Review

Journal of the Brazilian Chemical Society

https://dx.doi.org/10.21577/0103-5053.20250110

J. Braz. Chem. Soc. **2025**, *36*, 11, e-20250110, 1-24

Koninginins and Related Octaketides from *Trichoderma* and Other Fungi: Chemical Diversity and Biological Activities

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Koninginins and their derivatives represent a structurally diverse class of octaketides with notable biological activities, including antimicrobial, antiophidic, anti-inflammatory, cytotoxic properties, and potential for regulating plant growth. Originally discovered in 1989 with the isolation of koninginin A by Cutler and colleagues, numerous structural variants, such as koningiopisins, trichoketides, trichodermatides, and trichodermaketones have since been identified. While predominantly produced by *Trichoderma* species, koninginins have also been reported in other fungi, including basidiomycetes (*Pholiota*) and ascomycetes (*Aspergillus*, *Penicillium*, and *Diaporthe*). This review systematically compiles and analyzes over 80 compounds described between 1989 and 2024, focusing on their structural skeletons, cyclization patterns, functionalization, stereochemistry, nomenclature, biosynthesis, and biological activities. The findings provide perspectives for future research on this promising class of fungal polyketides.

Keywords: koninginin, polyketides, biosynthesis, chemodiversity, biological activities

1. Introduction

Trichoderma is a genus of filamentous fungi in the family Hypocreaceae, widely distributed in diverse global habitats, from tropical soils to extreme environments, such as Arctic soils.[1] Although they have a wide distribution, a higher concentration is observed in tropical forests, possibly due to high plant diversity, more availability of organic matter, as well as temperature and humidity optimal for their diversification.[2]

The genus has been intensively studied distinguished by the production of a variety of specialized metabolites, including polyketides (PKs) with antibacterial,[3,4] antifungal,[5,6] immunomodulator[7] and cytotoxic properties.[8,9] These characteristics make them suitable for the biological control of plant pathogens, the promotion of plant growth, and the maintenance of ecological balance in terrestrial ecosystems.[10-13]

In addition, they have promising applications in biotechnology, including the development of biofungicides, therapeutic agents, and plant growth promoters. Besides, recent research[14] has explored the pharmacological potential of these compounds, with emphasis on their anti-cancer activities.

Examples of the biosynthetic capacity of PKs in *Trichoderma* are numerous, but we highlight the production of groups of metabolites with complex structures, such as the recently discovered trichodenoids, such as trichodenoid A isolated from *T. reesei*[15] (Figure 1a), which have cardioprotective effects, nafuredins, such as nafuredin C (Figure 1a) isolated from *T. harzianum* with potent antifungal activity against *Magnaporthe oryzae*,[16] and the group of complex structures known as bisorbicillinoids, such as sorbiquinol (Figure 1a) produced by *T. longibrachiatum*, *T. reesei* and *T. citrinoviride* reported as antimicrobial agents.[17,18] In addition to these, we highlight the koninginins (Figure 1b), octaketides of main occurrence in the genus *Trichoderma*, but which have a structural complexity unknown to many.

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Editor handled this article: Albertina Moglioni (Associate)

This will be the central theme of this review, which also includes other related octaketides that share structural characteristics and/or have been named with distinct names. The following is a comprehensive review of this intriguing class of metabolites with approaches to their structural diversity, distribution, stereochemistry, biological activities, and curiosities. To accomplish this, we performed an extensive literature revision using the platforms SciFinder (Chemical American Society, CAS), Google Scholar, PubMed, Web of Science and Scopus. All articles were read and attentively analyzed for the chemical characteristics and stereochemical information. It is worth noticing that we standardized the drawings of all chemical structures by orienting the chromene system with the heteroatom positioned upward and the alkyl side chain to the right. This review aims to standardize structural representations, given that different authors have depicted these compounds in various ways.

2. Koninginins

2.1. History, biosynthesis and structural features

The term "koninginin" derives from the fungal species *T. koningii*, where the structural skeleton characteristic of these compounds was initially identified. Since then, new structural variants have been discovered and characterized. Throughout the process, some authors discovered new molecules with some of these three basic skeletons, but for their own reasons, they named the compounds in subgroups, such as koningiopisins, trichocetides, trichodermatides, and trichodermaketones, among others.[19,20] Currently, more than 80 derivatives of koninginins and related octaketides have been discovered.[21-28]

The history of this group of metabolites dates back to the end of the 1980s, more precisely in 1989 with the description of the first congener, called koninginin A (**1**) (Figure 1b) by Cutler *et al.*[19] in reference to the fungal species studied. Interestingly, this discovery began when the authors noticed an ornamental plant, *Diffenbachia* sp., that was suffering, and sought to isolate the microorganism responsible, coming across the species *Trichoderma koningii*, which until then had no reports of phytopathogenicity. After cultivation of the microorganism and prospection of its metabolites, compound **1** was isolated, which presented mild, but significantly, inhibition towards ethiolated wheat coleoptiles.

Subsequently, in 1991, the same research group reported the structure of koninginin B (**2**) (Figure 2d) from the same strain (ATCC 46314).[29] The two molecules have a chromene moiety linked to a saturated alkyl chain with six and seven carbon atoms, respectively. However, congener A (**1**) presents an epoxidation pattern between carbons C-5 and C-10, common in several structures of this group, which characterizes them as analogues with an octahydro-2*H*-epoxybenzo[*b*]oxepine nucleus (Figure 2c).

Over the years, these compounds were being reisolated, but the absolute stereochemistry of these compounds remained unknown until 1995, when Xu and Zhu,[30] through total synthesis, produced two diastereoisomers of compound **1** and, through extensive analysis of the nuclear magnetic resonance (NMR) data with the corresponding

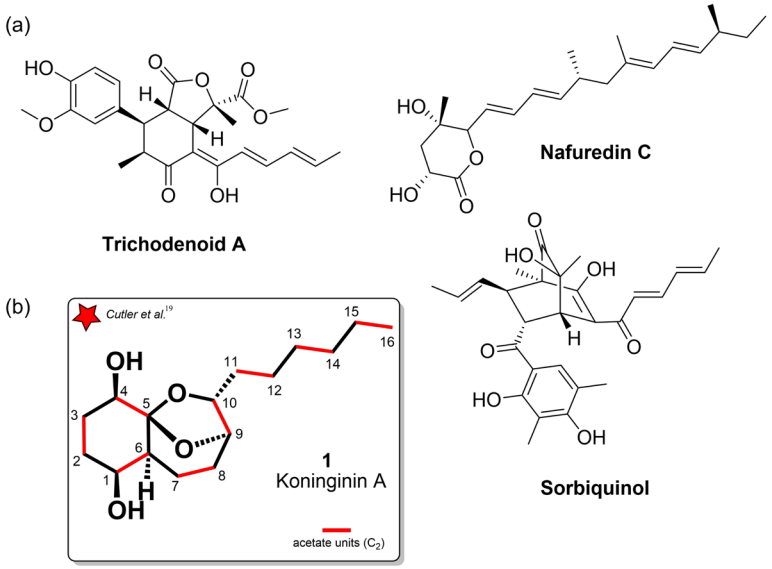


Figure 1. (a) Structural diversity of polyketides produced by fungi of the genus *Trichoderma*. (b) Chemical structure of the first described octaketide of the koninginin series, koninginin A (**1**).

Mosher esters reported the absolute stereochemistry as being 1*S*,4*R*,5*S*,6*S*,9*S*,10*S*. This stereochemistry was later confirmed by Mori *et al.*[31] through total synthesis followed by X-ray diffraction analysis. Similarly, the total synthesis of compound **2**, performed by Liu *et al.*,[32] allowed the correction of the position of the hydroxyl group from C-4 to C-2, but it was not possible to determine the absolute stereochemistry of C-2.

Concomitantly with the development of the first synthetic methodologies for koninginins, several new analogues with different patterns of cyclization, oxidation and different stereochemistry have been described year after year. Corroborating this, in 2016, a structural variant of the group of koninginins was isolated from *T. koningiopsis* and named koninginin N (**14**), which has an octahydrobenzofuran nucleus connected to a saturated alkyl chain of eight carbon atoms (Figure 2e).

To date, there are no studies on the biosynthesis of this group of compounds, but when analyzing the pattern of structures of koninginins and related-octaketides, a question arises: it is very unlikely that they are produced by other PKSs other than a highly reducing polyketide synthase (hrPKS)[33] (e.g., octaketide synthase)[34,35] (type I, iterative), responsible for condensing an acetyl-CoA initiator unit with seven malonyl-CoA extender units (Figure 2a). In this group of enzymes, the ketoreductase (KR), dehydratase (DH) and enoyl reductase (ER) domains should act to leave the carbon chain almost completely reduced, with the exception of carbons C-1 and C-9, where the former is necessary for cyclization by means of an aldol condensation (Figure 2b), leading to an intermediate, where the latter plays a crucial role in intramolecular cyclization with C-5 (Figure 2b). This set of reactions followed by post-PKS steps leads to the structural possibilities octahydro-2*H*-chromene and

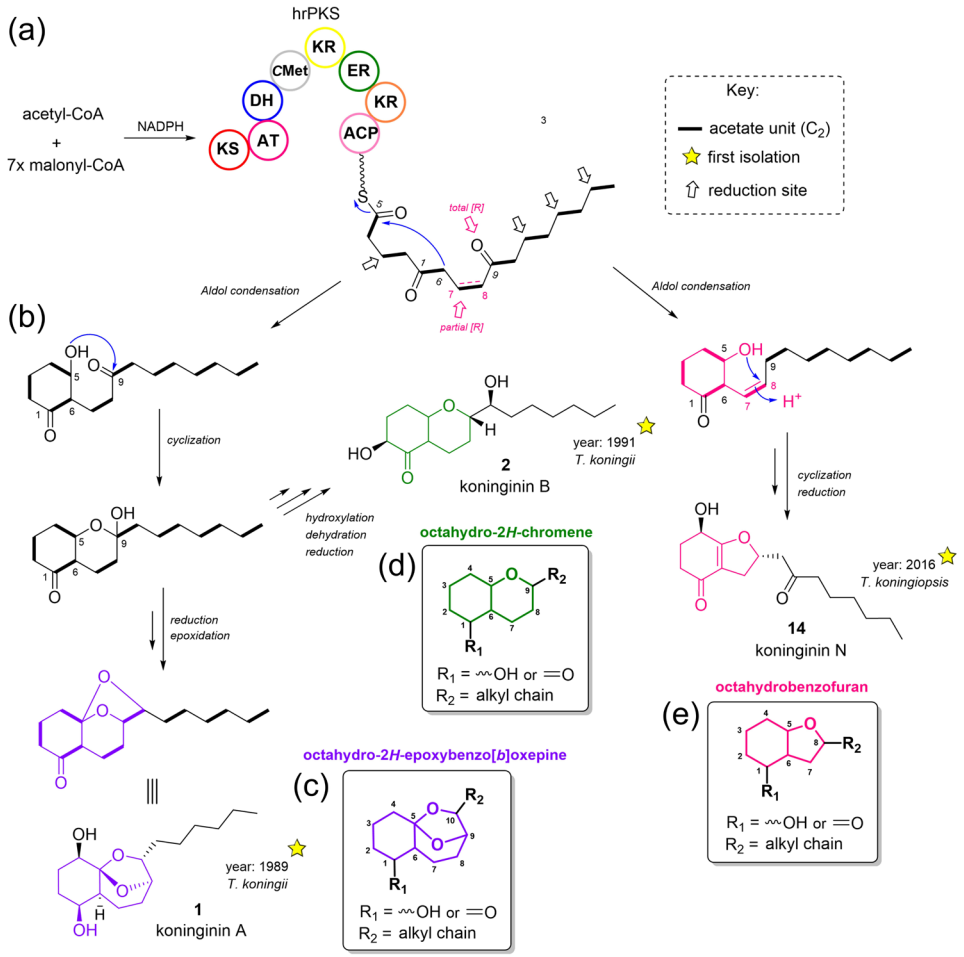


Figure 2. Plausible biosynthetic route for the main carbon skeletons of the koninginins. (a) Elongation of the octaketide chain, starting from acetyl-CoA and 7× malonyl-CoA, mediated by a highly reduce polyketide synthase (hrPKS) through iterative action of the functional domains: ketosynthase (KS), acyltransferase (AT), dehydratase (DH), ketoreductase (KR), enoyl reductase (ER), C-methyltransferase (CMet) and acyl carrier protein (ACP). (b) Proposal for assembling the basic skeleton, followed by modifications resulting from oxidation reactions, cyclization and structural rearrangements that define the rings and functional groups characteristic of koninginins. (c) General structure of analogues containing an octahydro-2*H*-epoxybenzo[*b*]oxepine core (e.g., koninginin A, **1**). (d) General structure of analogues containing an octahydro-2*H*-chromene core (e.g., koninginin B, **2**). (e) General structure of analogues containing an octahydrobenzofuran core (e.g., koninginin N, **14**).

octahydro-2*H*-epoxybenzo[*b*]oxepine (Figures 2c and 2d). Alternatively, it can be proposed that the formation of octahydrobenzofuran analogues occurs through intermediates that have an alkene between C-7 and C-8, as well as the total reduction of the carbonyl in C-9, allowing an intramolecular cyclization by connecting the C-5 and C-8 positions (Figures 2b and 2e). This difference in the possibilities speculated by us indicates the hypothesis that different hrPKS isoforms are responsible for the production of koninginins and related octaketides.

