Fluoxastrobin (HEC 5725) – the new dimension in strobilurin fungicides

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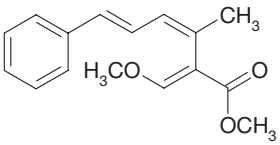
1 Introduction

Synthetic strobilurins derived from the basic lead structure of Strobilurin A (**1**)[1] are by far the most important chemical class of agricultural fungicides discovered in the second half of the 1980s and throughout the 1990s.



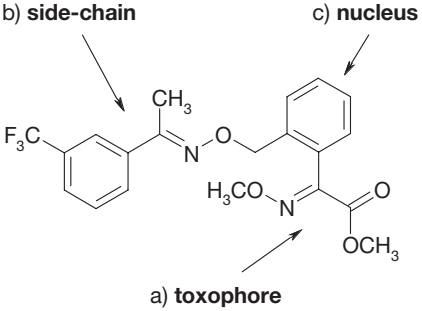
Strobilurin A

1

The extremely large structural variability of the core skeleton **1** has decisively inspired the discovery process for novel fungicides.

The design, syntheses, and properties of the synthetic strobilurins as well as their agro-industrial applications have recently been reviewed in the literature[2,3,4]. Until 2003 more than 900 patent applications worldwide were registered in the field of strobilurins and reflect their outstanding commercial importance. Agro-companies BASF, Bayer, and Syngenta represent the leading applicants.

All classes of strobilurins generally comprise three structural features, as will be outlined for trifloxystrobin (**2**), the first strobilurin fungicide in the Bayer CropScience product portfolio[5].



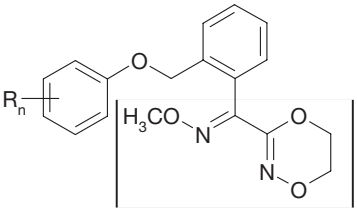
Trifloxystrobin

2

a) The **toxophore** is essential for biological activity.
b) The **side-chain** is responsible for an optimal adjustment of lipophilicity; it can be chemically modified within a broad range.
c) The **nucleus** acts as connecting element between toxophore and side-chain.

One of Bayer's research programmes focussed on the variation of the tox-

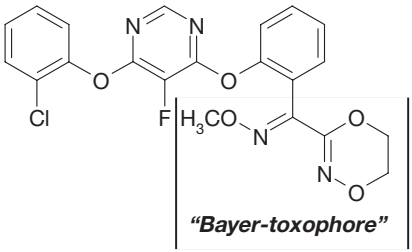
ophore moiety. The investigations amounted to basically innovative modifications and resulted in 1993 in a first breakthrough: Bayer found the methoxyimino dioxazene (= dihydro-dioxazine) derivatives **3** which exhibited an excellent fungicidal activity[6].



R$_n$ = broadly varied substitution patterns

3

Bayer designed and synthesised **3** as a novel class of strobilurins incorporating the carboxylic acid moiety of the toxophore into a six-membered heterocycle. This fundamental structural innovation proved to be a highly attractive lead structure for our further investigations. In straight-forward synthesis programmes we optimised **3** and achieved in 1994 significant progress resulting in the methoxyimino dihydro-dioxazine fluoxastrobin (HEC 5725) (**4**)[7], a milestone in the recent history of strobilurins.



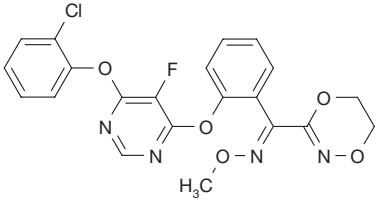
Fluoxastrobin

4

The structure of fluoxastrobin (**4**) combines an innovative toxophore, the so-called "Bayer-toxophore", with an optimally adjusted side-chain bearing a fluorine atom in the pyrimidine ring as an essential element.

Fluoxastrobin (**4**) represents a novel class of strobilurins with an outstanding biological performance[8,9]: It is the first commercial strobilurin fungicide demonstrating distinct foliar systemicity. It has been developed as a broad-spectrum fungicide for applications to cereal crops, potatoes, vegetables, and other crops.

2 Identity of the active substance

Common name:		Fluoxastrobin (ISO, accepted)
Chemical name:	IUPAC: (ACD)	(E)-(2-{[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl] oxy}phenyl) (5,6-dihydro-1,4,2 dioxazin-3-yl) methanone O-methyloxime
	CAS:	Methanone, [2-[[6-(2-chloro-phenoxy)-5-fluoro-4-pyrimidinyl] oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)-, O-methyloxime, (1E)-(9CI)
Code number:		HEC 5725 (applicant's code number)
CAS-No.:		361377-29-9 (E-isomer)
Molecular formula:		$C_{21}H_{16}ClFN_4O_5$
Structural formula:		
Molecular mass:		458.83 g/mol

3 Physical and chemical properties

Appearance:		crystalline solid
Colour:		white
Odour:		weak
Melting point:		103 - 108 °C
Boiling point:		not measurable 497 °C (estimated)
Vapour pressure:	(Pa at 20 °C)	6×10^{-10} (extrapolated)
Density (relative):		$D_4^{20} = 1.422$
Solubility	In water: (mg/L at 20 °C)	2.56 (unbuffered) 2.43 (at pH 4) 2.29 (at pH 7) 2.27 (at pH 9)
	In organic solvents: (g/L at 20 °C)	0.04 (n-heptane) 6.7 (2-propanol) 38.1 (xylene) >250 (dichloromethane)
Partition coefficient:	(log P_{ow} at 20°C)	2.86

