Agri Articles
(e-Magazine for Agricultural Articles)
Volume: 05, Issue: 04 (JULY-AUG, 2025)
Available online at http://www.agriarticles.com
©Agri Articles, ISSN: 2582-9882

Strobilurins: Evolution of a New Generation Fungicide

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Strobilurins are a novel class of agricultural fungicides inspired by natural products originally isolated from basidiomycete fungi such as *Strobilurus tenacellus* and *Oudemansiella mucida*. These natural compounds exhibit potent antifungal activity, primarily due to a conserved β-methoxyacrylate pharmacophore that inhibits mitochondrial respiration by targeting the Qo site of the cytochrome bc1 complex. This mode of action disrupts ATP production, leading to effective fungal control with low mammalian toxicity. The discovery of strobilurins in the late 1970s sparked intense industrial research focused on lead optimization, photostability, and formulation improvements. Through systematic structure–activity relationship (SAR) studies, both academic and industrial teams developed synthetic analogs with improved stability and field efficacy, overcoming the photolability and volatility of the natural prototypes. Landmark products such as azoxystrobin (Zeneca) and kresoxim-methyl (BASF) emerged from these efforts, offering broad-spectrum disease control in major crops.

Introduction

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The Natural Strobilurins

The natural strobilurins were first identified in the late 1970s during a targeted search for biologically active secondary metabolites from basidiomycetes—a group of higher fungi that had been largely overlooked in natural product research due to their slow-growing mycelial

cultures. In contrast to the extensively studied actinomycetes, basidiomycetes were found to possess a rich and unique secondary metabolism with potential for novel antibiotic discovery. Strobilurins A and B were initially isolated from *Strobilurus tenacellus*, a fungus growing on pinecones, and demonstrated strong antifungal activity against a variety of fungal species. Structural elucidation revealed a relatively simple molecular architecture characterized by a β-methoxyacrylate moiety—later recognized as the key pharmacophore responsible for their mode of action. Interestingly, similar compounds were also isolated from other fungi such as *Mycena* and *Oudemansiella mucida*, the latter yielding the closely related compound oudemansin A.

Abundance of Strobilurins in Fungi

Strobilurins and related compounds such as oudemansins are widely distributed among fungi, particularly within the Basidiomycota. With the exception of *Bolinea lutea*, an ascomycete, all known strobilurin-producing species belong to the basidiomycetes, a phylum that includes many wood-decaying and litter-decomposing fungi. These natural products have been identified in diverse fungal genera, including *Strobilurus*, *Mycena*, *Favolaschia*, *Cyphellopsis*, and *Oudemansiella*. Their presence has been documented across a wide range of ecological zones, from temperate forests to tropical environments, indicating a global and phylogenetically broad occurrence. The production of strobilurins appears to confer a competitive ecological advantage, enabling the producing fungi to inhibit the growth of other microbial species sharing the same substrate. For instance, strobilurin D has been detected both in fruiting bodies and in wood colonized by *Mycena tintinnabulum*, where concentrations are sufficient to inhibit competing fungi. These findings support the hypothesis that strobilurins function as chemical defense agents in natural ecosystems. The widespread abundance and ecological role of strobilurins underscore their evolutionary significance and highlight their value as lead structures in the development of synthetic fungicides.

Mode of Action

Studies on the mode of action of strobilurins and oudemansins revealed very early on that these compounds inhibit the respiration of fungi. Investigations with Ehrlich ascites carcinoma cell cultures showed that the site of action lay exclusively in the respiratory chain. Other effects such as the complete inhibition of protein, RNA, and DNA synthesis were attributed by one of us (T.A.) to the resulting intracellular deficiency in ATP. The oxygen uptake and ATP synthesis of rat liver mitochondria were inhibited with both a ketoglutarate and succinate as substrates; hence the site of action had to be in either complex III or IV of the respiratory chain. A fortunate turn of events led us to find in von Jagow a collaboration partner of the utmost competence, who succeeded in localizing fairly exactly the site of action of the strobilurins and oudemansins in the mitochondrial bc1 com plex. In our first joint publication we reported that strobilur ins A and B, oudemansin A, and myxothiazole, a compound isolated by the groups of Reichenbach and Höfle at the Gesellschaft für Biotechnologische Forschung (Society for Biotechnological Research) in Braunschweig, all bind at the same site of action. A common structural element of these compounds that is clearly essential to their mode of 1332 action is an (E)-b-methoxyacrylate subunit. Strobilurins, oudemansins, and myxothiazole bind reversibly to the ubihy droquinone oxidation (Qp) center of the bc1 complex, a finding that has helped further our understanding of the structure and function of this part of the respiratory chain. Antimycin, an antifungal antibiotic commonly found in streptomycetes that is toxic to mammals, binds to the other center of the bc1 complex, the Qn center. The crystal structure of the bc1 complex from bovine heart tissue was recently solved by the Deisenhofer group, and the binding sites for myxothiazole and antimycin A were identified.

