Orysastrobin - Critical Design Features for a New Rice Fungicide

Markus Gewehr[1*], Jochen Dietz[2], Thomas Grote[2], Egon Haden[1], Manabu Itoh[3], Kenichi Kojima[4], Axel Johansson[1], Gerd Stammler[1], Siegfried Strathmann[1], Akihide Watanabe[3].

[1] BASF SE, 67117 Limburgerhof, Germany
[2] BASF SE, 67056 Ludwigshafen, Germany
[3] BASF Agro Ltd., 106-0032 Minato-ku, Tokyo, Japan
[4] BASF Agro Ltd., 441-3413 Mutsure-cho, Tahara, Japan

* markus.gewehr@basf.com

Abstract

The latest achievement of BASF SE's successful fungicide research and development effort is Orysastrobin, a new rice fungicide which has recently been introduced as Arashi® 嵐 in Japan and Korea. It is highly effective against the major rice diseases leaf and panicle blast and sheath blight. Orysastrobin has protective, curative, translaminar, and systemic properties, offering a broad and flexible application window. Furthermore, Orysastrobin is characterized by excellent crop safety, has a favorable toxicological and eco-toxicological profile and is safe to users and the environment.

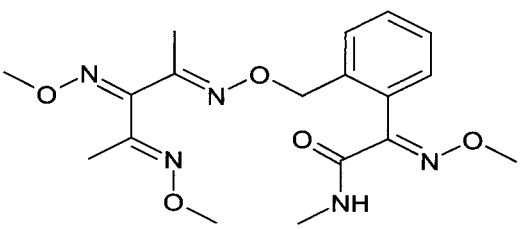
Introduction

After more than 20 years of research and development within the crop protection industry, strobilurins have become one of the most important classes of agrochemical agents. With a distributor sales value of 1.6 billion US$ in 2007 [1], strobilurins currently represent almost one-fifth of the world fungicide market. One of the leading companies in strobilurine reseach is BASF. After the successful launches of Kresoxim-methyl, Dimoxystrobin (co-developed with Shionogi) and Pyraclostrobin, Orysastrobin is the forth active ingredient from the class of strobilurins that has been introduced in the market.
Besides the enormous significance in crop protection, strobilurins represent one of the most instructive examples of how modern fungicide research is able to provide tailored solutions [2,3]. In particular the discovery of Orysastrobin demonstrates the benefits of an up-to-date approach in the lead identification and optimization of active ingredients, such as the combination of rational and market-driven research, the connection of target test activity to determine structure-activity relationships at the target level with biophysical properties and the use of modern scientific methods like automatized test systems.

The discovery of Orysastrobin

When in the mid 1990s, BASF set up a dedicated optimization program in strobilurin chemistry targeting the two major fungal rice pathogens, BASF's active ingredient research had already discovered and developed other strobilurins and was highly

experienced with this chemical class. However, as rice blast and sheat blight control in transplanted rice in Japan is mainly based on granule application in the seedling box, several specific properties of the active ingredient are essential for this application type. In particular, the fungicide has to be safe for rice seedlings, easily be taken up by roots, show long-lasting activity in the upper parts of the plant and feature a favorable aquatic toxicological profile.
Based on the profound knowledge on structure-activity-relationship, which BASF researchers gained while discovering Krexoxim-methyl and Pyraclostrobin, the strobilurin core structure was stepwise optimized towards rice diseases. In parallel, lipophilicity ($logP_{OW}$) was reduced, water solubility significantly increased. This rational adjustment of physicochemical properties went hand in hand with an improved aquatic toxicological profile, resulting in a novel and structurally unique strobilurin substructure cluster with two or even more oximether functions. Further optimization of the lead structure and additional requirements, such as a high metabolic stability and excellent residual efficacy, freedom to operate related to intellectual property rights and the development of a stereo-controlled method for the synthesis finally resulted in the discovery of Orysastrobin, consisting of four oximether functions:



Orysastrobin

Table 1: Chemical and physical properties

CAS number	*[248593-16-0]*
Chemical name (IUPAC)	(2*E*)-2-(methoxyimino)-2-{2-[(3*E*,5*E*,6*E*)-5-(methoxyimino)-4,6-dimethyl-2,8-dioxa-3,7-diazanona-3,6-dien-1-yl]phenyl}-*N*-methylacetamide
Molecular formula	$C_{18}H_{25}N_5O_5$
Molecular weight	391.43 g mol^{-1}
Melting point	99 °C
Vapour pressure	7×10^{-7} Pa (20 °C)
Partition coefficient n-octanol/water	$logP_{OW}$ = 2.36
Solubility in water	80.6 mg/L (20 °C)