4 Structural elucidation

4.1 Spectra of Fluoxastrobin

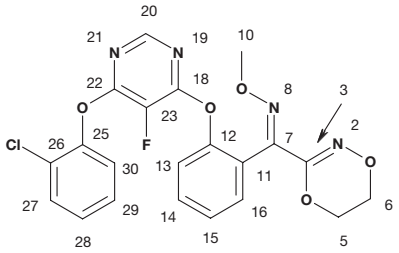
NMR

The chemical structure of fluoxastrobin (HEC 5725) was confirmed by ^{1}H, ^{13}C, ^{19}F, gradient enhanced Heteronuclear Multiple Quantum Correlation (gHMQC), and gradient enhanced Heteronuclear Multiple Bond Correlation (gHMBC) NMR spectra. The NMR signal assignments are summarised in table 4.1. The carbon assignments marked by a, b, and c could not clearly be distinguished. The ^{1}H, ^{13}C, gHMQC, and gHMBC spectra were recorded from a 0.2 mol/L solution in $CDCl_3$ on a 400 MHz spectrometer equipped with a 5 mm QNP probehead at +22 °C. The ^{15}N NMR shifts resulted from a gradient enhanced ^{15}N HMBC spectrum which was recorded on a 600 MHz spectrometer equipped with a 5 mm TXI probehead from a 0.2 mol/L solution in d_6-DMSO. The ^{1}H shifts are referred to internal TMS, the ^{19}F shifts to external CF_3COOH, the ^{13}C shifts to d_6-DMSO (39.7 ppm), and the ^{15}N shifts to external nitromethane (0 ppm).

Table 4.1: NMR signal assignments

H/C/N/F	δH/ppm	Mult.	rel.No.H	δC/ppm	Mult.	rel.No.C	δN/ppm	Mult.	δF/ppm
2							-66.4	S	
3				151.4	S	1			
5	4.46	M	2	64.1	T	1			
6	4.15	M	2	63.7	T	1			
7				145.6	S	1			
8							+12.0	S	
10	3.84	S	3	62.6	Q	1			
11				122.9	S	1			
12				148.5	S	1			
13	7.25-7.29	M	2	123.4	D	1			
14	7.47-7.51	M	2	130.2b	D	1			
15	7.31-7.41	M	4	126.6c	D	1			
16	7.31-7.41	M	4	130.3b	D	1			
18				157.0a	D	1			
19							-127.2	S	
20	8.06	S	1	149.9	DD	1			
21							-127.2	S	
22				157.3a	D	1			
23				132.4	D	1			-90.5
25				147.7	S	1			
26				126.6	S	1			
27	7.47-7.51	M	2	130.0b	D	1			
28	7.25-7.29	M	2	127.0c	D	1			
29	7.31-7.41	M	4	127.7c	D	1			
30	7.31-7.41	M	4	122.3	D	1			

a↔a, b↔b, c↔c



IR

Fluoxastrobin shows absorption peaks at the following wave lengths: 601, 671, 684, 711, 742, 759, 776, 798, 833, 840, 861, 910, 931, 954, 1001, 1046, 1068, 1092, 1117, 1186, 1217, 1239, 1267, 1306, 1369, 1389, 1417, 1423, 1443, 1477, 1572, 1600, 2820, 2935, 2985, 3011, 3072.

UV

A solution of fluoxastrobin in acetonitrile shows a single peak maximum at 250 nm in its UV spectrum.

4.2 Single crystal X-ray structure analysis

Fluoxastrobin (HEC 5725) crystallises under normal laboratory conditions and using common solvents in the form of colourless needle-like crystals containing no additional solvent or water molecules. The best quality crystals for X-ray structure analysis were obtained by slow evaporation of a hexane/acetone 70:30 solution at room temperature. Figure 4.2.1 shows a photograph using polarised light of typical crystal needles of fluoxastrobin. The crystal located at the right/top of the photograph with the dimensions 0.90 × 0.40 × 0.40 mm^3 was used for X-ray structure analysis [12]. After measurement a triclinic cell was indexed. Refinement of the structure in the space group $P\bar{1}$, converged to an R_1 value of 5.37 % (wR_2 = 14.72) [13,14]. Figure 4.2.2 shows the structure obtained after refinement.

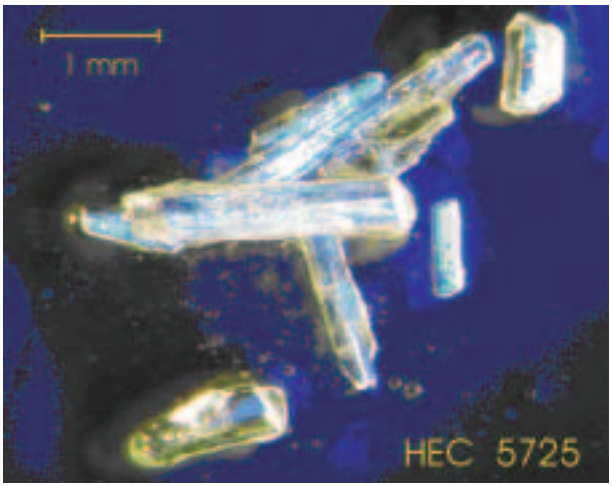


Fig. 4.2.1:
Digital stereo photomicrograph of single crystals of Fluoxastrobin grown from hexane/acetone at room temperature

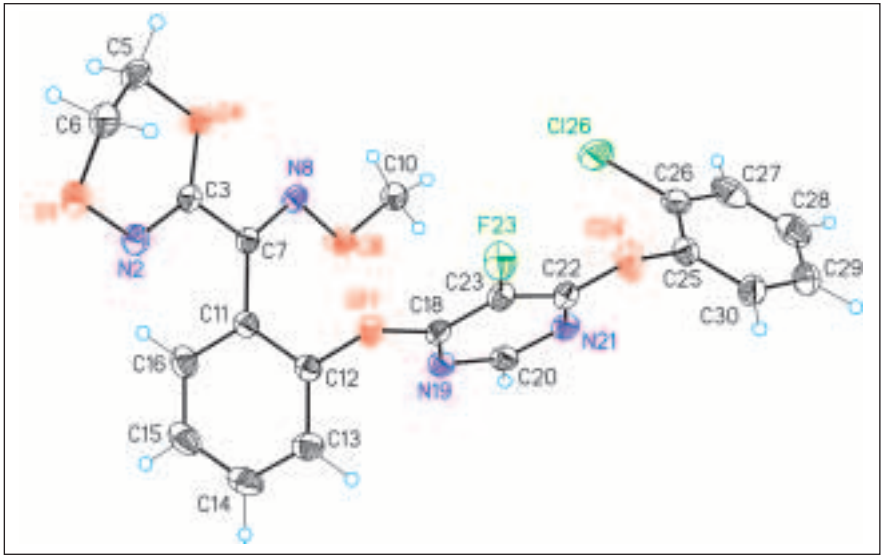


Fig. 4.2.2: Ortep plot (50 %) of Fluoxastrobin showing the numbering scheme of the non-hydrogen atoms