Biological Properties of the Strobilurins

Strobilurins are characterized by their broad-spectrum antifungal activity, targeting a wide range of economically significant phytopathogens, including *Erysiphe graminis*, *Puccinia recondita*, *Phytophthora infestans*, and *Venturia inaequalis*. Their primary biological action is fungistatic, achieved through inhibition of mitochondrial respiration via binding to the Qo site of the cytochrome bc_1 complex. This results in a disruption of ATP production, leading to energy starvation and eventual cessation of fungal growth. The β-methoxyacrylate pharmacophore is central to their mode of action and is responsible for their high specificity and potency. Early natural compounds such as strobilurin A and oudemansin A demonstrated strong in vitro activity but were prone to degradation under environmental conditions. Subsequent synthetic derivatives, including azoxystrobin, kresoxim-methyl, and trifloxystrobin, were optimized for improved photostability, systemic movement, and broader field performance.

Industrial Strobilurin Synthesis

The industrial synthesis of strobilurins involves the transformation of the natural β-methoxyacrylate pharmacophore into more stable and potent synthetic analogues suitable for agricultural use. The early natural products, such as strobilurin A, were chemically unstable due to their conjugated triene systems, which were highly sensitive to light and oxidation. To address this, industrial chemists focused on designing molecules that retained the essential pharmacophore while improving photostability, systemicity, and formulation compatibility.

One of the most successful early synthetic strobilurins was kresoxim-methyl, developed by BASF. Its synthesis involved the construction of an oxime ether pharmacophore as a bioisosteric replacement for the enol ether of the natural strobilurins. Key steps included the formation of a substituted phenylacetic acid derivative, condensation with hydroxylamine to form the oxime, and subsequent methylation to give the methoxyimino group. The side chain, often derived from simple starting materials like *o*-cresol, was introduced through etherification reactions. Another landmark compound, azoxystrobin, developed by Zeneca (now Syngenta), utilized an enol ether pharmacophore, with the molecule carefully engineered to achieve systemic movement in plants and broad-spectrum fungicidal activity.

In both cases, the industrial development process relied on extensive structure–activity relationship (SAR) studies and high-throughput biological screening to optimize efficacy and environmental properties. Photostabilization, ease of synthesis, and scalability were critical factors in selecting lead compounds. Industrial strobilurin synthesis typically involves multiple synthetic steps, use of robust catalysts, and protection/deprotection strategies, all fine-tuned for high yield and cost efficiency. These synthetic innovations enabled the commercial production of highly effective strobilurins such as trifloxystrobin, picoxystrobin, and fluoxastrobin, which continue to play a major role in global crop protection.

Effectiveness Against Diseases of Crops:

Strobilurins are highly effective fungicides widely used in modern agriculture due to their broad-spectrum activity, systemic movement, and preventive and curative properties. They inhibit mitochondrial respiration in target fungi, leading to rapid suppression of disease symptoms and protection of crop yields. Because of their unique mode of action and low toxicity to non-target organisms, strobilurins are applied across a diverse range of crops to control numerous fungal pathogens. Below is a list of major crops and the diseases effectively managed by strobilurin-based fungicides:

Strobilurins such as azoxystrobin, kresoxim-methyl, trifloxystrobin, pyraclostrobin, and picoxystrobin are widely used across these crops either alone or in mixtures with other fungicides for resistance management.

Conclusion

Strobilurins represent a major breakthrough in the field of fungicide chemistry, originating from natural products and evolving into one of the most successful classes of synthetic agricultural fungicides. Their unique mode of action—targeting the Qo site of the mitochondrial cytochrome bc_1 complex—provides potent, broad-spectrum activity against a wide array of plant pathogenic fungi. Through extensive structure–activity relationship studies and industrial innovation, natural strobilurins were chemically optimized to enhance photostability, systemic mobility, and efficacy under field conditions. Commercial products such as azoxystrobin, kresoxim-methyl, and trifloxystrobin have since become integral components of crop protection strategies worldwide.However, the high specificity of strobilurins also makes them vulnerable to resistance development, particularly through target-site mutations like G143A in fungal pathogens. As a result, their continued effectiveness depends on careful resistance management, including the use of mixtures, rotations with other fungicide classes, and integrated pest management (IPM) approaches. Despite these challenges, the success of strobilurins underscores the value of natural products as leads for synthetic agrochemicals and highlights the critical role of interdisciplinary research in bringing innovative solutions to global agriculture. Their legacy continues to shape the development of new fungicide classes and sustainable disease management practices.

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