On the other hand, koninginins and other derivatives, despite forming a complex group of structures, are restricted to only 10 species of *Trichoderma* to date (Figure 3).[19,25,36] The molecular systematics shows that koninginin-producing *Trichoderma* species group into clades.[37] In these clusters, species that have common derived genetic characteristics share phylogenetic topologies, confirming their evolutionary relationship.[38] In the Viridae clade, a cryptic complex is observed encompassing *T. koningii*, *T. koningiopsis*, *T. neokoningii*, *T. ovalisporum* and *T. gamsii*, exhibiting greater phylogenetic proximity, which supports the coevolution of secondary metabolic pathway.

The clade Virens aggregates *T. virens* and *T. aureoviride*, while the Harzianum, Hypocreanum and Longibrachiatum clades include *T. harzianum*, *T. applanatum* and *T. reesei*, respectively. Phylogenetic inference, based on specific deoxyribonucleic acid (DNA) barcodes, including the sequences of transcribed internal spacer 1 (ITS1), the translation elongation factor 1-α gene (TEF1) and the second largest ribonucleic acid (RNA) polymerase II subunit (RPB2), suggest the possibility that horizontal gene transfer events between sister clades may exert a modulating influence on the structural diversification of koninginins. Phylogenetic analysis has been decisive to establish the correlation between the structural diversity of compounds and the evolutionary traits of species.[39] Comparative studies suggest that variations in secondary metabolite profiles reflect specific ecological adaptations associated with each clade.

Although most koninginins are found in *Trichoderma*, isolated reports also associate them with genera such as Penicillium,[40] *Pholiota*,[41,42] *Emericella*[43] (currently *Aspergillus*) and *Phomopsis*[44] (currently *Diaporthe*). These findings, however, depart from the prevailing pattern and suggest that similar biosynthetic pathways may occur atypically in other fungi. Such atypical occurrences require further investigation to confirm their origin and relevance. Future research may shed light on whether these mechanisms represent evolutionary convergence or isolated events of horizontal gene acquisition.

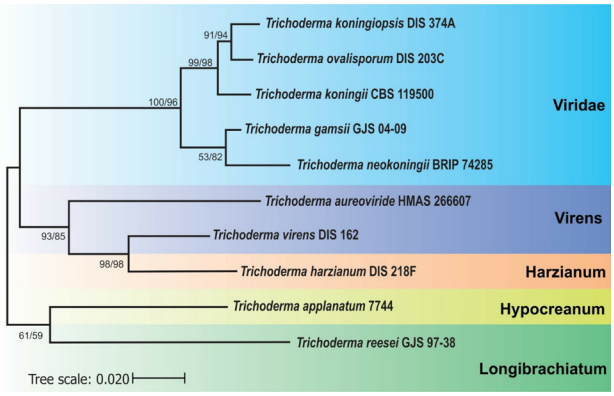


Figure 3. Phylogenetic tree of koninginin-producing *Trichoderma* species belonging to the clades Viridae, Virens, Harzianum, Hypocreanum and Longibrachiatum. The dendrogram was generated by concatenating the ITS1, TEF1 and RPB2 sequences. Bootstrap values (≥ 70%) obtained in analyses of maximum likelihood and maximum parsimony are indicated in well-supported nodes, along with thickened branches. The tree was rooted with *Trichoderma reesei* (GJS 97-38). The phylogenetic tree was generated using Mega7 software[45] and edited with the help of CorelDraw Graphics Suite 2018.[46]

2.2. Koninginins A-Z

After the discoveries of compounds **1** and **2**, more and more researchers around the world began to research *Trichoderma* strains in order to find different analogues of this class (Figure 4). In this sense, in 1995, koninginin C (**3**) was isolated from the fermentation of *T. koningii* in a medium based on ground wheat. Although it presents a tricyclic skeleton similar to that of compound **1**, no stereochemical analysis has been performed to date.[47]

In 1989, Dunlop *et al.*[48] isolated the compound named 4,8-dihidroxi-2-(1-hidroxiheptil)-3,4,5,6,7,8-hexahidro-2*H*-1-benzopiran-5-ona, from the soil used in a saprophytic growth bioassay of *Gaeumannomyces graminis* var. *tritici*.

However, it was only in 1995, in the study by Parker *et al.*,[49] that this compound began to be called koninginin D (**4**). It was isolated together with koninginin E (**5**), which was first described by Ghisalberti *et al.*,[50] in 1993, from liquid cultures of *T. harzianum* and *T. koningii*.

The absolute stereochemistry of compound **4**, a structural analogue of compound **1**, was studied by Liu and Wang[32,51] from total synthesis. The research was based on the hypothesis that the absolute configuration of the C-9 and C-10 centers in compound **4** would be identical to that in compound **1**. As a result, both the relative and absolute stereochemistry of compound **4** were determined to be 7*R*,9*S*,10*S*,[51] while the C-4 position remained undefined.

Together with compound **5**, Ghisalberti *et al.*[50] isolated koninginin F (**6**) from the species *T. harzianum*, obtained from wheat roots, this being an epimer of compound **2**.[32] Years later, Shi *et al.*[52] determined the absolute stereochemistry of this compound as being

2*R*,7*R*,9*S*,10*S*. Subsequently, koninginin G (**7**) was isolated from a strain of *T. aureoviride* collected in New Zealand, from necrotic stem tissue of *Salix matsudana* × *alba*, having its structure established by interpretation of spectroscopic data, only its relative stereochemistry being known.[25]

From orange peel collected in Tifton, Georgia, the fungus *Emericella nidulans* was isolated, which, in a wheat-based culture medium, produced koninginin H (**8**). Its structure was elucidated by spectroscopic and spectrometric analyses, including NMR and mass spectrometry. The comparison of the spectroscopic data of compound **8** with that of compound **5** indicated great similarity, differing only by the presence of an additional hydroxyl group on C-15 in compound **8**, which suggests that such structural variations may directly influence the biological properties of koninginins.[43] Interestingly, to date, there are no reports of isolation of compound **8** in fungi of the genus *Trichoderma*.

Three new koninginins were isolated from extracts of products from solid fermentation on potato dextrose agar plates of *T. neokongii*.[53] Compound **9** was obtained containing one more hydroxyl group compared to compound **4**. Based on the comparison of specific rotation, chemical shifts and coupling constants, the authors concluded that the relative configuration of compound **9** was identical to that of compound **4**, which allowed its elucidation as koninginin I (**9**).[11,53]

Likewise, compound **10** demonstrated great similarity to compound **2**, except for the oxidation of the methylene group at C-15 to a ketone, but with a relative configuration identical to compound **2**, thus being named as koninginin J (**10**).[29,32,53] Furthermore, compound **11** was similar to **2** but with the presence of a carboxylic acid at the end of the side chain, and was named koninginin K (**11**).[29,32,53]

Koninginins L (**12**) and M (**13**) were isolated as solid fermentation products of *T. koningii* in potato dextrose agar medium.[54] Compound **12** presented an epoxide between C-7 and C-10, unlike compound **1**, which has such a group between C-5/C-10.[28] Its absolute stereochemistry was deduced by X-ray diffraction as being 2*S*,7*S*,9*S*,10*S*. On the other hand, compound **13** was not amenable to crystallization, which led the authors to use the electronic circular dichroism (ECD) technique to determine the absolute configuration, demonstrating that **13** is the 2*R* epimer of **12**. To date, only compounds **12**, **13** and **20** deviate from the epoxidation pattern observed in **1** and several other analogues, this being a restricted subgroup with octahydro-5*H*-2,5-methanobenzo[*e*][1,4]dioxepine core.

Liu *et al*.[55] isolated four new analogues from the fungus *T. koningiopsis*, associated with the medicinal plant *Panax notoginseng*. Among these, the koninginins N-Q (**14-17**), stand out, some of them presenting an octahydrobenzofuran nucleus with an octyl group as a side chain. The absolute stereochemistry of these compounds was determined on the basis of ECD.[5]

Hu *et al*.[26] isolated the koninginins *R* (**18**) and *S* (**19**) from *T. koningiopsis*. Compound **18** has a structural skeleton identical to compound **4**, with the distinction of having an acetoxy group attached to C-7. Compound **19** has a structural skeleton similar to that of koninginin O, exhibiting hydroxyl groups in C-2 and C-16, as well as a carbonyl in C-10, having only its relative stereochemistry defined as 2*S*,8*S*.[56]

Shi *et al*.[56] isolated eight novel highly oxygenated fungal polyketides from a strain of *T. koningiopsis*, an endophyte obtained from the medicinal plant *Artemisia argyi*, cultivated in Qichun, central China. Among them, koninginin T (**20**), which has a hydroxyl group in C-4, presenting the absolute configuration of 4*S*,7*S*,9*S*,10*S*.[56,57] In addition to this compound, the metabolites koninginin U (**21**), koninginin V (**22**) have also been described. In 2020, Biasetto *et al*.[27] isolated the koninginins T (**20a**) and U (**21a**) from the fungus *Phomopsis stipata*. However, the proposed structures present discrepancies in relation to the structural pattern common to koninginins, since the isolated compounds are hexaketides. Furthermore, the work of Shi *et al*.,[56] who had already used the nomenclatures koninginin T (**20**) and U (**21**)[52] went unnoticed.

Koninginin W (**23**) was obtained from the culture of *T. koningiopsis*. Compound **23** has a bicyclic structure, composed of a cyclohexanone core that has a carbonyl group at the C-1 position. At the C-6 position, this nucleus is linked to a furan ring, which is replaced by hydroxyl groups at the C-9 position, and at the C-10 position there is an *n*-hexyl side chain. The data obtained by X-ray diffraction allowed to determine, conclusively, the absolute configuration of **23** as 4*S*,7*R*,9*S*,10*S*.[24,58]

Completing the A-Z series, Peng *et al*.[59] isolated koninginins X (**24**), Y (**25**) and Z (**26**) from rice culture of the endophytic fungus *T. koningiopsis*, endophytic of *Pedicularis integrifolia* in southwest China. Compounds **24** and **25** presented a furan-like structure linked to a cyclohexane ring with C-4 and C-9 hydroxylation pattern.[59] In turn, koninginin Z (**26**), was revealed to be an ethoxylated derivative of compound **4**. The absolute chemistry of **26** was determined by X-ray diffraction and electron circular dichroism (ECD).[5,59]

2.3. Koninginins derived from the A-Z series

The derivatives, called *ent*-koninginin A (**27**), 6-di-*epi*-koninginin A (**28**) and 15-hydroxykoninginin A (**29**),