A second crystal modification of fluoxastrobin can be grown by crystallisation in toluene at temperatures lower than 8 °C. In this case the toluene solvate obtained is only stable in presence of the solvent. After removal of the solvent the crystal loses by diffusion the co-crystallised toluene and decays to a metastable modification that is only stable for a short time. This metastable modification recrystallises in approximately 48 hours under normal laboratory conditions or by heating back to the first described structure of fluoxastrobin. In order to distinguish the X-ray structures obtained they will be called fluoxastrobin and fluoxastrobin toluene solvate. The unstable crystal needles of fluoxastrobin toluene solvate were prepared at –18 °C, embedded in perfluoropolyether and cooled immediately at –120 °C for measurement. A monoclinic cell was indexed obtaining a structure solution in the space group $P2_1/c$. The structure was refined to an R_1 value of 5.65 % (wR_2 = 15.79). In this case the elementary cell contains in addition to fluoxastrobin a molecule of toluene. This molecule of toluene is disordered in two positions with a ratio of 57:43. The structure obtained is represented in figure 4.2.3.

Measurements of fluoxastrobin and fluoxastrobin toluene solvate were made on a Siemens P4 diffractometer equipped with a SMART-CCD-1000 area detector, a MACScience Co. high brilliance rotating anode with $Mo_{K\alpha}$ radiation, a graphite monochromator, and a Siemens LT2 low-temperature device. The crystals were measured at –120 °C, shock-cooled under inert oil (perfluoropolyether RS 3000; Riedel-de Haën). Full-

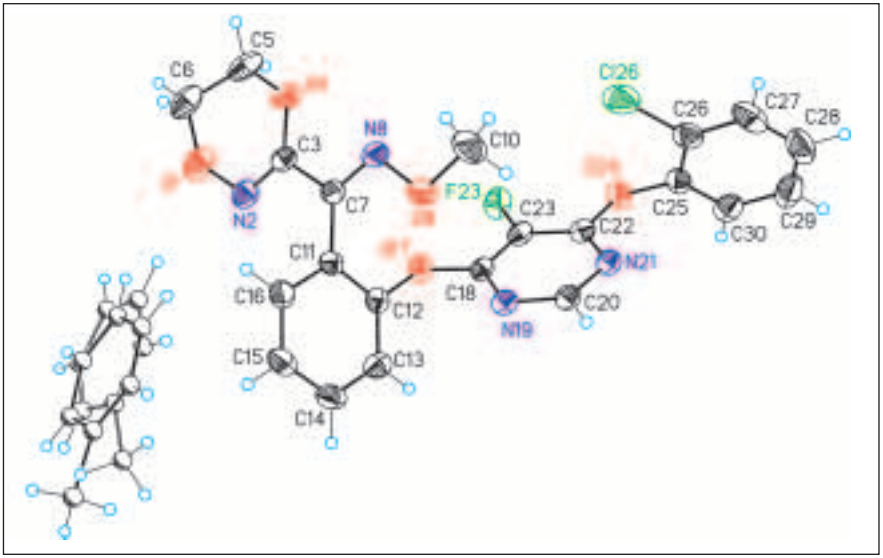


Fig. 4.2.3: Ortep plot (50 %) of Fluoxastrobin toluene solvate showing the numbering scheme of the non-hydrogen atoms. The toluene molecule is disordered in two positions

sphere data collection was used with ω and φ scans. Programmes used: data collection, Smart V. 5.060 (Bruker AXS 1999); data reduction, Saint+ Version 6.02 (Bruker AXS 1999); absorption correction, SADABS (Bruker AXS 1999). Structural solution and refinement were carried out using SHELXTL[15]. A summary of the measurement conditions and results are given in table 4.2.1.

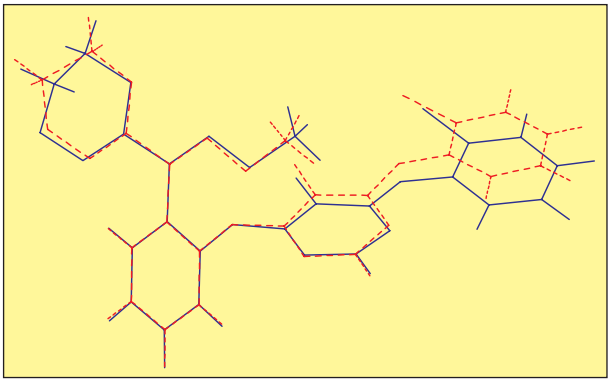


Fig. 4.2.4: Overlay of the molecular structures obtained for Fluoxastrobin and Fluoxastrobin toluene solvate showing the conformative differences

Consideration of the bond lengths in fluoxastrobin did not reveal any values outside the expected standard distances. At the toxophore moiety the atoms C10, O9, N8, C7, C3, N2, O1, O4, and C5 are located in the same plane (main deviation from plane 0.0261 Å) having double bonds localised at C3-N2 (1.2818(16) Å) and C7-N8 (1.2914(16) Å). In respect to the aromatic ring C11-C16 the toxophore moiety shows a torsion angle of approx. 64° (C3-C7-C11-C16: 64.05(16)°). The bond distances C23-C18 (1.3768(17) Å) and C22-C23 (1.3846(17) Å) in the pyrimidine ring are elongated compared to similar C-C-bonds (approx. 1.327 Å), probably due to the electronic effects of the fluorine atom. The bond distances in fluoxastrobin toluene solvate are, considering the standard deviations, identical to those discussed for fluoxastrobin. In the case of the solvate the torsion angle in respect to the aromatic ring of the toxophore moiety is approx. 71° (C3-C7-C11-C16: 70.6(3)°). The most marked differences are found in the conformation of the dioxazine ring and in the torsion angles of the side-chain. An overlay of both structures is presented in figure 4.2.4. The envelope conformation of the atoms C5-C6-O1 at the dioxazine moiety is inverted in the solvate crystal. These differences are probably due to the packing effects in the crystal. A summary of selected bond lengths and bond angles with standard deviations for both structures is given in tables 4.2.2 and 4.2.3.