Biological profile, toxicity and fungicidal efficacy

Biochemically, Orysastrobin acts like all strobilurins as an inhibitor of the cytochrome bc_1 complex at the Qo site in mitochondrial respiration [3]. In a yeast electron transport particle preparation, the rate of ubihydroquinone:cytochrome-c oxidoreductase was inhibited by 50% by 2.5×10^{-7} mol/L Orysastrobin in comparison with the untreated control.
Orysastrobin is characterised by outstanding long-lasting disease control due to its strong inhibition of spore germination. Furthermore, the compound is able to

suppress mycelial growth reliably, ultimately resulting in very good curative efficacy. The excellent root uptake and translocation behaviour of Orysastrobin builds the basis for successful applications in seedling boxes and paddy fields. Distinct acropetal transport in the leaves as well as translaminar activity are additional benefits of the compound.
Orysastrobin is furthermore characterised by excellent crop safety in a broad range of rice varieties. At the recommended rates, no crop injuries have been observed either in seedling boxes or after water surface applications. The compound has a favorable toxicological and eco-toxicological profile and is safe to users and the environment (tables 2-4) [4].

Table 2: Mammalian toxicity data of Orysastrobin

Acute oral LD_{50}	Rat	356 mg/kg
Acute dermal LD_{50}	Rat	> 2000 mg/kg
Eye irritation	Rabbit	no irritation
Skin irritation	Rabbit	no irritation
Skin sensitisation	Guinea pig	no sensitisation
Inhalation, dust LD_{50}	Rat	2.02 mg/L

Table 3: Wildlife toxicity data of Orysastrobin

Bird	Colinus virginianus	LD_{50} > 2000 mg/kg
Fish	Rainbow trout	LC_{50} = 0.89 mg/L (96h)
Daphnia	Daphnia magna	LC_{50} = 1.3 mg/L (24h)
Earthworm	Eisenia fetida	LC_{50} > 1000 mg/kg
Bees	Honey bee (adult)	NOEC > 142 µg a.i./bee
Algae	Green algae (Selenastrum capricornutum)	EbC_{50} (0~72h) = 7.1 mg/L

Table 4: Environmental fate data of Orysastrobin

Hydrolysis in water	DT_{50}	> 365 days
Photolysis in water	DT_{50}	0.8 days (natural water, irradiated)
Degradation in soil	DT_{50}	51-58 days (field)
Mobility in soil	K_{OC}	17.9-146

In all field trials, conducted as described in [5], Orysastrobin provides excellent control of leaf blast and panicle blast with outstanding long-lasting activity. The efficacy is equal or superior to the standard products under different disease pressure. Trials with different application timing (seeding, greening, transplanting) also show excellent efficacy of Orysastrobin against leaf and panicle blast independent of the application timing.
In order to maintain Orysastrobin's outstanding activity, resistance management strategies have been developed [5]. The cultivation of less pathogen-susceptible rice varieties and usage of healthy seeds is recommended together with a restriction of the number of applications of strobilurin fungicides. In addition, alternating applications with rice fungicides with a different mode of action, such as dicyclomet, probenazole, pyroquilon, furametpyr, tiadinil or thifluzamide, are recommended.

Conclusion

The strobilurin class of active substances represents one of the most significant product innovations in crop protection. Among these, BASF's new structurally unique strobilurin fungicide Orysastrobin was specifically designed to target the rice market. Orysastrobin has outstanding long-lasting efficacy on leaf and panicle blast and

sheath blight, independent from application timing and disease pressure. Furthermore, Orysastrobin shows excellent crop safety. It has a favourable toxicological and eco-toxicological profile and is safe to users and the environment. Four formulations have been developed for use in seedling boxes or for water surface application, including combinations with the insecticide fipronil. These Orysastrobin-containing products have been introduced successfully into the Japanese and Korean markets in 2007.

Acknowledgements

The authors would like to thank all colleagues worldwide who have contributed to the development of Orysastrobin.

References

[1] Philips McDougall AgriService, Product Section, November **2008**.
[2] Hubert Sauter, Wolfgang Steglich, Timm Anke: Strobilurins - Evolution of a new class of active substances. *Angew. Chem. Int. Ed.*, **1999**, *38*, 1328-1349.
[3] Hubert Sauter: Strobilurins and other complex III inhibitors. in: Wolfgang Krämer, Ulrich Schirmer (Eds): Modern Crop Protection Compounds, Wiley-VCH, Weinheim **2007**.
[4] B.v.Ravenzwaay et.al.: Toxicological overview of a novel strobilurin fungicide - orysastrobin. *J. Pestic. Sci.*, **2007**,*32*, 270-277.
[5] Gerd Stammler, Manabu Itoh, Isao Hino, Akihide Watanabe, Kenichi Kojima, Masatoshi Motoyoshi, Andreas Koch, Egon Haden: Efficacy of orysastrobin against blast and sheath blight in transplanted rice. *J. Pestic. Sci.*, **2007**, *32*, 10-15.