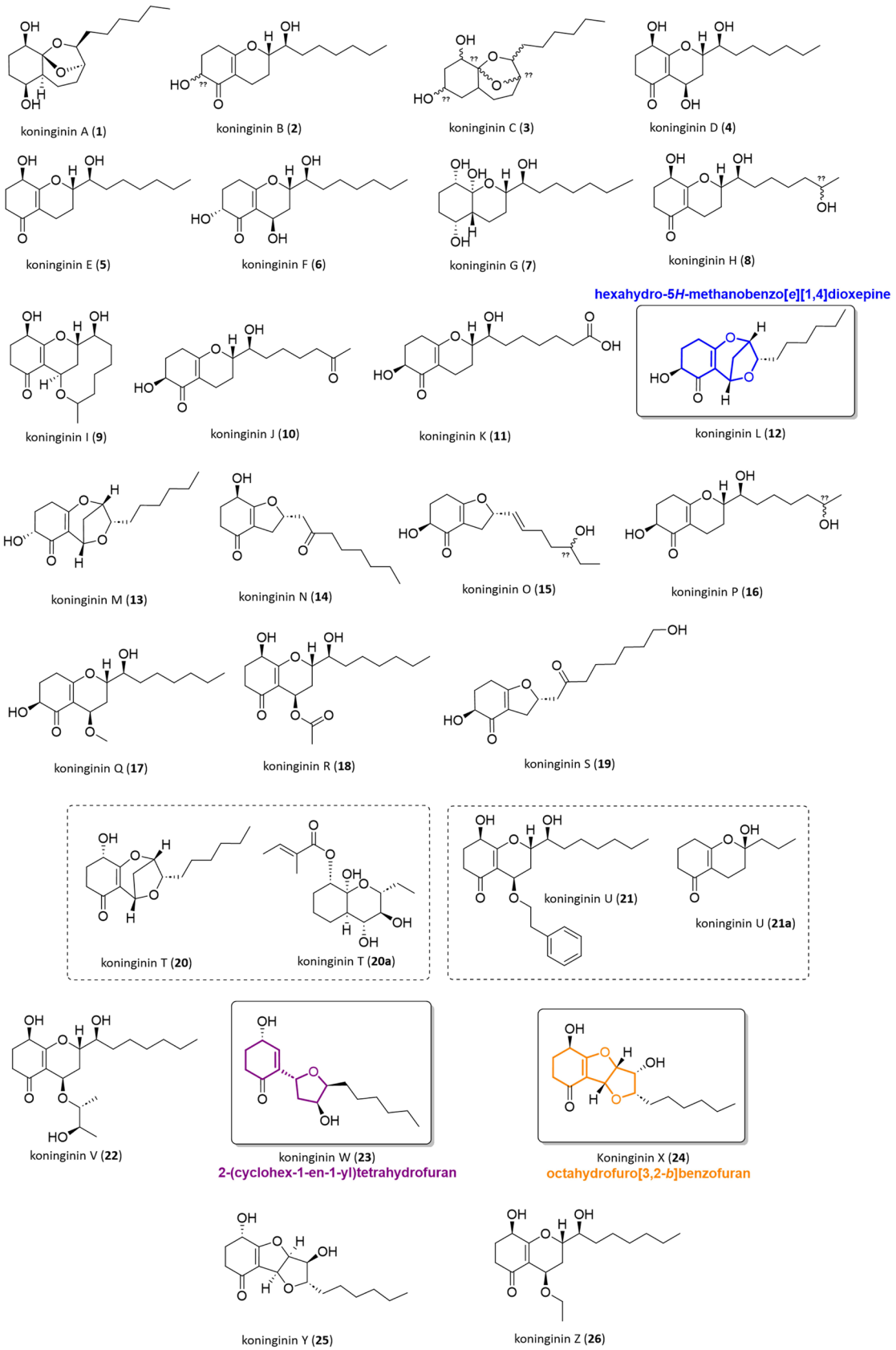


Figure 4. Chemical structures of koninginins A-Z (**1-26**). Highlighted in blue: the first example of a dioxepine-like analogue; highlighted in purple the first example of a cyclohex-1-*en*-yl tetrahydrofuran-like system; highlighted in orange the first example of a koninginin bearing a benzofuran system. The dashed boxes indicate molecules with repeated names.

were isolated together in the same study that discovered compound **20** (Figure 5).[56] Although the nuclear Overhauser effect spectroscopy (NOESY) data used by the authors did not define some configurations, they used X-ray diffraction, which accurately determined the absolute stereochemistry of these compounds as being 1*R*,4*S*,5*R*,6*R*,9*R*,10*R*, 1*R*,4*R*,5*S*,6*R*,9*S*,10*S* and 1*S*,4*R*,5*S*,6*S*,9*S*,10*S*,15*S*, respectively.[19,31,56,60]

In the same study in which Shi *et al.*[52] described compounds **21** and **22**, 14-ketokoninginin B (**30**), 14-hydroxykoninginin B (**31**), 7-*O*-methylkoninginin B (**32**), 14-hydroxykoninginin E (**35**), 15-hydroxy-1,4,5,6-tetra-*epi*-koninginin G (**36**) and 4'-hydroxykoninginin U (**37**), have been described.

Among these compounds, **21** and **37** share the same structural skeleton as compound **4**, although the OH

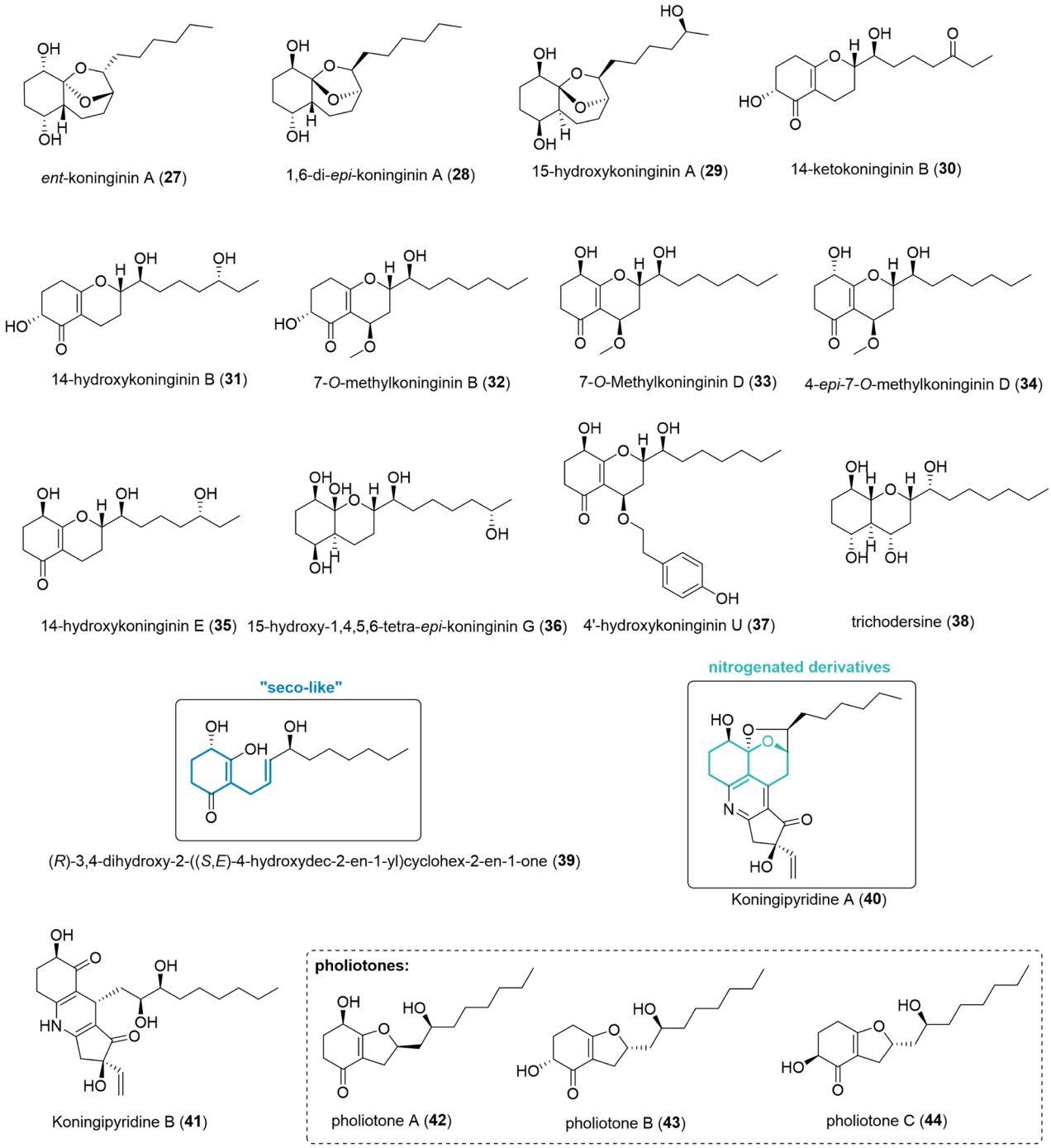


Figure 5. Chemical structures of compounds **27-44**. Highlighted in blue: the first example of a *seco*-like analogue; highlighted in cyan the first example of a nitrogenated koninginin. The dashed boxes highlight the pholiotones isolated from a Basidiomycete.

group on C-7 has been replaced by phenethoxy and *para*-hydroxyphenethoxy, respectively.[32,52] In contrast, compound **32** has a structure similar to that of compound **2**, with the particularity of having a 3-hydroxybutan-2-oxyl group attached to C-7. Its absolute configuration was determined as 2*R*,7*R*,9*S*,10*S*.[5,52]

Compounds **30**, **31**, and **32** resemble **2**, having a ketone group at C-14 (**30**), a hydroxyl group at C-14 (**31**), and a methoxyl at C-7 (**32**), respectively.[32,52] Additionally, compound **35** (14-hydroxykoninginin E) has a structural skeleton analogous to that of compound **5**, with the addition of a hydroxyl group at C-14. Its absolute configuration was defined as 4*R*,9*S*,10*S*,14*R*, based on X-ray diffraction analysis.[49,52] Compound **36** was isolated and exhibits the same bicyclic skeleton as compound **7**, but with the addition of a hydroxyl group in C-15 and with absolute configuration 1*S*,4*R*,5*R*,6*S*,9*S*,10*S*,15*S*.[25,52]

Isolated from marine sediments from the South China Sea, the fungus *T. koningii*, produced 7-*O*-methylkoninginin D (**33**), which differs from **4** only by the presence of a methoxyl group attached to C-7.[5] The compound 4-*epi*-7-*O*-methylkoninginin D (**34**) isolated from the endophyte *T. koningiopsis* was shown to be an epimer of compound **33**, information confirmed by X-ray diffraction analysis.[3]

Wang *et al*.[61] isolated a new koninginin derivative, which they chose to call trichodersin (**38**), of an unidentified strain at the species level of *Trichoderma* obtained from the roots of *Aconitum carmichaeli*. The compound has a structure like that of compound **7**, differing by the addition of a hydroxyl group at C-4 and the absence of a hydroxyl at C-3. The absolute configuration of **38** was determined by X-ray crystallography, revealing the 2*S*,4*S*,4a*R*,5*R*,8*R*,8a*R*,9*R* configuration.[59,61]

Interestingly, compound **39**, isolated from *T. harzianum*, presents a koninginin skeleton without the formation of the pyran ring and with two hydroxyls at the C-4*R* and C-10*R* positions, suggesting that it is a probable precursor in the koninginin biosynthetic pathway.[11,50] When discovered more than 30 years ago, and to the present moment, this compound did not receive a trivial name.

2.4. Nitrogen-containing derivatives

Peng *et al*.[62] isolated two new nitrogen derivatives of koninginin, named koningipyridines A (**40**) and B (**41**), from *T. koningiopsis*. Compound **40** exhibited an unprecedented pentacyclic ketal skeleton characterized by a complex fused ring system in the sequence 6/6/5/6/5, while compound **41** exhibited a unique dihydropyridine skeleton with a 6/6/5 arrangement (Figure 5).

2.5. Pholiotones

It is important to highlight that polyketides with structures related to koninginins have also been reported in other distinct fungal genera of *Trichoderma*. An example of this is pholiotones A-C (**42-44**) (Figure 5), isolated from the basidiomycete *Pholiota* sp., obtained from a soil sample collected on the surface of *Camellia sinensis* in China. These compounds have a tetra-hidrobenzofuran-4(2*H*)-one core, accompanied by a heptyl side chain, a carbonyl group at the C-1 position, and a hydroxyl group at C-10. Compound **42** differs from the others in that it exhibits an OH group at the C-4 position, while compounds **43** and **44**, which are epimers, exhibit the OH group at the C-2 position. It is worth mentioning that the stereochemistry of compound **42** was fully resolved, being established as 4*R*,8*R*,10*S*, while compounds **43** and **44** present absolute epimeric configurations at C-2, with 8*S*,10*S*.[41,42]

2.6. Koningiopisins

In 2016, Liu *et al*.[55] isolated new koninginins from the endophytic fungus *T. koningiopsis*, which the authors decided to name koningiopisins (Figure 6).