There are no relevant intramolecular and intermolecular contacts in the crystal packing of fluoxastrobin. The shortest intermolecular distances in the crystal packing are localised at Cl26···C29' (3.527(3) Å), O1···C29'' (3.257(3) Å) and N2···C27' (3.351(4) Å). Due to the

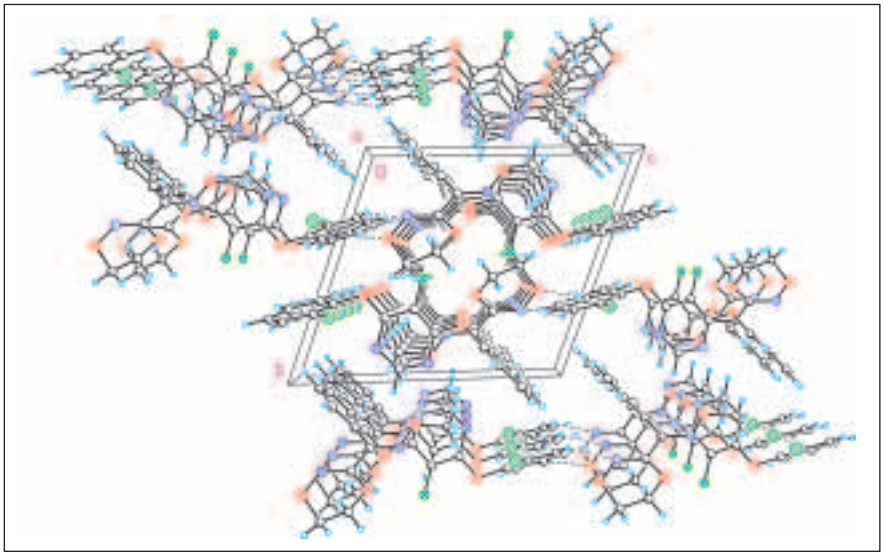


Fig. 4.2.5: Crystal packing of Fluoxastrobin, looking down the a-axis

presence of toluene in the crystal packing of fluoxastrobin toluene solvate the contact environment of the molecules of fluoxastrobin is changed. The shortest contacts are located at O9···C20' (3.304(5) Å), O9···C5'' (3.329(5) Å) , O4···C16' (3.338(5) Å) and N2···C5'' (3.403(5) Å). There are also some weak contacts to the disordered toluene molecules. In any case relevant hydrogen bondings can be located. The crystal packings of both structures looking down the a-axis are represented in figures 4.2.5 and 4.2.6. In fluoxastrobin toluene solvate the disordered solvent molecules are packed linearly in a wave form along the crystal in elliptical cavities (see figure 4.2.6, coloured molecules).

CCDC-242590 and CCDC-242591 (fluoxastrobin and fluoxastrobin toluene solvate) contain supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union road, Cambridge CB2 1EZ, UK; fax (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

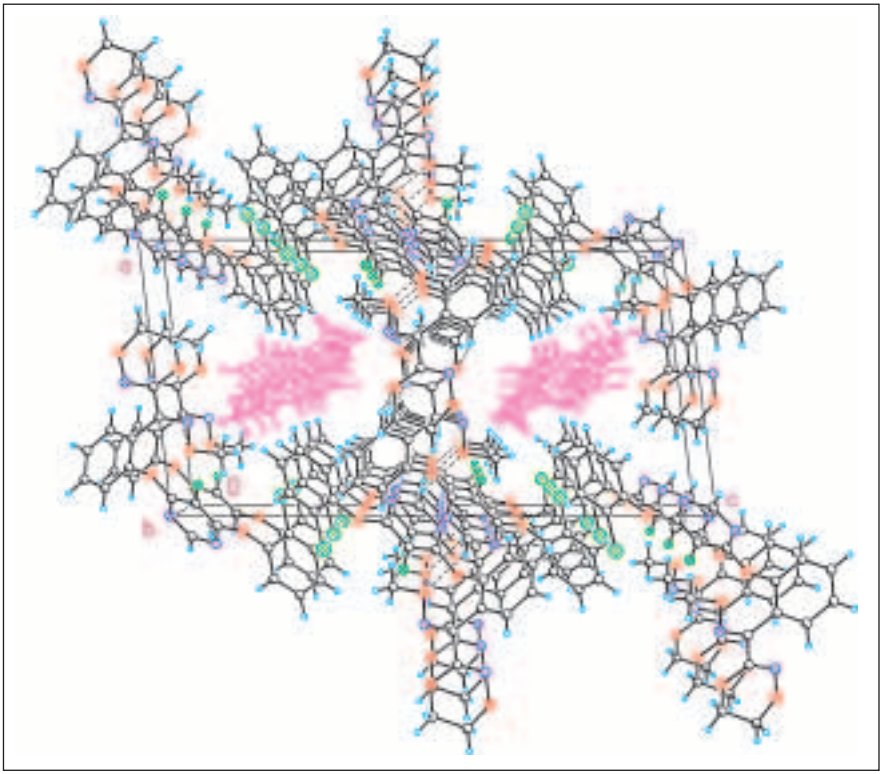


Fig. 4.2.6: Crystal packing of Fluoxastrobin toluene solvate, looking down the a-axis

Table 4.2.1: Crystallographic data as well as details of the structure solution and refinement procedures

