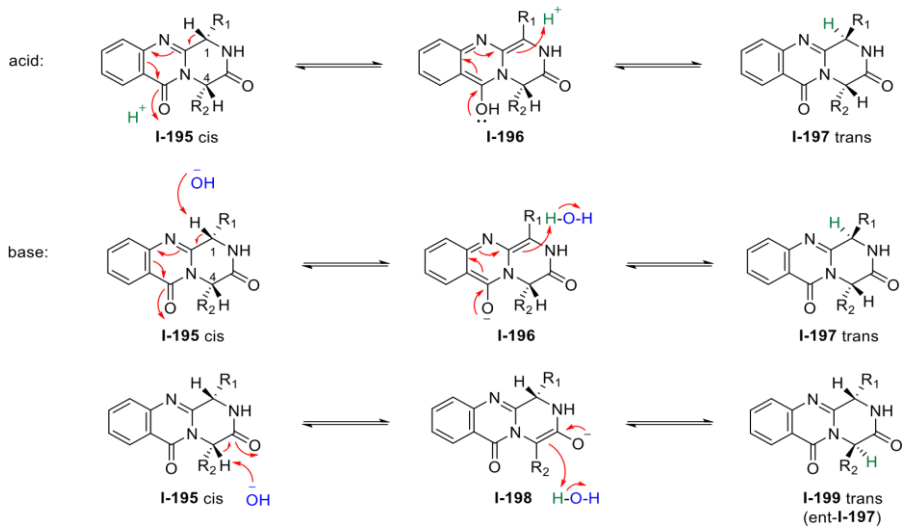

Figure 33: Possible mechanisms of epimerization at C-1 and C-4 positions.

Furthermore, it was found that anacine and verrucine B exhibit instability, degrading in DMSO-d6 and methanol when stored at room temperature and exposed to air for several weeks. In particular, verrucine B can undergo oxidation at the C-1 position, resulting in the formation of an alcohol group in the derivative compound. This observation has prompted further exploration into the oxidation processes occurring at the C-1 position **Figure 34**.

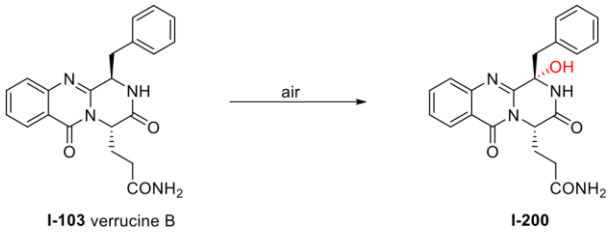

Figure 34: Oxidation of verrucine B.

Building on these studies, our research group has invested significant effort in the synthesis of this class of compounds, focusing on both the development of the core structures and the subsequent post-modification processes.[78-81]

3.3.3. Research on the total synthesis of ardeemin and *N*-acetylardeemin

In 1994, a total synthesis of N-acetylardeemin was achieved from tryptophan, alanine, and another precursor. This strategy was further optimized in subsequent studies, leading to the successful synthesis of both ardeemin and N-acetylardeemin. The approach involved first synthesizing fragment I-203 from triprotected tryptophan, followed by the application of the aza-Wittig method to complete the synthesis of the target products **Figure 35**.