Koningiopsin A (**45**) has a structural skeleton similar to that of compound **6**, however, the hydroxyl group present at C-7 was replaced by a butoxyl group. In contrast, koningiopisin B (**46**) has the butoxyl group attached to C-8. Based on NMR data, the relative stereochemistry of the compounds was found to be identical to that of compound **2**.[23,32] Koningiopisin C (**47**) has the same skeleton as compound **1**, but with a bond between C-6 and C-7.[30] In turn, koningiopisin D (**48**) has the same structural skeleton as compound **14**, but with significant differences such as the hydroxyl at C-2 and the acetoxy group.[23,55]

The structure of koningiopisin E (**49**) was initially elucidated by Liu *et al*.[23] as identical to that of koninginin G (**7**). However, a more detailed analysis revealed that its structure more closely resembles that of compound **46**, evidenced by the absence of the butoxyl group at position C-8 and the presence of an acetoxy group at C-10.[23] Koningiopisin F (**50**) has the same structural skeleton as compound **48**, but with the addition of a double trans bond between C-9 and C-10. In turn, the skeleton of koningiopsin G (**51**) is similar to that of compound **50**, but with the inclusion of a carbonyl group in C-14. Finally, koningiopisin H (**52**) maintains the structural skeleton of compound **50**, presenting a carbonyl group at C-10.[23]

In 2023, Huang *et al*.[63] isolated twelve new koningiopisins, indicated as I-P series (**53**-**60**) from the endophytic fungus

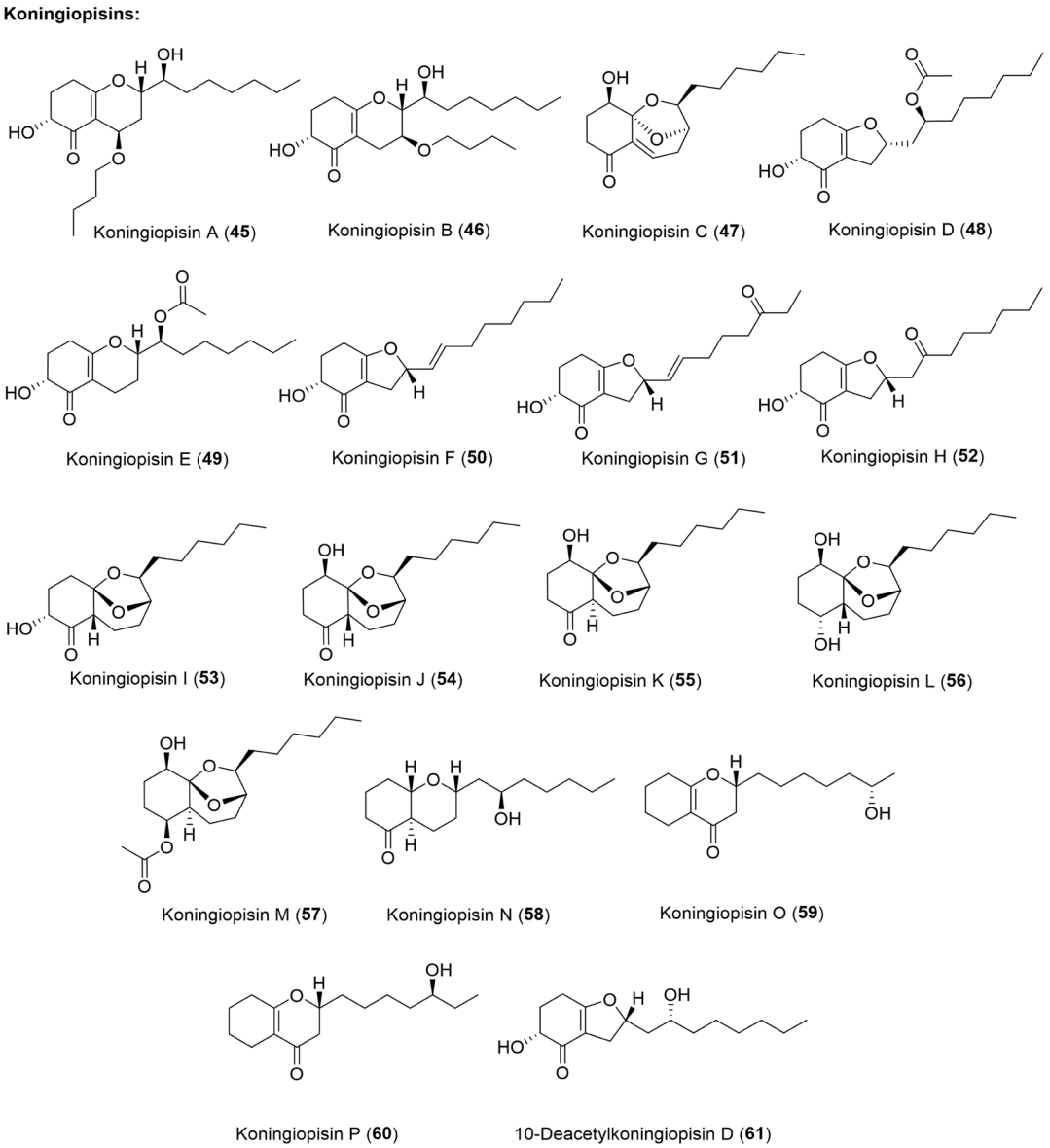


Figure 6. Chemical structures of koningiopsins (**45-61**).

T. koningiopsis, originating from the medicinal plant *Polygonum paleaceum* in China. Compounds **53**-**57** are tricyclic polyketides of structure analogous to compound **1**. Koningiopsin I (**53**) has a hydroxyl at the C-12 position, a carbonyl at the C-1 position, and an *n*-hexyl side chain attached to the C-10 carbon. The absolute stereochemistry was determined by X-ray diffraction, defining the stereogenic centers as 2*R*,5*R*,6*R*,9*S*,10*S*.

Koningiopisins J (**54**) and K (**55**) showed similarities with compound **53**. In both cases, the hydroxyl group is located at C-4, unlike compound **53**, which has this group at C-2. Compounds **54** and **55** are epimers, and their absolute configurations were established by single-crystal X-ray diffraction and defined as 4*R*,5*S*,6*R*,9*S*,10*S* and 4*R*,5*S*,6*S*,9*S*,10*S*, respectively.[63]

Koningiopsin L (**56**) has a structure like that of compound **54**, with the replacement of carbonyl by a hydroxyl in C-2. The absolute configuration of compound **56** was unequivocally established by X-ray diffraction as 1*R*,4*R*,5*S*,6*R*,9*S*,10*S*. Similarly, koningiopsin M (**57**) was also obtained as colorless crystals and has a structure analogous to that of compound **56**, with the difference of the presence of an additional acetyl group bound to C-1. The absolute configuration of compound **57** was determined as 1*S*,4*R*,5*S*,6*S*,9*S*,10*S*.[63]

Koningiopisin N (**58**) has a structural skeleton similar to that of compound **7**.[25] In compound **58**, the hydroxyl group in C-1 present in koninginin G was oxidized to a carbonyl group, while the groups in C-4, C-5 and C-10 were reduced; in addition, a hydroxyl group was incorporated at C-11. To

confirm both the skeleton and the absolute configuration of compound **58**, crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of compound **58** in MeOH/H_2O. The analysis determined the absolute configuration of **58** as 5*S*,6*R*,9*S*,11*R*.[63]

Koningiopisin O (**59**) has a structural skeleton that includes an α,β-unsaturated carbonyl between C-5 and C-6, in addition to a hydroxyl group at C-15. Koningiopsin P (**60**) has a structure very similar to that of **59**, except for the location of hydroxyl, which is found in C-14. The absolute configuration was defined as 9*R*,15*S* for compound **59** and 9*R*,14*S* for compound **60**. This is the first report of a compound of the koningiopisin family with a carbonyl group at C-7.[63]

The structural skeleton of 10-deacetylkoningiopisin D (**61**) was established as identical to that of koningiopisin D. However, in compound **61**, the acetoxy group attached to C-10 has been replaced by a hydroxyl group. The absolute configuration was determined by X-ray crystallography as 2*R*,8*S*,10*R*.[56,64]

2.7. Trichodermaketones

Trichodermaketones are polyketides that were first isolated together with compound (**33**), from *T. koningii*, by Song *et al*.[5] Trichodermaketones A (**62**) and B (**63**) have an octahydrofuro[3,2-*b*]benzofuran system identical to that of compound **25**. Compounds **62** and **63** are epimers, presenting absolute configurations of 4*R*,7*R*,8*R*,9*R*,10*S* and 4*R*,7*S*,8*S*,9*S*,10*R*, respectively.

In turn, trichodermaketones C (**64**) and D (**65**) are epimers with absolute configurations of 4*R*,8*S* and 4*R*,8*R*, respectively, and present a bicyclic furan skeleton like that of compound **50**. The fundamental difference between them is the position of the hydroxyl group, which is located at C-4 in compounds **64** and **65**, while in compound **50** it occurs at C-2.[5,63]

Discovered by Shi *et al*.[3] the trichodermaketone E (**66**), isolated from *T. koningiopsis*, presents structural similarity with compound **62**. However, the hydroxyl group present in compound **62** at the C-4 position appears in compound **66** at the C-2 position. The determination of the relative and absolute configurations of compound **66** by X-ray diffraction unequivocally confirmed its absolute configuration as 2*R*,7*R*,8*R*,9*R*,10*S*.

2.8. Trichoketides

The search for new bioactive compounds resulted in the discovery of new koninginins from the culture broth of the marine fungus *Trichoderma* sp., isolated from seawater samples collected in Japan. These compounds, called trichoketides A (**67**) and B (**68**) had their structures unequivocally elucidated (Figure 7).

Trichoketides C-F (**69**-**72**) were isolated from *T. koningiopsis*, together with compounds **53**-**60**, as described by Huang *et al*.[63] Compound **69** has a similar structural skeleton to compound **42**,[42] and the main difference is only in the configuration of the C-8 carbon. Determination of its absolute configuration revealed the 4*R*,8*S*,10*S* arrangement. In turn, compounds **70**, **71** and **72** exhibit a benzofuran skeleton not previously seen in this group of metabolites. Compound **70** has a hydroxyl group at the C-14 position, while compound **71** has hydroxyl groups at the C-1 and C-10 positions. In contrast, compound **72** contains a single hydroxyl group located at C-10. The absolute configurations of the compounds were determined to be 8*R*,14*S* (**70**), 8*S*,9*S* (**71**) and 8*R*,9*R* (**72**).[63]

2.9. Trichodermatides

In 2008, Sun *et al*.[21] first isolated trichodermatides A-D (**73**-**76**) (Figure 8) of the fungus *T. reesei*, obtained from a sediment sample in China. Compound **73** has a cyclohexanone ring with an α,β-unsaturated group with the carbonyl at C-1, a pyran ring resulting from a bond between C-5 and C-9, in addition to the presence of a ketal group and an aliphatic chain.[21,65] Stereochemical analysis, based on NOESY correlations, coupling constants and ECD spectroscopy, allowed assigning the absolute configuration as 2*R*,7*R*,8*S*,9*S*,10*S*,13*R*,15*S*,16*S*. Thus, trichodermatide A represents the first octaketide of this group with a pentacyclic skeleton, demonstrating a unique structure among the isolated derivatives of the genus *Trichoderma*.[66-68]

The structure of trichodermatide B (**74**) is quite like that of compound **2**, except for the oxidation of the hydroxy group attached to C-10. The absolute configuration of compound **74** was determined as 2*S*,9*S*.[21,69] Trichodermatides C (**75**) and D (**76**) share the same structural skeleton of compound **74**. In compound **75**, an unsaturation at position C-10/C-11 is observed, while compound **76** has a hydroxy group at C-3, differentiating it from compound **74**, which has hydroxyl at C-2. The absolute configurations of compounds **75** and **76** were determined as 2*S*,9*S* and 3*R*,9*R*, respectively.[21,66,70]

In 2018, Chen *et al*.[71] isolated trichodermatides E (**77**) and F (**78**) from the endophytic fungus *T. applanatum*. Compound **77** has a tetracyclic skeleton consisting of a cyclohexenone ring with hydroxyl in C-1, a γ-pyran ring, a cyclohexene ring and a second pyran ring associated with a hemicetal group at C-9, in addition to an *n*-heptyl side chain linked to C-15. Compound **78** exhibits structural similarity

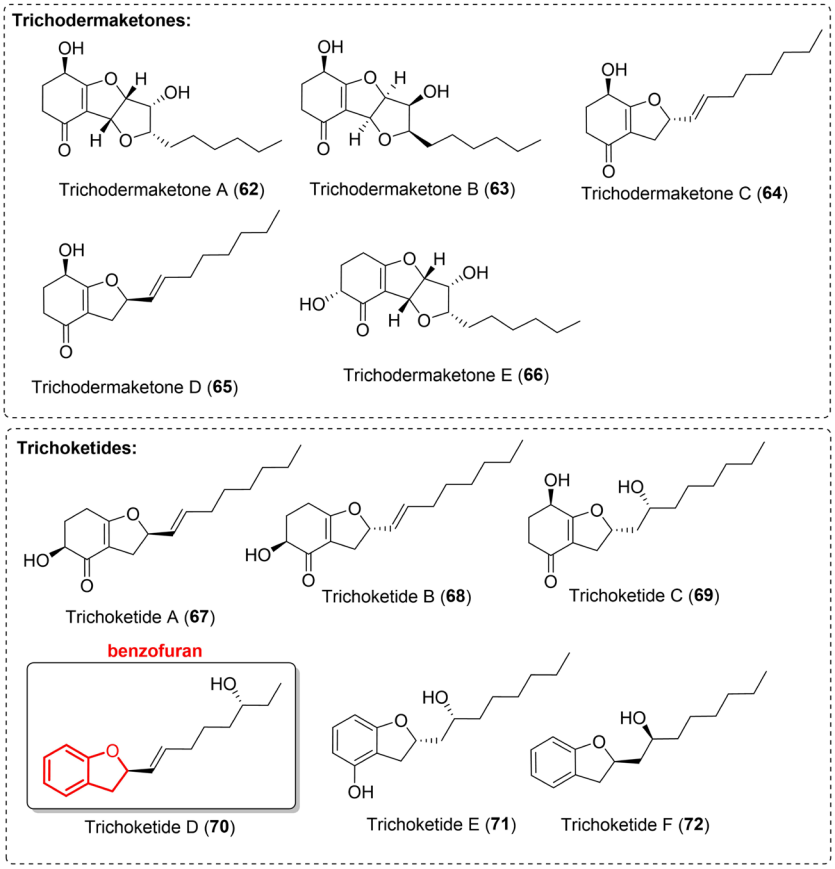


Figure 7. Chemical structures of trichodermaketones (**62-66**) and trichoketides (**67-72**). Highlighted in red: the first example of a koninginin-like benzofuran analogue.

to **77**, distinguished by the transfer of the hydroxyl unit from the C-2 to C-4 position. These compounds represent unprecedented examples of polyketides with a 6/6/6/6 tetracyclic skeleton, being the first members of this class.