Compound	Fluoxastrobin	Fluoxastrobin toluene solvate
Formula	$C_{21}H_{16}Cl_1F_1N_4O_5$	$C_{28}H_{24}Cl_1F_1N_4O_5$
Formula mass [g mol^{-1}]	458.83	550.96
T [K]	153 K	153 K
Space group	$P\bar{1}$	$P2_1/c$
a [Å]	7.4637(2)	12.1387(6)
b [Å]	11.8581(3)	12.1387(6)
c [Å]	13.0503(3)	23.6768(12)
α [°]	105.8810(10)	90
β [°]	102.0200(10)	96.915(2)
γ [°]	105.0310(10)	90
V [Å^3]	1023.31(4)	2508.2(2)
Z	2	4
d_{calcd} [Mg m^{-3}]	1.489	1.459
μ [mm^{-1}]	0.239	0.208
F(000)	472	1144
Crystal size [mm^3]	0.90 x 0.40 x 0.40	0.50 x 0.20 x 0.04
ϑ range [°]	1.90 to 31.52	1.69 to 28.00
Reflections collected	15794	14263
Independent reflections	6283 [R(int) = 0.0468]	6032 [R(int) = 0.0553]
Obs. Reflections, Fo > 4σ(Fo)	5104	3910
Data/restraints/parameters	6283 / 0 / 353	6032 / 81 / 388
Goodness-of-fit on F^2	1.047	0.996
Final R1, wR2 [I > 2σ(I)]	0.0537, 0.1399	0.0565, 0.1579
Final R1, wR2 (all data)	0.0640, 0.1472	0.0876, 0.1749
Max., min. diff. [e$^-$ Å^{-3}]	0.583 and -0.467	0.509 and -0.617

Table 4.2.2: Selected bond lengths [Å] in Fluoxastrobin and Fluoxastrobin toluene solvate

Compound	Fluoxastrobin	Fluoxastrobin toluene solvate	Compound	Fluoxastrobin	Fluoxastrobin toluene solvate
O(1)-N(2)	1.4062(14)	1.410(2)	O(17)-C(18)	1.3520(14)	1.354(2)
O(1)-C(6)	1.4319(18)	1.429(3)	C(18)-N(19)	1.3261(15)	1.324(3)
N(2)-C(3)	1.2818(16)	1.277(3)	C(18)-C(23)	1.3768(17)	1.380(3)
C(3)-O(4)	1.3453(15)	1.338(3)	N(19)-C(20)	1.3282(16)	1.327(3)
C(3)-C(7)	1.4798(15)	1.475(3)	C(20)-N(21)	1.3275(17)	1.335(3)
O(4)-C(5)	1.4441(14)	1.445(3)	N(21)-C(22)	1.3246(16)	1.325(3)
C(5)-C(6)	1.4927(19)	1.481(4)	C(22)-O(24)	1.3507(15)	1.360(3)
C(7)-N(8)	1.2914(16)	1.286(3)	C(22)-C(23)	1.3846(17)	1.369(3)
C(7)-C(11)	1.4888(17)	1.490(3)	F(23)-C(23)	1.3422(14)	1.348(2)
N(8)-O(9)	1.3852(12)	1.399(2)	O(24)-C(25)	1.3948(16)	1.403(3)
O(9)-C(10)	1.4337(15)	1.437(3)	C(25)-C(30)	1.3759(19)	1.375(4)
C(11)-C(12)	1.3899(17)	1.382(3)	C(25)-C(26)	1.381(2)	1.375(3)
C(11)-C(16)	1.3962(17)	1.395(3)	Cl(26)-C(26)	1.7271(15)	1.728(3)
C(12)-C(13)	1.3813(19)	1.380(3)	C(26)-C(27)	1.383(2)	1.376(4)
C(12)-O(17)	1.4018(15)	1.409(3)	C(27)-C(28)	1.379(3)	1.370(5)
C(13)-C(14)	1.384(2)	1.376(3)	C(28)-C(29)	1.378(3)	1.364(5)
C(14)-C(15)	1.382(2)	1.385(4)	C(29)-C(30)	1.388(2)	1.388(4)
C(15)-C(16)	1.389(2)	1.382(3)			

Table 4.2.3: Selected bond angles [°] in Fluoxastrobin and Fluoxastrobin toluene solvate

Compound	Fluoxastrobin	Fluoxastrobin toluene solvate	Compound	Fluoxastrobin	Fluoxastrobin toluene solvate
N(2)-O(1)-C(6)	113.02(9)	113.41(18)	C(12)-C(11)-C(16)	117.70(12)	118.1(2)
C(3)-N(2)-O(1)	116.81(11)	116.6(2)	C(12)-C(11)-C(7)	121.06(10)	122.02(19)
N(2)-C(3)-O(4)	129.00(11)	129.4(2)	C(16)-C(11)-C(7)	121.24(11)	119.83(19)
N(2)-C(3)-C(7)	116.49(11)	116.3(2)	C(13)-C(12)-C(11)	122.18(12)	122.0(2)
O(4)-C(3)-C(7)	114.51(10)	114.28(19)	C(13)-C(12)-O(17)	120.05(11)	120.54(19)
C(3)-O(4)-C(5)	114.36(10)	114.25(19)	C(11)-C(12)-O(17)	117.60(11)	117.34(19)
O(4)-C(5)-C(6)	108.74(11)	108.6(2)	C(12)-C(13)-C(14)	119.24(14)	119.1(2)
O(1)-C(6)-C(5)	109.04(11)	109.9(2)	C(15)-C(14)-C(13)	119.94(13)	120.3(2)
N(8)-C(7)-C(3)	115.06(11)	115.40(19)	C(14)-C(15)-C(16)	120.39(14)	120.0(2)
N(8)-C(7)-C(11)	125.42(10)	124.88(19)	C(15)-C(16)-C(11)	120.54(13)	120.5(2)
C(3)-C(7)-C(11)	119.51(10)	119.67(18)	C(18)-O(17)-C(12)	118.21(9)	118.02(16)
C(7)-N(8)-O(9)	110.88(10)	110.49(18)	N(19)-C(18)-O(17)	120.77(11)	120.63(19)
N(8)-O(9)-C(10)	109.69(9)	108.66(18)	N(19)-C(18)-C(23)	121.79(11)	121.59(18)

Table 4.2.3: (contd)