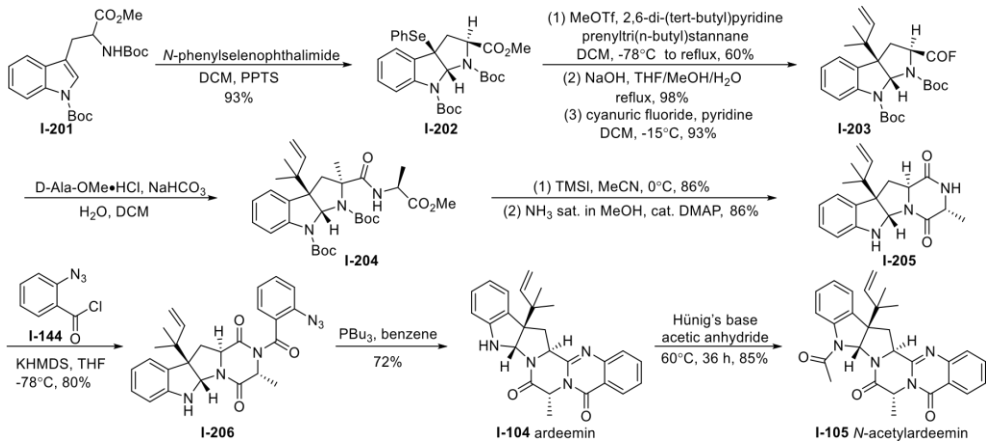

Figure 35: Total synthesis of ardeemin and *N*-acetylardeemin.

Following these studies, a solvent-free cyclocondensation of imidate with anthranilic acid was developed under microwave irradiation to synthesize the diastereomeric de-prenylardeemins. Additionally, a three-step one-pot cascade reaction and an intermolecular cyclopropanation method were employed to produce indolylacetate, ultimately leading to the synthesis of ardeemin. The synthesis of N-acetylardeemin was accomplished using a combination of olefination/isomerization/Claisen rearrangement, reductive cyclization, and regioselective oxidation,

followed by a Ugi three-component reaction and subsequent cyclization **Figure 36**.

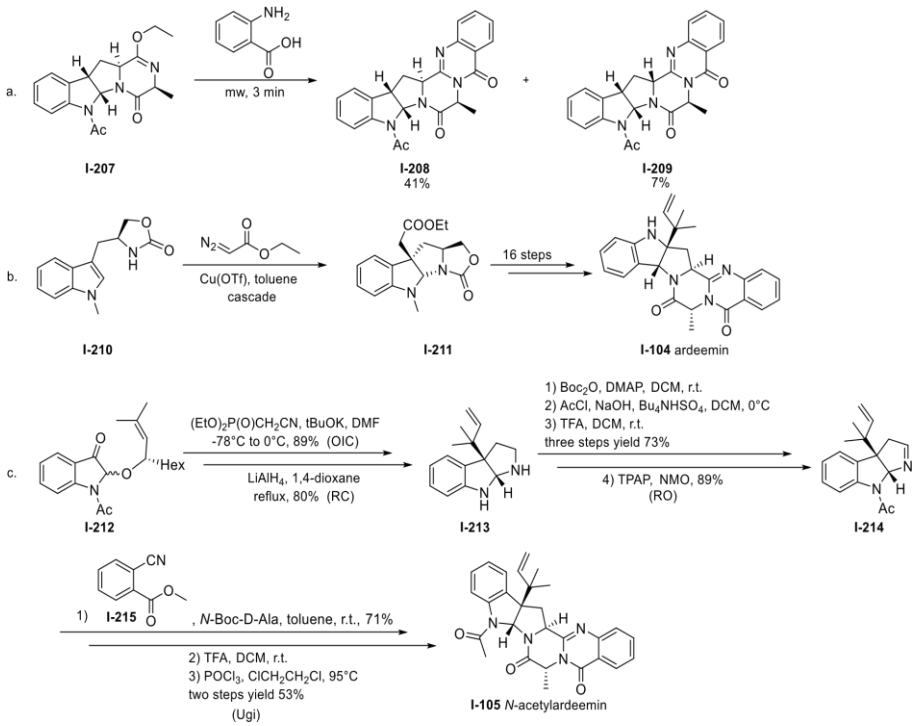

Figure 36: Total synthesis of diastereomeric de-prenylardeemins, ardeemin and *N*-acetylardeemin by other methods.