Recently, new trichodermides have been isolated from the fungus *Trichoderma* sp. Although Zhou *et al.*[64] have described them as trichodermatides A-D, these names had already been established for other compounds 15 years ago. Since these are new substances, we will refer to these compounds as "compounds" **79**-**82**.[21,64] Compound **79** is characterized as an analogue of compound **5**, differentiating itself in the degree of unsaturation of its carbon chain. The absolute stereochemistry of this compound was determined as 4*R*,5*E*,9*S*,10*S*,14*E*.[64]

In turn, compounds **80** and **81** are epimers and analogues of compound **23**. Their absolute configurations were determined by X-ray diffraction, revealing the configurations 4*R*,5*Z*,7*R*,9*S*,10*S* for compound **80** and 4*R*,5*Z*,7*S*,9*S*,10*S* for compound **81**. Finally, compound **82** has the same planar structure as compound **61**. However, unlike **61**, which has the configuration 2*R*,5*E*,8*S*,10*R*, compound **82** has the configuration 8*R*, so its absolute configuration was established as 2*R*,5*E*,8*R*,10*R*.[64]

Table 1 summarizes all compounds found between the years 1989 to 2024, with details on the producing strains, location of isolation of the microorganism from the first report of the molecule and availability of spectroscopic data.

3. Biological Activities of Koninginins and Derivatives

Some koninginins and their analogues have demonstrated significant potential in several biological assays with applications ranging from plant growth regulation to pharmacological action, including cytotoxic, anti-inflammatory, antidiabetic properties, among others. This functional diversity highlights the possibility of applying these metabolites both in agriculture, to control pathogens and stimulate plant development, and in the medical field, with the development of new therapeutic agents. However, it is important to highlight that not all koninginins discovered have shown significant biological activities or have been tested to date. In this review, the main experimental findings related to the different biological activities attributed to these compounds are presented and discussed (Table 2).

Table 1. Koninginins, their derivatives and analogues isolated from 1989 to 2024

Compound	Producing strain	Environment source	Geographic area of isolation	Stereochemistry data	Reference
Koninginin A (**1**)	*T. harzianum* WU 71; ***T. koningii* ATCC 46314**;[a] *T. koningiopsis* DAOM 2422933; *T. neokongii* 8722; *T. ovalisporum* PRE-5; *P. corylophilum* DAOM 242293	soil and rhizosphere of the ornamental plant *Dieffenbachia* sp.	United States	X-ray crystallography: absolute (1*S*,4*R*,5*S*,6*S*,9*S*,10*S*)	19,28,30,31,36, 40,53,60,72
Koninginin B (**2**)	*T. applanatum* CGMCC 3.17526; *T. harzianum* WU 71; *T. koningiopsis* DAOM 2422933; *T. neokongii* 8722; ***T. koningii* ATCC 46314**[a]			decoupling, X-ray diffraction: absolute (2*S*,9*S*,10*S*)	28,29,32,49, 50,53,71
Koninginin C (**3**)	***T. koningii* ATCC 46314**[a]			not determined	47
Koninginin D (**4**)	*T. applanatum* CGMCC 3.17526; *T. harzianum* WU 71; *T. gamsii*; ***T. koningii* IMI 308477**;[a] *T. asperellum*; *T. koningiopsis* DAOM 2422933; *T. neokongii* 8722; *T. virens* MUCL 18139	suppressive soil to the saprophytic growth of the take-all fungus, *G. graminisvar*. tritici	Australia	total synthesis, X-ray crystallography: (4*R*,7*R*,9*S*,10*S*)	32,49,50,53, 55,71
Koninginin E (**5**)	*T. applanatum* CGMCC 3.17526; *T. neokongii* 8722; ***T. harzianum* WU 71**;[a] *T. koningii* ATCC 46314; *T. koningiopsis* YIM PH30002; *P. corylophilum* DAOM 242293	wheat and ryegrass roots	Western Australia	total synthesis: absolute (4*R*,9*S*,10*S*)	32,40,49,50,53, 55,71
Koninginin F (**6**)	*T. applanatum* CGMCC 3.17526; *T. koningii* MF349; ***T. harzianum* WU 71**;[a] *T. koningiopsis* DAOM 2422933			total synthesis, X-ray crystallography: absolute (2*R*,7*R*,9*S*,10*S*)	5,28,32,50,52,71
Koninginin G (**7**)	***T. aureoviride***;[a] *P. corylophilum* DAOM 242293	necrotic stem tissue of *Salix matsudana* × *alba*	Shannon, North Island, New Zealand	X-ray crystallography: absolute (2*R*,4*S*,5*S*,6*R*, 9*S*,10*S*)	25,40,73
Koninginin H (**8**)	***Emericella nidulans* UM-032009**[a]	orange peel	Tifton, Georgia, United States	NOESY: relative (4*R*,9*S*,10*S*)	43
Koninginin I (**9**)	*T. neokongii* 8722; *T. koningiopsis* YIM PH30002; ***T. neokongii* 8722**[a]	source was not given	China	ROESY: relative (4*R*,7*R*,9*S*,10*S*)	53
Koninginin J (**10**)				ROESY: relative (2*S*,9*S*,10*S*)	53,55
Koninginin K (**11**)				ROESY: relative (2*S*,9*S*,10*S*)	53
Koninginin L (**12**)	***T. koningii* 8662**;[a] *T. koningiopsis* QA-3			ECD, X-ray crystallography: absolute (2*S*,7*S*,9*S*,10*S*)	54,56,74
Koninginin M (**13**)	***T. koningii* 8662**[a]			ECD, X-ray crystallography: absolute (2*R*,7*S*,9*S*,10*S*)	54
Koninginin N (**14**)	***T. koningiopsis* YIM PH30002**[a]	*Panax notoginseng*	Wenshan, Yunnan, China	ECD: absolute (4*R*,8*S*)	55
Koninginin O (**15**)				ECD: absolute (2*S*,8*S*,9*E*)	
Koninginin P (**16**)				ECD: absolute (2*S*,9*S*,10*S*)	
Koninginin Q (**17**)				ECD: absolute 2*S*,7*R*,9*S*,10*S*)	
Koninginin R (**18**)				ECD: absolute (4*R*,7*R*,9*S*,10*S*)	26
Koninginin S (**19**)				ECD: absolute (2*S*,8*S*)	
Koninginin T (**20**)	***T. koningiopsis* QA-3**[a]	*Artemisia argyi*	Qichun, Hubei, China	ECD: absolute (4*S*,7*S*,9*S*,10*S*)	56
Koninginin U (**21**)				ECD: absolute (4*R*,7*R*,9*S*,10*S*)	52
Koninginin V (**22**)				ECD: absolute (2'*R*,3'*R*,4*R*,7*R*,9*S*,10*S*)	
Koninginin W (**23**)	***T. koningiopsis* YIM PH30002**[a]	*Panax notoginseng*	Wenshan, Yunnan, China	ECD, X-ray crystallography: absolute (4*S*,7*R*,9*S*,10*S*)	24

Table 1. Koninginins, their derivatives and analogues isolated from 1989 to 2024 (cont.)

Compound	Producing strain	Environment source	Geographic area of isolation	Stereochemistry data	Reference
Koninginin X (**24**)	***T. koningiopsis* SC-5**[a]	*Pedicularis integrifolia*	Li County, Aba Prefecture, Sichuan, China	ECD: absolute (4*R*,7*R*,8*R*,9*R*,10*S*)	59
Koninginin Y (**25**)				ECD: absolute (4*S*,7*S*,8*S*,9*S*,10*S*)	
Koninginin Z (**26**)				ECD, X-ray crystallography: absolute (4*R*,8*R*,9*S*,10*S*)	
ent-Koninginin A (**27**)	***T. koningiopsis* QA-3**[a]	*Artemisia argyi*	Qichun, Hubei, China	X-ray crystallography: absolute (1*R*,4*S*,5*R*,6*R*,9*R*,10*R*)	56
1,6-di-*epi*-Koninginin A (**28**)				X-ray crystallography: absolute (1*R*,4*R*,5*S*,6*R*,9*S*,10*S*)	
15-Hydroxy-koninginin A (**29**)				X-ray crystallography: absolute (1*S*,4*R*,5*S*,6*S*,9*S*,10*S*,15*S*)	
14-Ketokoninginin B (**30**)				ECD: absolute (2*R*,9*S*,10*S*)	52
14-Hydroxykoninginin B (**31**)				ECD: absolute (2*R*,9*S*,10*S*,14*R*)	
7-*O*-Methylkoninginin B (**32**)				ECD: absolute (2*R*,7*R*,9*S*,10*S*)	
7-*O*-Methylkoninginin D (**33**)	*T. applanatum* CGMCC 3.17526; *T. koningiopsis*; ***T. koningii* MF349**[a]	marine sediments	South China Sea	ECD, X-ray crystallography: absolute (4*R*,7*R*,9*S*,10*S*)	5,22,52
4-*epi*-7-*O*-Methylkoninginin D (**34**)	***T. koningiopsis* QA-3**[a]	*Artemisia argyi*	Qichun, Hubei, China	ECD, X-ray crystallography: absolute (4*S*,7*R*,9*S*,10*S*)	3
14-Hydroxykoninginin E (**35**)				ECD, X-ray crystallography: absolute (4*R*,9*S*,10*S*,14*R*)	52
15-Hydroxy1,4,5,6-tetra-*epi*-koninginin G (**36**)				X-ray crystallography: absolute (1*S*,4*R*,5*R*,6*S*,9*S*,10*S*,15*S*)	
4'-Hydroxykoninginin U (**37**)				ECD: absolute (4*R*,7*R*,9*S*,10*S*)	
Trichodersine (**38**)	***Trichoderma* sp. MWTGP-04**[a]	*Aconitum carmichaeli*	Guiyang City, Guizhou province of China	X-ray crystallography: absolute (2*S*,4*S*,4a*R*,5*R*,8*R*,8a*R*,9*R*)	61
seco-Koninginin (**39**)	***T. harzianum* WU 71**[a]	wheat and ryegrass roots	Western Australia	decoupling: relative	11,50
Koningipyridine A (**40**)	***T. koningiopsis* SC-5**[a]	*Pedicularis integrifolia*	Sichuan, China	ECD: absolute (4*R*,5*S*,9*S*,10*S*,19*R*)	62
Koningipyridine B (**41**)				ECD: absolute (4*R*,7*S*,9*S*,10*S*,19*R*)	
Ppholiotone A (**42**)	***Pholiota* sp. SCK05-7-ZP19**[a]	isolated from the surface of *Cordyceps sinensis*	Kangding, Sichuan, China	ECD: absolute (4*R*,8*R*,10*S*)	42
Pholiotone B (**43**)				ECD: absolute (2*R*,8*S*,10*S*)	41
Pholiotone C (**44**)				ECD: absolute (2*S*,8*S*,10*S*)	
Koningiopisin A (**45**)	***T. koningiopsis* YIM PH30002**[a]	*Panax notoginseng*	Wenshan, Yunnan, China	ECD: relative 2*R*,7*R*,9*S*,10*S*)	23
Koningiopisin B (**46**)				ECD: relative (2*R*,8*S*,9*R*,10*S*)	
Koningiopisin C (**47**)				ECD: relative (4*R*,5*S*,9*S*,10*S*)	
Koningiopisin D (**48**)				ECD: relative (2*R*,8*S*,10*S*)	
Koningiopisin E (**49**)				ECD, X-ray crystallography: absolute (2*R*,9*S*,10*S*)	23,52
Koningiopisin F (**50**)				ECD: relative (2*R*,8*S*,9*E*)	23
Koningiopisin G (**51**)				ROESY: relative (2*R*,8*S*,9*E*)	
Koningiopisin H (**52**)				ECD: relative (2*R*,8*S*)	

Table 1. Koninginins, their derivatives and analogues isolated from 1989 to 2024 (cont.)