Compound	Fluoxastrobin	Fluoxastrobin toluene solvate	Compound	Fluoxastrobin	Fluoxastrobin toluene solvate
O(17)-C(18)-C(23)	117.42(10)	117.79(18)	C(30)-C(25)-C(26)	120.34(13)	120.6(2)
C(18)-N(19)-C(20)	115.76(11)	116.16(19)	C(30)-C(25)-O(24)	118.65(12)	120.2(2)
N(21)-C(20)-N(19)	127.69(12)	127.1(2)	C(26)-C(25)-O(24)	120.89(12)	119.0(2)
C(22)-N(21)-C(20)	115.43(11)	115.25(18)	C(25)-C(26)-C(27)	120.14(14)	120.3(2)
N(21)-C(22)-O(24)	120.46(11)	119.01(18)	C(25)-C(26)-Cl(26)	119.56(11)	119.71(19)
N(21)-C(22)-C(23)	122.02(12)	122.6(2)	C(27)-C(26)-Cl(26)	120.30(12)	120.0(2)
O(24)-C(22)-C(23)	117.51(11)	118.40(19)	C(28)-C(27)-C(26)	119.29(15)	119.2(3)
F(23)-C(23)-C(18)	121.57(10)	121.4(2)	C(29)-C(28)-C(27)	120.88(14)	120.9(3)
F(23)-C(23)-C(22)	121.15(11)	121.31(19)	C(28)-C(29)-C(30)	119.54(15)	120.3(3)
C(18)-C(23)-C(22)	117.27(11)	117.31(19)	C(25)-C(30)-C(29)	119.80(15)	118.7(3)
C(22)-O(24)-C(25)	116.46(10)	116.42(17)			

4.3 Quantum chemistry of Fluoxastrobin

Potential energy surface

The conformational space accessible to fluoxastrobin was investigated using high level quantum theoretical methods (DFT/TZVP)[16]. For reasons given below, force field methods are not appropriate to describe this class of molecules. The different structures were characterised by their energy relative to the minimum conformation given by the experimental structures and by three torsional angles, i.e. the torsion around the toxophore single bond, N=C-C=N, the rotation of the nucleus, N=C-C_{ar}-C_{ar}, and the orientation of the side-chain described by the nucleus-ether bond, $C_{ar}C_{ar}OC_{ar}$. The rotational barriers shown below (figures 4.3.1-3) were obtained by incrementing the torsional angle under investigation in steps of 10° and relaxing the rest of the molecule. Results for selected minima are summarised in table 4.3.1.

Starting point for all the calculations were the two X-ray-structures described in 4.2 which are simply mirror images of each other. Their energies are virtually identical. This also holds true for those conformations having the 2-Cl-phenyl rings switched by 180°, i.e. the chlorine atoms pointing away from the methoxy group. Two other geometries can be constructed from the X-ray structures by rotating the nucleus by 180° leading to side-chains oriented towards the dioxazine. These structures are slightly higher in energy, the energy difference of 0.3 kcal/mol with respect to the experimental minima, however, is negligible.

All geometries considered so far have an *s-trans* conformation of the toxophore; the *s-cis* conformations are maxima (3.4 and 3.7 kcal/mol) on the energy surface. Force fields are not reliable in this case as they tend to overemphasise the lone pair repulsions and hence erroneously predict a perpendicular minimum orientation.

Contrary to fluoxastrobin, in trifloxystrobin[5] *s-cis* conformations are observed in both single crystal X-ray structures available, but the *s-trans* arrangement was

Table 4.3.1: Characterisation of minimum-energy Fluoxastrobin conformations (X-ray data given in parentheses)

Calculated minimum energy conformation	Torsion N=C-C=N [°]	Torsion N=C-C_{ar}-C_{ar} [°]	Torsion C_{ar}-C_{ar}-O-C_{ar} [°]	E_{rel} [kcal/mol]
X-ray	(178°) 180°	(63°) 69°	(243°) 229°	0.0
X-ray_toluene	(177°) 174°	(291°) 294°	(114°) 131°	0.0
Nucleus rotation of				
X-ray	173°	110°	131°	0.3
X-ray_toluene	181°	252°	229°	0.3
Toxophore rotation of				
X-ray	52°	59°	228°	2.4
	318°	135°	253°	1.4
X-ray_toluene	50°	229°	92°	2.3
	310°	300°	132°	1.5

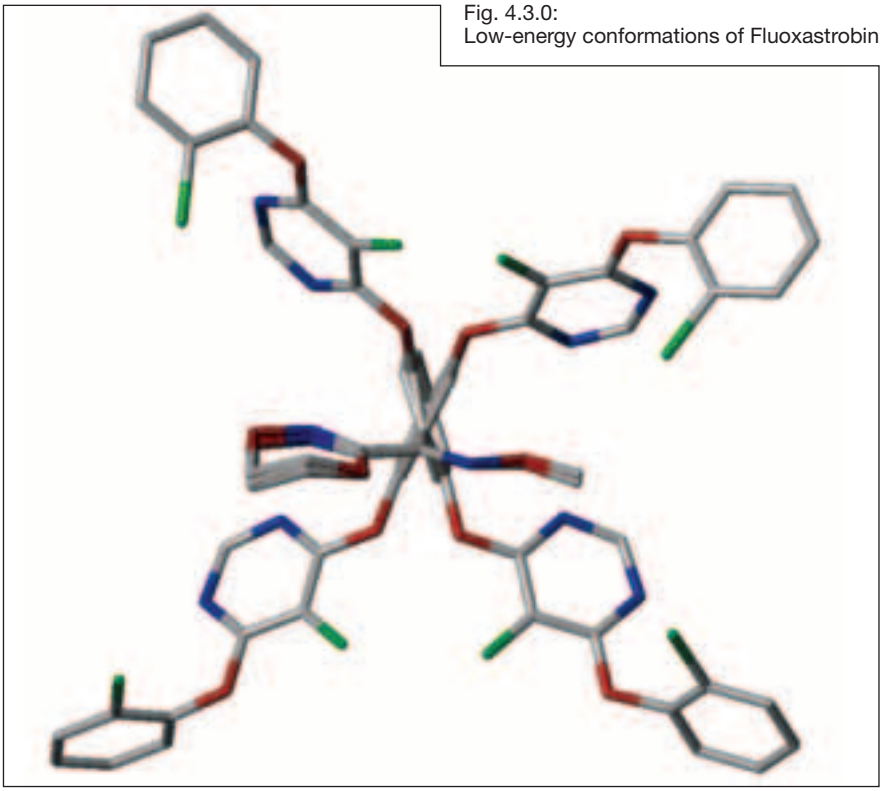


Fig. 4.3.0:
Low-energy conformations of Fluoxastrobin

found in the co-crystallised protein stucture. Under the provision that fluoxastrobin and trifloxystrobin both bind to their target in similar ways, we assume fluoxastrobin to have an advantage as no reorientation of the toxophore is necessary for binding to its target.