3.4. Recent works related to this project in our group

My colleague focused on the synthesis of the piperazino[2,1-b]quinazolin-3,6-dione heterotricyclic core and the introduction of the target carbonyl group at the C-1 position using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). She also proposed rational strategies for the total synthesis of natural products, including anacine and aurantiomides A, B, and C, although she encountered challenges with the Michael addition step **Figure 37**.

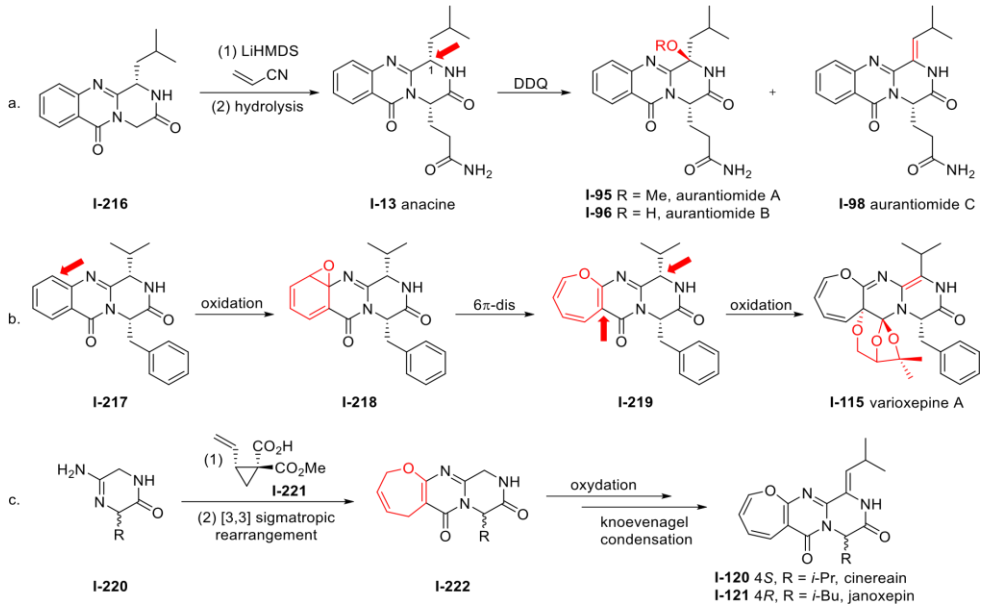

Figure 37: Propose strategies of the synthesis of natural products in different strategies.

More importantly, in alignment with the initial objectives of this project, the exploration of the synthetic route from piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides to oxepine compounds, such as varioxepine A, involved challenging oxidation steps. However, this approach was unsuccessful with both chemical and microbial methodologies. Consequently, a new route for synthesizing oxepine natural products was proposed,

which included a retro-Claisen condensation reaction for the total synthesis. This study was completed with the successful total syntheses of cinereain and janoxepin.

3.4.1. Synthesis of the piperazino[2,1-b]quinazolin-3,6-dione heterocyclic core

A rapid synthetic route was initially developed using isatoic anhydride and amino acids, featuring cyclization under microwave conditions. This method incorporates two consecutive peptide couplings to produce a linear tripeptide intermediate, followed by cyclocondensation under microwave conditions to form the heterotricyclic structure. This process utilizes Chu's microwave method for enhanced efficiency **Figure 38**.

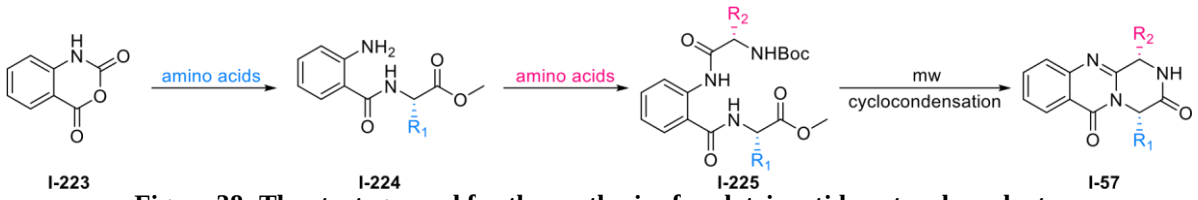

Figure 38: The strategy used for the synthesis of cyclotripeptide natural products.