Compound	Producing strain	Environment source	Geographic area of isolation	Stereochemistry data	Reference
Koningiopisin I (**53**)	***T. koningiopsis* 414-HLP-100**[a]	rhizosphere of *Polygonum paleaceum*	Dali, Yunnan, China	ECD, X-ray crystallography: absolute (2*R*,5*R*,6*R*,9*S*,10*S*)	63
Koningiopisin J (**54**)				ECD, X-ray crystallography: absolute (4*R*,5*S*,6*R*,9*S*,10*S*)	
Koningiopisin K (**55**)				ECD, X-ray crystallography: absolute (4*R*,5*S*,6*S*,9*S*,10*S*)	
Koningiopisin L (**56**)				ECD, X-ray crystallography: absolute (1*R*,4*R*,5*S*,6*R*,9*S*,10*S*)	
Koningiopisin M (**57**)				ECD, X-ray crystallography: absolute (1*S*,4*R*,5*S*,6*S*,9*S*,10*S*)	
Koningiopisin N (**58**)				ECD, X-ray crystallography: absolute (5*S*,6*R*,9*S*,11*R*)	
Koningiopisin O (**59**)				ECD: absolute (9*R*,15*S*)	
Koningiopisin P (**60**)				ECD: absolute (9*R*,14*S*)	
10-Deacetylkoningiopisin D (**61**)	***T. koningiopsis* QA-3**[a]	*Artemisia argyi*	Qichun, Hubei, China	ECD, X-ray crystallography: absolute (2*R*,8*S*,10*R*)	57,64
Trichodermaketone A (**62**)	***T. koningii* MF349**[a]	marine sediments	South China Sea	ECD: absolute (4*R*,7*R*,8*R*,9*R*,10*S*)	5
Trichodermaketone B (**63**)				ECD: absolute (4*R*,7*S*,8*S*,9*S*,10*R)*	
Trichodermaketone C (**64**)				ECD: absolute (4*R*,8*S)*	5,75
Trichodermaketone D (**65**)				ECD: absolute (4*R*,8*R*)	
Trichodermaketone E (**66**)	***T. koningiopsis* QA-3**[a]	*Artemisia argyi*	Qichun, Hubei, China	X-ray crystallography: absolute (2*R*,7*R*,8*R*,9*R*,10*S*)	3
Trichoketide A (**67**)	***Trichoderma* sp. TPU1237**;[a] *T. koningiopsis* QA-3	seawater	Mutsu, Aomori, Japan	ECD: absolute (2*S*, 8*R*)	75
Trichoketide B (**68**)	***Trichoderma* sp. TPU1237**[a]			ECD: absolute (2*S*,8*S*)	
Trichoketide C (**69**)	***T. koningiopsis* 414-HLP-100**[a]	rhizosphere of *Polygonum paleaceum*	Dali, Yunnan, China	ECD: absolute (4*R*,8*S*,10*S*)	63
Trichoketide D (**70**)				ECD: absolute (8*R*,14*S*)	
Trichoketide E (**71**)				ECD: absolute (8*S*,9*S)*	
Trichoketide F (**72**)				ECD: absolute (8*R*,9*R*)	
Trichodermatide A (**73**)	***Trichoderma reesei***[a]	marine sediments	Lianyungang, China	ECD: absolute (2*R*,7*R*,8*S*,9*S*,10*S*,13*R*, 15*S*,16*S*)	21,66
Trichodermatide B (**74**)				ECD: absolute (2*S*,9*S*)	21
Trichodermatide C (**75**)				ECD: absolute (2*S*,9*S*)	
Trichodermatide D (**76**)				ECD: absolute (3*R*,9*R*)	
Trichodermatide E (**77**)	***T. applanatum* CGMCC 3.17526**[a]	source was not given		ROESY: relative (2*R*,7*S*,10*S*,13*R*,15*S*,16*S*)	71
Trichodermatide F (**78**)				NOESY: relative (4*S*,7*S*,10*S*,13*R*,15*S*,16*S*)	
Trichodermatide A (**79**)	***Trichoderma* sp. XM-3**[a]	soil	Xuefeng Mountain, Hunan, China	X-ray crystallography: absolute (4*R*,5*E*,9*S*,10*S*,14*E*)	64
Trichodermatide B (**80**)				X-ray crystallography: absolute (4*R*,5*Z*,7*R*,9*S*,10*S*)	
Trichodermatide C (**81**)				ECD: absolute (4*R*,5*Z*,7*S*,9*S*,10*S*)	
Trichodermatide D (**82**)				ECD: absolute (2*R*,5*E*,8*R*,10*R*)	

[a]Bold values represent the first strain producing the compound. NOESY: nuclear Overhauser effect spectroscopy; ROESY: rotating frame Overhauser enhancement spectroscopy; ECD: electronic circular dichroism.

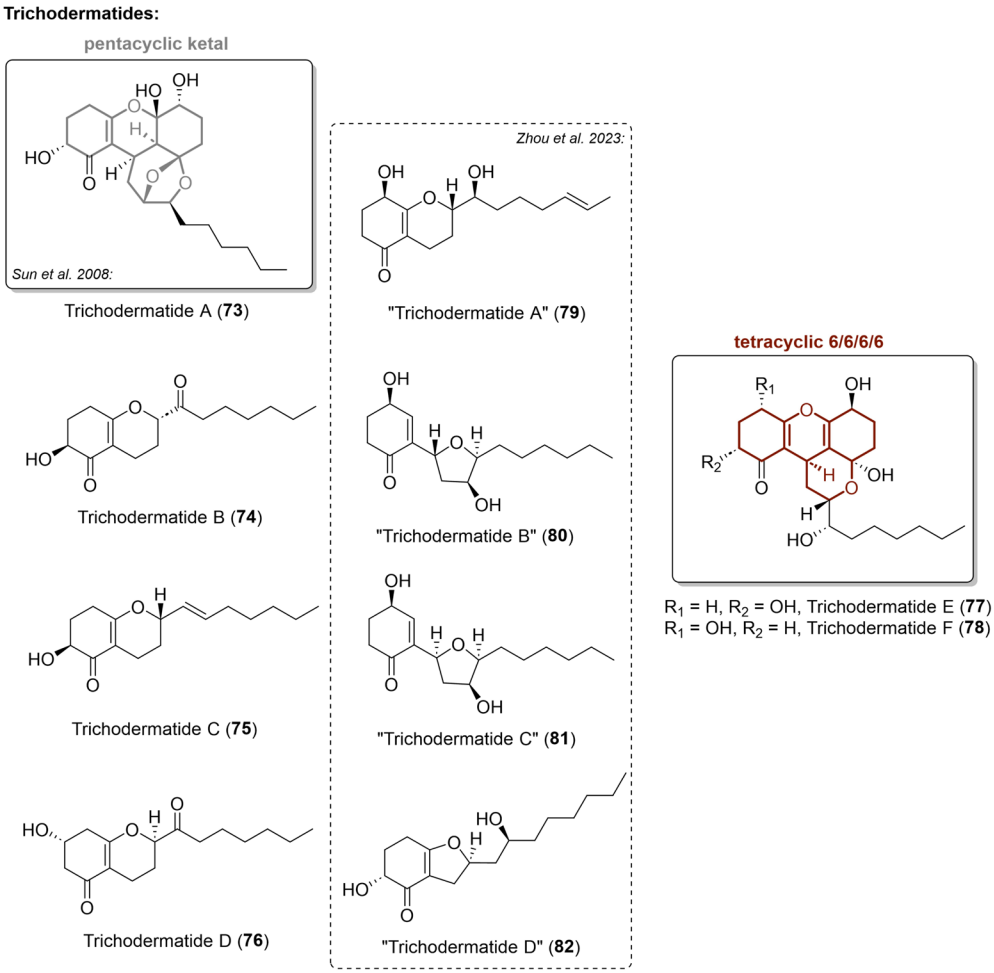


Figure 8. Chemical structures of trichodermatides A-F (**73-82**). Highlighted in gray: the first example of a pentacyclic ketal-like analogue; highlighted in dark red the first example of a 6/6/6/6 tetracyclic structure. The dashed boxes denote molecules with repeated names.

3.1. Plant growth regulation

Using etiolated wheat coleoptiles as an experimental model, it was observed, at a concentration of 10^{-3} M, that koninginin A (**1**) significantly inhibited coleoptile elongation. The growth was reduced by 57%, indicating a strong interference in the process of cell elongation, possibly by antagonistic action to auxins or by interference in signaling pathways related to plant development.[19]

Other koninginins, such as compounds **2**, **3**, **5** and **7**, were also evaluated, showing significant inhibitory effects, although with variations in intensity and response pattern.[25,29,47,49] Such differences can be attributed to the structural specificities of the compounds and the interaction with the endogenous signaling systems of plants. Comparative analysis of these variants is critical to identify compounds with the greatest regulatory potential and to elucidate the underlying mechanisms of action.

Given the importance of coleoptile elongation during etiolation, an essential step in which the shoot must reach the surface, protecting the primordial meristems and leaves, and initiate photosynthesis, it is crucial to carefully evaluate any modulation of this process.[80] The bioassay with etiolated choleoptyls serves as an initial screening, where if a compound inhibits or stimulates the growth of the choleoptyls, this indicates that it may have regulatory activity in plants, acting as a clue for further investigations into its mechanism of action and potential application.

3.2. Tumor induction in plants

The tumor-inducing activity was investigated using *Agrobacterium tumefaciens*, a bacterium known for its ability to cause tumors in plants. In the experiment, potato disks were placed in petri dishes containing agar, and a solution with the B6 strain of *A. tumefaciens* was applied together with compound **1** at a concentration of 25 μg $disk^{-1}$.[77]

Exposure of the disks to compound **1** resulted in the formation of cell agglomerations, indicating that the compound may interfere with signaling pathways and cell

Table 2. List of biological activities of koninginins isolated from *Trichoderma* sp.