Rotation of the toxophore single bond leads to some surprises. In addition to the absolute minima at the optimised crystal structures we find two local minima at approx. 1.4 and 2.4 kcal/mol for two orientations of the dioxazine ring rotated by approx. ±45° (see figure 4.3.1). The unsymmetrical shapes of both curves indicate that the side-chains are affected differently by the slightly puckered dioxazine ring.

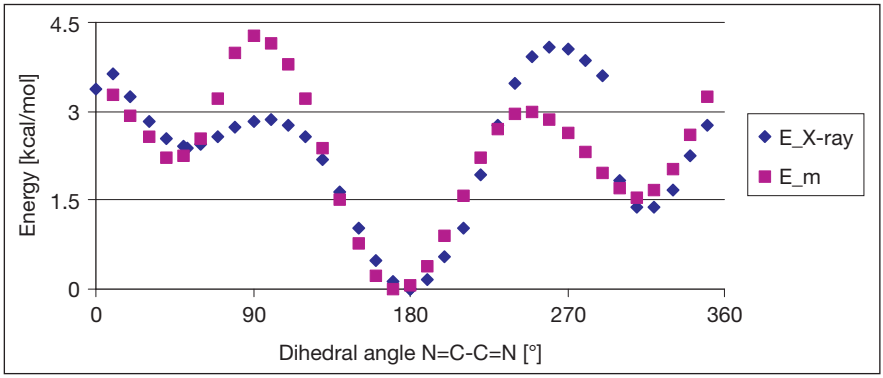


Fig. 4.3.1: Fluoxastrobin, X-ray structures, toxophore rotation

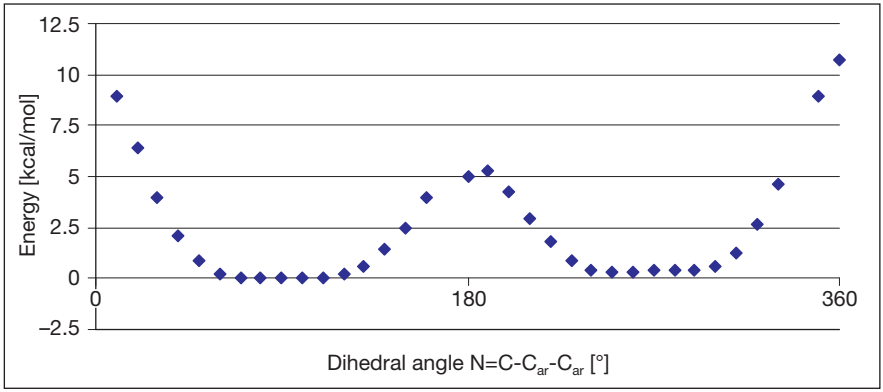


Fig. 4.3.2: Fluoxastrobin, X-ray structures, nucleus rotation

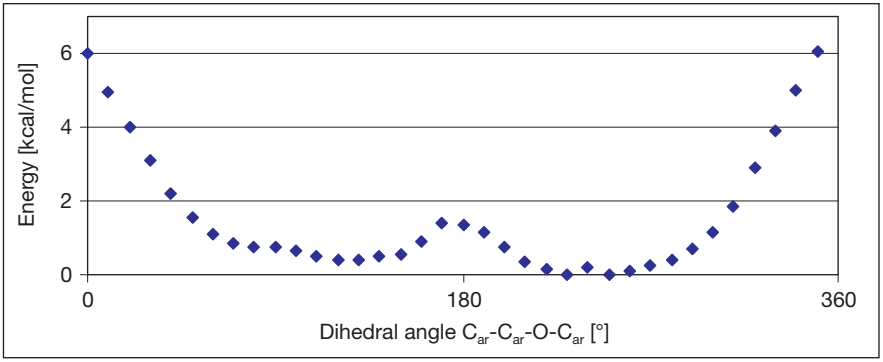


Fig. 4.3.3: Fluoxastrobin, X-ray structures, side-chain rotation

The local minima facilitate the interconversion of the X-ray geometries, as the minimum energy path from one X-ray structure, say X-ray_toluene, to its mirror image involves a concerted counterclockwise rotation of the nucleus phenyl ring by 220° together with the torsion of the dioxazine ring, followed by a 180° torsion of the phenyl-ether bond and a final readjustment of the toxophore. For the concerted motion the barrier is about 5 kcal/mol while it is twice as large in the clockwise direction and even this barrier (see figure 4.3.2) is no hindrance at room temperature. The final side-chain reorientation proceeds almost without a barrier. Even a 360° rotation of the etherbond is possible within a 6 kcal/mol range (see figure 4.3.3); however, this is feasible only if the pyrimidine orientation varies accordingly to avoid collision with the toxophore.

In conclusion, with the exception of its preferred toxophore orientation, fluoxastrobin is a molecule with an extremely flexible side-chain and a broad range of possible nucleus orientations. This flexibility makes it capable of responding to a variety of external influences by changing its shape accordingly, and this might be a reason for its outstanding foliar systemicity.

Conformational dependence of NMR spectra

NMR-Spectra (^{1}H, ^{13}C, ^{14}N, ^{17}O, ^{19}F, ^{35}Cl) for all the conformations listed in table 4.3.1 have been calculated using GIAO-DFT/BP/TZVP [16], as contributions from low-energy conformations should show up in the observed spectra. However, as the calculations refer to isolated molecules in the gas phase at 0 K, comparison with experimental data is difficult. The results for ^{1}H and ^{13}C are shown in tables 4.3.2 and 4.3.3. In the last columns the maximum variation of the NMR shifts upon geometry changes is shown. Surprisingly, rotation of the toxophore and switching the orientation of the nucleus have almost no effect on the shieldings. Even the ^{13}C shifts of the dioxazine ring do not vary significantly.