The initial acylation step using isatoic anhydride was facilitated by DMAP catalysis, and three distinct methods were investigated for the subsequent peptide coupling in the synthesis of tripeptides. Method A involved coupling under alkaline conditions, followed by the removal of the Fmoc-protecting group through elution with piperidine and dichloromethane, resulting in products with lower yields. This approach was adapted from a prior strategy. In contrast, satisfactory yields were obtained using either 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) or hexafluorophosphate benzotriazole tetramethyl uronium (HBTU) in combination with N,N-diisopropylethylamine (DIPEA). Due to the simpler post-processing associated with the EEDQ reaction, this method was chosen for use in subsequent studies **Figure 39**.

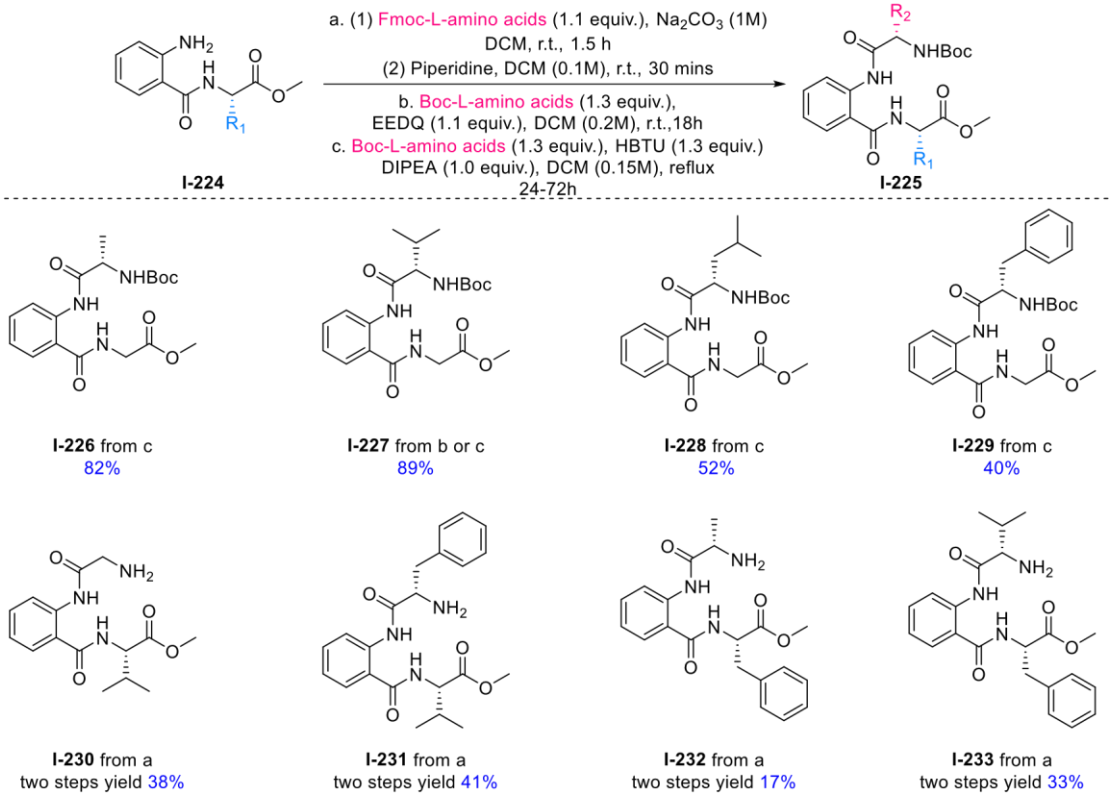

Figure 39. Methods to generate tripeptide compounds.