Compound	Bioactivities	Antagonist / suppressor / target	Concentration	Reference
1	plant growth regulator	etiolated wheat coleoptiles	10^{-3} M	19
	antifungal	*G. graminis* var. *tritici*	not reported	50,72
		Fusarium oxysporum, *Alternaria panax*	256 μg mL^{-1}	23
	nematicidal	*Panagrellus redivivus*, *Caenorhabditis elegan*	not reported	53
	antiophidic	*Bothrops jararacussu*	1-25 μg	76
	tumor induction	*Agrobacterium tumefaciens*	25 μg disk	77
	antibacterial	*Escherichia coli*	128 μg mL^{-1}	24
		Bacillus subtilis, *Pseudomonas aeruginosa*	256 μg mL^{-1}	78
	cytotoxic	AGP01, AGP01 PIWIL1-/-, ACP02, ACP03, SK-MEL 19	IC_{50} 147.8-190 μM	
2	plant growth regulator	etiolated wheat coleoptiles	10^{-3} M	29
	antifungal	*G. graminis* var. *tritici*	not reported	50
		F. oxysporum	256 μg mL^{-1}	23
		A. panax, *Plectosphaerella cucumerina*	128 μg mL^{-1}	
		Ceratobasidium cornigerum	32 μg mL^{-1}	52
	antibacterial	*E. coli*, *Edwardsiella megi*, *Vibrio alginolyticus*	64 μg mL^{-1}	
	cytotoxic	AGP01, AGP01 PIWIL1-/-, ACP02, ACP03, SK-MEL 19	IC_{50} 7.09-49.63 μM	78
3	antifungal	*G. graminis var. tritici*	not reported	72
	plant growth regulator	etiolated wheat coleoptiles	10^{-3} M	47
4	antibacterial	*Listeria monocytogenes*	256 μg mL^{-1}	24
		B. subtilis, *P. aeruginosa*	128 μg mL^{-1}	
		E. coli, *E. megi*, *V. alginolyticus*	64 μg mL^{-1}	52
	antifungal	*G. graminis var. tritici*, *Bipolaris sorokiniana*, *Pythium middletonii*, *F. oxysporum*, *Phytophthora cinnamomi*, *Rhizoctonia solani*	10 μg disk	48
		C. cornigerum	64 μg mL^{-1}	52
	cytotoxic	A549, Hela, HepG2	50 μM	63
5	plant growth regulator	etiolated wheat coleoptiles	10^{-3} M	49
	antifungal	*G. graminis* var. *tritici*	not reported	50
		C. cornigerum	16 μg mL^{-1}	52
	antibacterial	*E. coli*, *E. megi*, *V. alginolyticus*	64 μg mL^{-1}	
	antiophidic	*B. jararacussu*	1-25 μg	76
	cytotoxic	A549, Hela, HepG2	50 μM	62
		AGP01, AGP01 PIWIL1-/-, SK-MEL 19	IC_{50} 10.63-24.81 μM	78
6	antifungal	*B. sorokiniana*; *C. cornigerum*	32.0 μg mL^{-1}	52
	antibacterial	*E. coli*; *E. megi*; *V. alginolyticus*	64 μg mL^{-1}	52
	antiophidic	*Bothrops jararacussu*	1-25 μg	76
	cytotoxic	A549, Hela, HepG2	50 μM	62
7	antifungal	*G. graminis* var. *tritici*	not reported	79
	plant growth regulator	etiolated wheat coleoptiles	10^{-3} M	25
11	antibacterial	*E. coli*, *Edwardsiella tarda*, *V. alginolyticus*	64 μg mL^{-1}	56
		Vibrio anguillarum	32 μg mL^{-1}	
	antifungal	*C. cornigerum*	16 μg mL^{-1}	
15	antifungal	*F. oxysporum*, *P. cucumerina*	128 μg mL^{-1}	55
17				
18	antibacterial	*F. oxysporum*, *Fusarium flocciferum*	128 μg mL^{-1}	26
19		*F. oxysporum*		
20	antibacterial	*B. subtilis*	256 μg mL^{-1}	24
		E. coli, *E. tarda*	64 μg mL^{-1}	56
		V. alginolyticus, *V. anguillarum*	32 μg mL^{-1}	
	antifungal	*Penicillium digitatum*	16 μg mL^{-1}	
21	antibacterial	*E. coli*, *V. alginolyticus*	64 μg mL^{-1}	52
		E. megi	16 μg mL^{-1}	
		Vibrio harveyi	4 μg mL^{-1}	
	antifungal	*C. cornigerum*	8 μg mL^{-1}	
22	antibacterial	*E. coli*, *E. megi*, *V. alginolyticus*	64 μg mL^{-1}	52
23	antifungal	*Phoma herbarum*, *Aspergillus niger*, *F. oxysporum*	256 μg mL^{-1}	61

Table 2. List of biological activities of koninginins isolated from *Trichoderma* sp. (cont.)

Compound	Bioactivities	Antagonist / suppressor / target	Concentration	Reference
23	antifungal	*Fusarium solani*, *P. cucumerina*	128 μg mL^{-1}	
24	antibacterial	*Staphylococcus aureus*	256 μg mL^{-1}	24
		B. subtilis, *E. coli*	128 μg mL^{-1}	
		Salmonella typhimurium	64 μg mL^{-1}	
27	antibacterial	*E. coli*, *E. tarda, Micrococcus luteus*, *P. aeruginosa*, *V. alginolyticus*, *Vibrio parahemolyticus*	64 μg mL^{-1}	56
		V. anguillarum	8 μg mL^{-1}	
		Vibrio vulnificus	4 μg mL^{-1}	
	antifungal	*B. sorokiniana*, *F. oxysporum*	64 μg mL^{-1}	
		Physalospora piricola	32 μg mL^{-1}	
		P. digitatum	16 μg mL^{-1}	
		C. cornigerum	8.0 μg mL^{-1}	
28	antibacterial	*E. coli*, *E. tarda, M. luteus*, *V. alginolyticus*	64 μg mL^{-1}	56
		V. anguillarum	32 μg mL^{-1}	
	antifungal	*C. cornigerum*, *F. oxysporum*, *P. piricola*	64 μg mL^{-1}	
29	antibacterial	*E. coli*, *E. tarda*, *V. alginolyticus*	64 μg mL^{-1}	56
		V. anguillarum	16 μg mL^{-1}	
	antifungal	*C. cornigerum*, *P. digitatum*	64 μg mL^{-1}	
30	antibacterial	*E. coli*, *V. alginolyticus*	64 μg mL^{-1}	52
		E. megi	32 μg mL^{-1}	
		E. tarda	2 μg mL^{-1}	
	antifungal	*C. cornigerum*	8 μg mL^{-1}	
31	antibacterial	*E. coli*, *E. megi*, *V. alginolyticus*	64 μg mL^{-1}	52
32	antibacterial	*E. coli*, *V. alginolyticus*	64 μg mL^{-1}	52
		E. megi	32 μg mL^{-1}	
	antifungal	*C. cornigerum*	32 μg mL^{-1}	
33	antibacterial	*E. coli*, *E. megi*, *V. alginolyticus*	64 μg mL^{-1}	24
		S. typhimurium	128 μg mL^{-1}	
	antifungal	*P. cucumerina*	128 μg mL^{-1}	55
		C. cornigerum	16 μg mL^{-1}	52
	cytotoxic	A549, Hela, HepG2	50 μM	62
34	antibacterial	*P. aeruginosa*	8 μg mL^{-1}	3
35	antibacterial	*E. coli*, *E. megi*, *V. alginolyticus*	64 μg mL^{-1}	52
	antifungal	*C. cornigerum*	8 μg mL^{-1}	
		F. oxysporum	256 μg mL^{-1}	61
		P. herbarum	128 μg mL^{-1}	
		A. panax, *A. niger*	32 μg mL^{-1}	
		F. solani, *P. cucumerina*	4 μg mL^{-1}	
36	antibacterial	*E. coli*	64 μg mL^{-1}	52
		E. megi	32 μg mL^{-1}	
		V. alginolyticus	1 μg mL^{-1}	
37	antibacterial	*E. coli*, *E. megi*, *V. alginolyticus*	64 μg mL^{-1}	52
	antifungal	*B. sorokiniana*	8 μg mL^{-1}	
		Helminthosporium maydis	16 μg mL^{-1}	
38	antifungal	*P. herbarum*, *F. oxysporum*	128 μg mL^{-1}	61
		A. niger	32 μg mL^{-1}	
		A. panax	16 μg mL^{-1}	
		F. solani, *P. cucumerina*	4 μg mL^{-1}	
39	antifungal	*G. graminis* var. *tritici*	not reported	50
40	cytotoxic	A549, Hela, HepG2	50 μM	62
41				
45	antifungal	*F. oxysporum*, *A. panax*, *F. solani*	256 μg mL^{-1}	23
		P. cucumerina	128 μg mL^{-1}	
46	antifungal	*F. oxysporum*, *F. solani*, *P. cucumerina*	256 μg mL^{-1}	
		A. panax	64 μg mL^{-1}	
47	antifungal	*A. panax*	64 μg mL	
		F. oxysporum, *F. solani*	32 μg mL^{-1}	

Table 2. List of biological activities of koninginins isolated from *Trichoderma* sp. (cont.)

Compound	Bioactivities	Antagonist / suppressor / target	Concentration	Reference
47	antifungal	*P. cucumerina*	16 μg mL^{-1}	23
	antibacterial	*S. aureus*	64 μg mL^{-1}	
	anti-inflammatory	BV-2 (murine microglial)	IC_{50} 8.9 μM	63
48	antifungal	*P. cucumerina*	128 μg mL^{-1}	23
49	antibacterial	*E. coli*, *V. alginolyticus*	64 μg mL^{-1}	52
		E. megi	16 μg mL^{-1}	
	antifungal	*C. cornigerum*	16 μg mL^{-1}	
		H. maydis	4 μg mL^{-1}	
50	antifungal	*F. solani*, *P. cucumerina*	256 μg mL^{-1}	23
		F. solani	256 μg mL^{-1}	
		F. oxysporum	128 μg mL^{-1}	
51	antifungal	*A. panax*, *P. cucumerina*	256 μg mL^{-1}	
52	antifungal	*A. panax*	64 μg mL^{-1}	
53	anti-inflammatory	BV-2 (murine microglial)	IC_{50} 14 μM	63
54	anti-inflammatory	BV-2 (murine microglial)	IC_{50} 3 μM	
61	antibacterial	*E. coli*, *E. tarda*, *V. alginolyticus*	64 μg mL^{-1}	56
		V. anguillarum	16 μg mL^{-1}	
	antifungal	*C. gloeosporioides*, *F. oxysporum*	64 μg mL^{-1}	
		C. cornigerum	32 μg mL^{-1}	
		P. digitatum	8 μg mL^{-1}	
64	antifungal	*F.* solani	256 μg mL^{-1}	23
		A. panax, *P. cucumerina*	128 μg mL^{-1}	
	antidiabetic	inhibition of enzymatic activity of PTP1B	IC_{50} 68 μM	75
65	antidiabetic	inhibition of enzymatic activity of PTP1B	IC_{50} 56 μM	
	antibacterial	*P. aeruginosa*	inhibition zone 16mm	64
66	antibacterial	*E. coli*, *V. parahemolyticus*	16 μg mL^{-1}	3
		P. aeruginosa, *V. anguillarum*	8 μg mL^{-1}	
67	antibacterial	*E. coli*, *E. tarda*, *M. luteus*, *V. alginolyticus*, *V. parahemolyticus*	64 μg mL^{-1}	56
		V. anguillarum	32 μg mL^{-1}	
		V. vulnificus	16 μg mL^{-1}	
	antifungal	*Fusarium graminearum*, *V. mali*	64 μg mL^{-1}	
		B. sorokiniana, *C. gloeosporioides*, *F. oxysporum*, *P. piricola*	8 μg mL^{-1}	
		C. cornigerum, *P. digitatum*	4 μg mL^{-1}	
	antidiabetic	inhibition of enzymatic activity of PTP1B	IC_{50} 53 μM	75
68	antidiabetic	inhibition of enzymatic activity of PTP1B	IC_{50} 65 μM	75
73	cytotoxic	A375-S2 (human melanoma)	IC_{50} 102.2 μg mL^{-1}	21
74	cytotoxic	A375-S2 (human melanoma)	IC_{50} 187.3 μg mL^{-1}	21
	antifungal	*Cryptococcus neoformans*	IC_{50} 4.9 μg mL^{-1}	43
75	cytotoxic	A375-S2 (human melanoma)	IC_{50} 38.8 μg mL^{-1}	21
76	cytotoxic		IC_{50} 222 μg mL^{-1}	

MIC: minimum inhibitory concentration; IC_{50}: 50.0% inhibitory concentration.

differentiation processes. Although this effect is considered undesirable in terms of pathogenicity, it provides relevant information on the biochemical mechanisms involved in the interaction between the compound and plant cell systems.

3.3. Nematicidal activity

Zhou *et al.*[53] conducted tests that showed the nematicide effect of compound **1**, demonstrated in tests against nematodes such as *Panagrellus redivivus* and *Caenorhabditis elegans*. The results indicated a significant reduction in the viability and mobility of these organisms, reinforcing the potential of compound **1** as a biological control agent. This activity is particularly relevant for integrated pest management, as it can decrease dependence on chemical pesticides and promote more sustainable and ecologically balanced agriculture.

3.4. Antiophidic activity

The results obtained in the study of Souza *et al.*[76] indicate that compounds **5** and **6**, isolated from the

endophytic fungus *Trichoderma koningii*, isolated from a plant *Strychnos cogens* that grows around Manaus (AM, Brazil), have a significant potential for the development of new antiophidic and anti-inflammatory agents. With a structure similar to that of flavonoids and vitamin E, these molecules inhibit phospholipase A2 (PLA2), a key enzyme in the inflammatory cascade, and act significantly against the effects of the snake venom *Bothrops jararacussu*.