Building on previous findings, $Zn(OTf)_2$ has demonstrated greater efficacy in facilitating double cyclodehydration. Nonetheless, the inherent challenges of this reaction, coupled with the generally low yields, indicate that further optimization is necessary, a topic we will explore in future research. During the optimization of reaction conditions, it was found that using water as a solvent could yield higher amounts of I-235 without the addition of a Lewis acid catalyst, despite the limited

solubility of both the reactants and products in this medium.[80-82]

Under microwave irradiation, all compounds, with the exception of I-239, were produced in poor to moderate yields. Notably, compounds monosubstituted at positions C-1 or C-4 (I-234 to I-238) were obtained in higher yields compared to their doubly substituted counterparts (I-239 to I-241). Furthermore, the inclusion of Lewis acids such as $Sc(OTf)_3$ or $Zn(OTf)_2$ resulted in epimerization at position C-1 (I-240 and I-241), a phenomenon well-documented in existing literature. Interestingly, trans isomers appeared to be favored under these conditions. However, this observation contrasts with findings from subsequent investigations, which will be elaborated upon later. Epimerization was also noted in other compounds (I-234 to I-239), but due to an oversight, initial observations of this effect were missed, and their proportions were not calculated **Figure 40**.

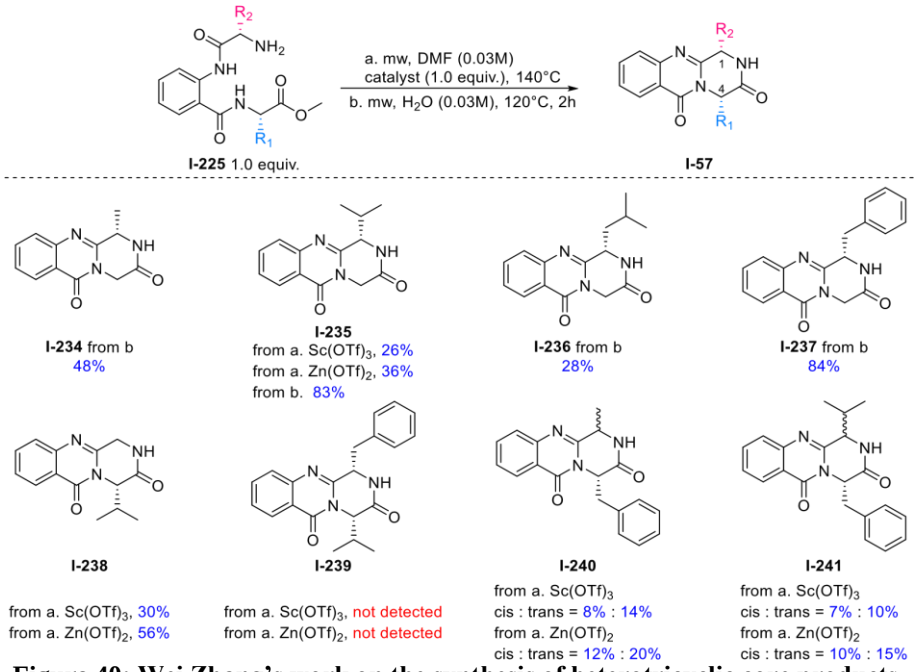

Figure 40: Wei Zhang's work on the synthesis of heterotricyclic core products.

3.4.2. Late-oxidations to form natural products

Due to unsuccessful attempts to oxidize the aromatic ring of the anthranilic residue in cyclotripeptides into an oxepine ring, efforts shifted toward oxidizing position C-1 with the aim of advancing the total synthesis of natural products such as aurantiomides A (I-95), B (I-96), and C (I-98). Building on prior research, it was noted that there is a distinct difference in reactivity between the oxidations at positions C-1 and C-4. Consequently, it was hypothesized that appropriate oxidants could selectively functionalize the substituted position C-1. A comprehensive screening of various oxidants was conducted, which included peroxides, halogenating agents, transition metal catalysts, biomimetic catalytic systems, and microbial oxidation methods. Ultimately, DDQ was identified as an effective reagent for selectively functionalizing the substituted position C-1, resulting in the formation of methyl ether I-242 at a yield of 77%, or alcohol I-243 at a yield of 39%, depending on the reaction conditions employed.[83,84]

While methoxylation was explored with several other substrates, conclusive evidence regarding the general applicability of DDQ for C-1 oxidation has yet to be established. This investigation will continue as part of the ongoing research in this doctoral thesis. Successfully oxidizing the C-1 position could facilitate the synthesis of natural products such as aurantiomides A (I-95) and B (I-96) **Figure 41**.

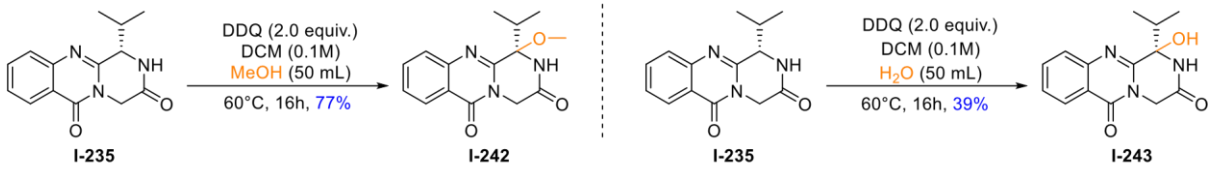

Figure 41. Oxidation on C-1 position with DDQ.

Furthermore, it was found that under microwave reaction conditions, the methoxy substituent in compound **I-242** can be eliminated to form a double bond in compound **I-244**. This result further supports the possibility to synthesize natural product aurantiomide C (**I-98**) **Figure 42**.

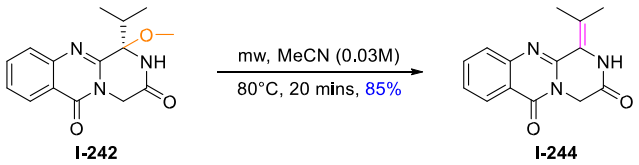

Figure 42: Microwave-promoted elimination of the methoxy group.

3.4.3. Synthesis of oxepine compounds

Building on a previously established method for synthesizing dihydrooxepine via retro-Claisen rearrangement, a new strategy was employed to create oxepine-containing cyclotripeptides. The approach involved the coupling of a hindered 2-vinylcyclopropane-1-acyl fluoride and an electron-deficient cyclic amidine, resulting in the formation of an unstable spiro[2-vinylcyclopropane-1,5'-pyrimidine-4',6'-dione] product. This intermediate was capable of undergoing a spontaneous retro-Claisen rearrangement, yielding a 7-membered oxacycle that serves as a precursor to the oxepine structure.This innovative methodology significantly advanced the total syntheses of cinereain and janoxepin in a highly convergent fashion. The process also incorporated a late palladium-catalyzed β-hydride elimination, which facilitated the release of the oxepin and the subsequent addition of further side chains **Figure 43**.