The investigation revealed that by reducing the formation of edema, one of the main signs of inflammation, and by mitigating myotoxic activity, as assessed by quantification of plasma creatine kinase (CK), compounds **5** and **6** demonstrated efficacy in protecting against muscle damage induced by poisoning. Furthermore, the compounds showed more pronounced inhibition of the enzymatic activities of isolated PLA2, especially that of group IIB (bjPLA2), compared to that of group IIA (hsPLA2), showing a selective action on the toxic components of the poison.[76]

The structural similarity to vitamin E suggests that the mechanisms of action of koninginins may be analogous to those of this vitamin, interfering with the inflammatory cascade and reducing the deleterious effects of the poison.

3.5. Cytotoxic activity

Studies carried out to investigate the cytotoxicity of koninginins have shown that compounds of this class exhibit potential as anticancer agents, evidenced by the results obtained in different cell lines. In assays performed with human lung adenocarcinoma (A549), human cervical adenocarcinoma (HeLa) and human hepatocellular carcinoma (HepG2) cells, against derivatives of the koninginins family, including compounds **4**, **5**, **6**, **33**, **40** and **41**, were tested at a concentration of 50 μM, demonstrating significant cytotoxic activity.[62] This uniformity in concentration allowed comparisons that suggest that small structural changes can significantly modulate the efficacy of these agents, even without the quantitative determination of their 50.0% inhibitory concentration (IC_{50}) values.

In addition, compounds **1**, **2** and **5** were evaluated at concentrations of 40 μg mL^{-1} against the cell lines AGP01 (intestinal gastric adenocarcinoma), AGP01 PIWIL1-/- (intestinal gastric adenocarcinoma with PIWIL1 gene inactivated), ACP02 and ACP03 (gastric adenocarcinoma of diffuse type), SK-MEL 19 (human metastatic melanoma) and the control cell line MRC5 (human pulmonary fibroblast). The IC_{50} values observed for compound **1** were 190 (AGP01), 147.8 (AGP01 PIWIL1-/-), 161.9 (ACP02), 158.3 (ACP03) and 168.9 (SK-MEL 19) μM, while compound **2** showed IC_{50} of 10.63 (AGP01), 28.36 (AGP01 PIWIL1-/-), 49.63 (ACP02), 7.09 (ACP03) and 35.44 (SK-MEL 19) μM. In turn, compound **5** presented IC_{50} of 17.72 (AGP01), 10.63 (AGP01 PIWIL1-/-) and 24.81 (SK-MEL 19) μM.[78]

In parallel, compounds **73**-**76** were evaluated in the human melanoma cell line (A375-S2), presenting IC_{50} values that ranged from 38.8 to 222 μg mL^{-1}. In particular, compound **75**, with an IC_{50} of 38.8 μg mL^{-1}, stood out for its higher cytotoxic potency when compared to the others, which exhibited progressively higher values.[21]

3.6. Anti-inflammatory activity

Studies on the anti-inflammatory activity of koninginins demonstrate their potential in modulating the immune response and reducing inflammatory mediators. Inflammation is a natural response of the body, but its chronic persistence can contribute to diseases such as arthritis, cardiovascular problems and autoimmune conditions. *In vitro* models using murine microglial cells (BV-2), compounds **47**, **53** and **54** presented IC_{50} values of 8.9, 14 and 3 μM, respectively, with emphasis on compound **54** due to its greater potency.[63]

The mechanisms of action of these compounds include the inhibition of inflammatory enzymes, such as PLA2 and cyclooxygenase (COX), responsible for the synthesis of inflammatory mediators, in addition to the reduction in the production of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6). Their antioxidant action also contributes to the neutralization of free radicals and the reduction of oxidative stress. In addition, these compounds can modulate the immune response, balancing inflammation and preventing exacerbated reactions.[63]

3.7. Antidiabetic activity

Recent studies demonstrate that the antidiabetic activity of certain compounds may be directly related to the inhibition of the protein tyrosine phosphatase 1B (PTP1B), a crucial negative regulator in insulin signaling. PTP1B inhibition represents a promising therapeutic strategy, since its reduced activity can contribute to the improvement of insulin sensitivity, offering a new approach in the treatment of diabetes mellitus. Compounds **64**, **65**, **67** and **68**, *in vitro* assays, demonstrated IC_{50} values of 68, 56, 53 and 65 μM, respectively, indicating a consistent efficacy in modulating the enzymatic activity of PTP1B.[75]

The similarity of IC_{50} values between these compounds suggests that small structural variations may not significantly compromise the inhibitory potential, but at the same time highlights the importance of future investigations

to establish detailed structure-activity relationships. Considering that PTP1B plays a key role in the regulation of insulin signaling, its inhibition may be decisive to reverse or minimize the effects of insulin resistance. The analyzed compounds may be positioned as relevant candidates for the development of new antidiabetic therapeutic strategies.[81]

3.8. Antifungal activity

The antifungal activity of koninginins has been extensively documented, evidence of its potential in managing fungal diseases in agricultural contexts. *In vitro* assays showed that these compounds inhibit the growth of relevant pathogens, such as *Fusarium oxysporum*, *Alternaria panax*, *G. graminis* var. *tritici* and *Pythium middletonii*, corroborating their applicability as biological control agents.[19,72]

Each koninginin derivative exhibited a distinct antifungal activity profile. For example, compound **1** inhibited the growth of *F. oxysporum* and *A. panax*, exhibiting a minimum inhibitory concentration (MIC) of 256 μg mL^{-1}.[72] In contrast, compound **2** demonstrated greater potential against *Ceratobasidium cornigerum*, with MIC of 32 μg mL^{-1}, although higher concentrations were required for inhibition *F. oxysporum* and *A. panax*.[72] Other derivatives, such as compound **4**, demonstrated a broad antifungal spectrum, inhibiting pathogens such as *G. graminis* var. *tritici*, *Bipolaris sorokiniana*, *P. middletonii*, *F. oxysporum*, *Phytophthora cinnamomi* and *Rhizoctonia solani* at a concentration of 10 μg $disk^{-1}$, in addition to inhibiting *C. cornigerum* with an MIC of 64 μg mL^{-1}.[48,72] Furthermore, compound **5** showed activity against *G. graminis* var. *tritici* and inhibited *C. cornigerum* with an MIC of 16 μg mL^{-1}, while compound **6** inhibited *B. sorokiniana* and *C. cornigerum*, with an MIC of 32 μg mL^{-1}.[52,72]

Similarly, compound **45** inhibited the growth of *F. oxysporum*, *A. panax* and *Fusarium solani*, presenting MIC between 128 μg mL^{-1} and 256 μg mL^{-1}. Compound **46** demonstrated relevant activity, inhibiting *F. oxysporum*, *F. solani* and *Plectosphaerella cucumerina* with MIC of 256 μg mL^{-1}, as well as suppressing the growth of *A. panax* with MIC of 64 μg mL^{-1}. In contrast, compound **47** revealed antifungal potential, with MIC of 64 μg mL^{-1} for *A. panax*, 32 μg mL^{-1} for *F. oxysporum* and *F. solani*, and 16 μg mL^{-1} for *P. cucumerina*.[23]

Notably, compound **67** showed promising results, inhibiting the growth of fungal pathogens *B. sorokiniana*, *Colletotrichum gloeosporioides*, *F. oxysporum* and *Valsa mali* with a MIC of 8 μg mL^{-1}, in addition to demonstrating outstanding activity against *C. cornigerum* and *Penicillium digitatum* with MIC of 4 μg mL^{-1}.[56] The variation in MIC values among these compounds suggests that subtle changes in their chemical structures can significantly impact antifungal efficacy, allowing the selection of more potent candidates for future applications.

3.9. Antibacterial activity

In vitro studies, several metabolites derived from koninginins demonstrated the ability to inhibit the growth of relevant pathogenic bacteria, such as *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Vibrio* spp., among others, with minimum inhibitory concentration (MIC) ranging from 32 to 256 μg mL^{-1}. These results suggest that these molecules act by interfering with the integrity or function of essential cellular components of microorganisms.[72]

In the koninginin class, compound **1** demonstrates antibacterial activity with MIC of 128 μg mL^{-1} against *E. coli* and 256 μg mL^{-1}, against *B. subtilis* and *P. aeruginosa*.[72] Compound **2** demonstrates efficacy with MIC of 64 μg mL^{-1} against *E. coli*, *Edwardsiella megi* and *Vibrio alginolyticus*.[72] Compound **4** exhibits a broader spectrum, showing activity against *Listeria monocytogenes* (256 μg mL^{-1}), *B. subtilis* and *P. aeruginosa* (128 μg mL^{-1}) and against *E. coli*, *E. megi* and *V. alginolyticus* (64 μg mL^{-1}).[24,52] Compounds **5** and **6** also demonstrated antibacterial activity, with an MIC of 64 μg mL^{-1} for *E. coli*.[52]

Specific structural modifications appear to significantly influence antibacterial activity. For example, compound **30** has an MIC of 64 μg mL^{-1} for *E. coli* and *V. alginolyticus*, reaching a remarkably low value of 2 μg mL^{-1}, against *Edwardsiella tarda*.[52] Derivatives such as compounds **27**, **28** and **29** demonstrate robust antibacterial profiles, with MICs generally around 64 μg mL^{-1}, but reaching 4 μg mL^{-1} against *Vibrio vulnificus* and 8 μg mL^{-1} against *Vibrio anguillarum*.[56] Furthermore, compound **34** showed antibacterial activity with a MIC of 64 μg mL^{-1} against *E. coli*, *E. megi* and *V. alginolyticus*, in addition to a MIC of 128 μg mL^{-1} against *Salmonella typhimurium.*[56] Besides, compound **36** showed good activity against the aquatic pathogen *V. alginolyticus*, with a MIC value of 1 μg mL^{-1}.[52]

In the koningiopisins group, compound **47** has antibacterial activity against *S. aureus* with MIC of 64 μg mL^{-1}, while compound **49** acts against *E. coli* and *V. alginolyticus* (64 μg mL^{-1}) and against *E. megi* (16 μg mL^{-1}).[23,52] Similarly, compound **61** demonstrates an antibacterial profile with MIC of 64 μg mL^{-1} for *E. coli*, *E. tarda* and *V. alginolyticus*, and 16 μg mL^{-1} for *V. anguillarum*.[56]

Other metabolites, such as compounds **65** and **66**,

also showed antibacterial activity. While compound **65** showed an inhibition zone of 16 mm against *P. aeruginosa*, compound **66** revealed MIC of 16 μg mL^{-1} for *E. coli*, and 8 μg mL^{-1}, for *P. aeruginosa* and *V. anguillarum*.[3,64] Furthermore, compound **67** demonstrated a broad antibacterial spectrum, with MIC of 64 μg mL^{-1} against *E. coli*, *E. tarda*, *Micrococcus luteus*, *V. alginolyticus* and *Vibrio parahemolyticus*, 32 μg mL^{-1} against *V. anguillarum* and 16 μg mL^{-1} against *V. vulnificus*.[56]

4. Conclusions and Perspectives

The structural diversity of koninginins and related octaketides, together with their biological activities, highlights the importance of this group of compounds in the chemistry of microbial natural products, as well as indicating possible applications. Since the discovery of koninginin A, more than 80 derivatives have been identified and described in this review article, which systematically addressed the structural features, nomenclature, stereochemistry and biological activities of this intriguing group of molecules.

We conclude that there is much to be studied about koninginins, especially with the continuous discovery of new structural skeletons, the biosynthesis of these compounds, as well as new biological properties *in vitro* and *in vivo*. Above all, future studies may further explore the relationship of these compounds with the biocontrol potential of producing species, in order to enable the use of these compounds in agricultural practices.

Data Availability Statement

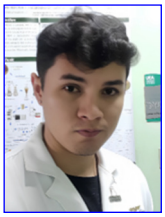
All data are available in the text.

Acknowledgments

The authors thank the Fundação de Amparo à Pesquisa do Estado do Amazonas (FAPEAM) for their support under the funding calls 010/2021 - CT&I Áreas Prioritárias, 008/2021 - PROSPAM, 002/2024 - POSGRAD 2024/2025, and grant number 01.02.016301.00260/2024-02. We also would like to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) under grants 443823/2024-3 and 407108/2023-8, as well as from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), finance Code 001, grant number 88881.200469/2018-01 (Procad AmazonMicro), and 88887.510218-2020-00 (CAPES-Amazônia-Legal).

Author Contributions

José C. I. Silva was responsible for the literature search, conceptualization, data curation, manual selection of articles, definition of the methodology, writing, reviewing and editing of the original draft; Felipe M. A. Silva for reviewing the original draft; Gilvan F. Silva for reviewing the original draft, supervision, project administration and resource management; Hector H. F. Koolen designed the study, developed the draft of the methodology, writing, reviewing and editing, and supervised and managed the project.



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Submitted: April 29, 2025
Final version online: July 8, 2025