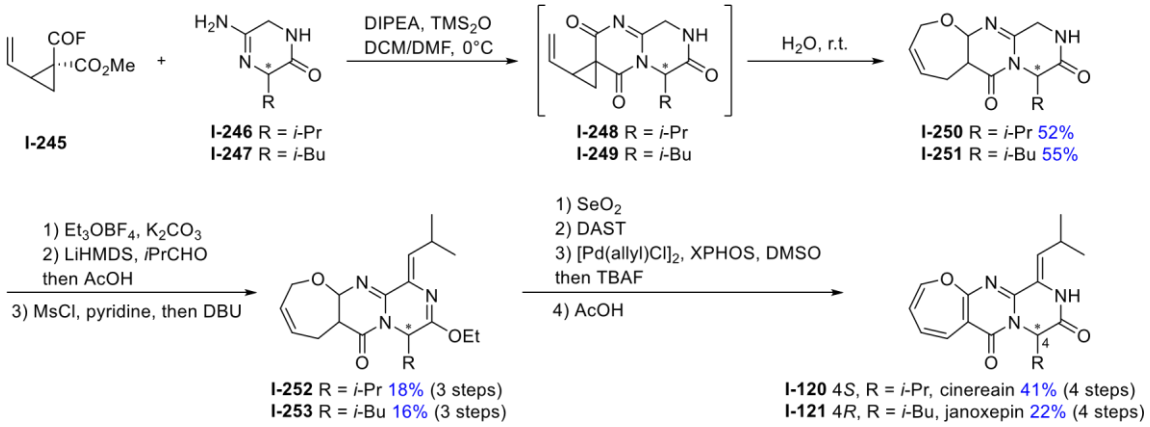

Figure 43: Total synthesis of natural products janoxepin and cinereain (adapted from Quentin Ronzon.

CONCLUSION

The synthesis of cyclotripeptidic natural products, particularly those in the aurantiomide series, represents a significant advancement in the field of natural product chemistry. This exploration has highlighted the rich chemical diversity inherent in marine natural products and their potential as therapeutic agents. The intricate structural frameworks of these compounds, notably the piperazino[2,1-b]quinazolin-3,6-dione core, have been shown to confer a variety of biological activities, including anticancer and antimicrobial effects. As we have discussed, the total synthesis of these compounds has historically posed numerous challenges, primarily due to their complex structures and the unique biosynthetic pathways involved in their formation. However, recent advancements in synthetic methodologies, including microwave-assisted synthesis and biomimetic oxidation, have significantly improved the efficiency and selectivity of these reactions. The incorporation of innovative techniques, such as retro-Claisen rearrangements and late-stage functionalization, has provided new strategies for overcoming the limitations associated with traditional synthesis methods.

Despite these advancements, the pursuit of optimizing reaction conditions and enhancing yields remains an ongoing challenge in the synthesis of cyclotripeptides. The difficulties encountered in synthesizing oxepine-containing derivatives illustrate the complexities inherent in these chemical processes. Future research efforts should focus on refining these methodologies and exploring alternative synthetic routes to facilitate the production of these valuable compounds. This document has also explored the biosynthetic pathways of piperazino[2,1-b]quinazolin-3,6-dione cyclotripeptides, shedding light on the enzymatic processes that govern their formation. Understanding these pathways not only enriches our knowledge of natural product biosynthesis but also informs the development of synthetic strategies that mimic nature's processes. The insights gained from studying marine organisms and their associated microorganisms underscore the importance of biodiversity in the discovery of novel bioactive

compounds. Moreover, the structural diversity of compounds derived from marine sources, such as those isolated from sponges, continues to inspire researchers in the quest for new medications. The significant biological activities exhibited by these compounds reaffirm their potential in addressing unmet medical needs. Efforts to synthesize compounds like anacine and ardeemin further illustrate the promise of marine-derived natural products in drug development.

The journey through the synthesis of cyclotripeptidic natural products emphasizes the intricate interplay between natural product chemistry and synthetic methodologies. By addressing the challenges and breakthroughs encountered in this field, we move closer to unlocking the full therapeutic potential of marine biodiversity. Continued exploration and innovation in synthetic strategies will be crucial in advancing the development of these compounds for medicinal applications. As research progresses, it is hoped that the lessons learned will catalyze further discoveries, ultimately leading to the identification and synthesis of new natural products that can contribute significantly to the pharmaceutical landscape. The ongoing collaboration between synthetic chemists, biologists, and pharmacologists will be essential in realizing the full potential of these remarkable marine-derived compounds in future therapeutic interventions.

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