Table 4.3.2: Calculated ^{13}C spectra for low-energy Fluoxastrobin conformations

		X-ray			X-ray_toluene			X-ray_rot	X-ray_rot toluene	$\Delta^{13}C$ max
	NC–CN	52°	180°	318°	40°	174°	310°	173°	181°	
Atom	E_rel / [kcal]	2.4	0.0	1.4	2.3	0.0	1.5	0.3	0.3	
3		160.2	160.1	160.1	159.8	160.3	160.3	159.9	159.3	1.1
5		69.9	68.8	68.8	70.7	68.4	69.1	68.4	68.6	2.3
6		68.3	70.0	70.0	67.7	70.4	69.7	70.1	70.4	2.7
7		152.6	153.6	153.6	152.7	153.6	152.9	154.9	154.3	2.3
10		66.3	66.5	66.5	66.4	66.4	66.3	66.7	66.6	0.4
13		127.4	126.7	126.7	127.4	127.1	127.3	127.3	127.6	0.9
11		131.6	129.7	129.7	131.0	130.3	131.6	130.5	131.1	2.0
12		159.2	157.5	157.5	157.8	157.8	158.9	157.5	158.2	1.7
14		132.3	131.9	131.9	134.4	131.9	132.3	131.8	131.8	2.6
15		128.3	127.8	127.8	129.5	127.6	128.3	127.8	127.6	1.9
16		133.6	136.3	136.3	139.1	136.6	133.5	135.9	135.9	5.5
18		162.3	162.4	162.4	164.6	162.4	162.2	162.0	161.8	2.8
20		152.6	152.7	152.7	153.3	152.6	152.6	153.0	152.9	0.7
22		163.8	163.7	163.7	163.7	163.7	163.8	163.6	164.1	0.5
23		144.0	143.9	143.9	144.1	143.9	144.0	143.5	143.6	0.7
25		157.1	157.7	157.7	157.1	157.6	157.4	157.6	157.2	0.6
26		143.5	143.7	143.7	144.0	143.7	143.9	144.0	143.9	0.5
27		134.1	134.0	134.0	134.1	134.0	134.1	134.2	134.2	0.2
28		130.7	130.4	130.4	130.6	130.4	130.6	130.5	130.5	0.3
29		130.5	130.3	130.3	130.1	130.4	130.5	130.4	130.2	0.4
30		128.6	128.6	128.6	128.4	128.6	128.4	128.3	129.0	0.6

Table 4.3.3: Calculated ^{1}H spectra for low-energy Fluoxastrobin conformations

		X-ray			X-ray_toluene			X-ray_rot	X-ray_rot toluene	$\Delta^{1}H$ max
	NC–CN	52°	180°	318°	40°	174°	310°	173°	181°	
Atom	E_rel / [kcal]	2.4	0.0	1.4	2.3	0.0	1.5	0.3	0.3	
H_5		4.52	4.59	4.59	4.56	4.57	4.44	4.48	4.49	0.22
H_6		4.23	4.28	4.28	4.47	4.36	4.30	4.03	4.07	0.52
H_10		3.82	3.83	3.83	4.11	3.82	3.85	4.18	4.19	0.42
H_13		7.67	7.68	7.68	7.37	7.72	7.71	7.81	7.74	0.44
H_14		7.66	7.67	7.67	7.69	7.67	7.67	7.70	7.70	0.04
H_15		7.58	7.59	7.59	7.52	7.56	7.59	7.57	7.57	0.07
H_16		7.65	7.52	7.52	7.98	7.52	7.6	7.53	7.59	0.46
H_20		8.00	7.99	7.99	7.83	8.00	8.01	8.00	7.99	0.18
H_27		7.72	7.75	7.75	7.71	7.74	7.74	7.76	7.74	0.05
H_28		7.49	7.53	7.53	7.43	7.53	7.51	7.52	7.49	0.10
H_29		7.55	7.58	7.58	7.5	7.58	7.56	7.56	7.54	0.08
H_30		7.54	7.52	7.52	7.48	7.52	7.53	7.45	7.43	0.11

Exceptions are found in the nucleus (C16 Δ^{13}C: 5.5ppm) and in signals of the CH_3- and CH_2 groups of the toxophore (H6 Δ^1H: 0.77 ppm) when comparing crystallographic and non-crystallographic conformations. While the methyl signals show up at the highest field in the X-ray structures, followed by the H6 signals, this order is reversed when the side-chains point to the dioxazine moiety, hence providing additional theoretical evidence for the X-ray conformations also being present in solution.

5 Summary

Fluoxastrobin – the new dimension in strobilurin fungicides

Synthetic strobilurins derived from the basic lead structure of Strobilurin A are the most important chemical class of agricultural fungicides discovered in the second half of the 1980s and throughout the 1990s. Many variations of side-chains and toxophores of the core skeleton Strobilurin A have been performed and are covered by more than 900 patent applications worldwide.

The combination of the fundamentally innovative "Bayer-toxophore" with an optimally tuned side-chain culminated in the methoxyimino dihydro-dioxazine fluoxastrobin (HEC 5725), a milestone in the recent history of strobilurins.

Fluoxastrobin exhibits a product profile that combines an excellent fungicidal performance with outstandingly favourable toxicological and ecotoxicological properties.

The physical and chemical properties of the pure active substance, the spectroscopic data (NMR, IR, UV), as well as the single crystal X-ray structure analysis are presented. Finally, the quantum chemistry of fluoxastrobin is outlined.

Zusammenfassung

Fluoxastrobin – die neue Dimension bei den Strobilurin-Fungiziden

Synthetische Strobilurine, die sich von der grundlegenden Leitstruktur des Strobilurin A ableiten, sind die bedeutendste chemische Klasse von Agrarfungiziden, die in der zweiten Hälfte der 80er Jahre und in den 90er Jahren des vorigen Jahrhunderts entdeckt wurden. Vielfältige Variationen an Seitenketten und Toxophoren am Grundgerüst des Strobilurin A wurden erarbeitet und sind Gegenstand von mehr als 900 Patentanmeldungen weltweit.

Die Kombination des völlig neuartigen „Bayer-Toxophors" mit einer optimal angepassten Seitenkette gipfelte im Methoxyimino-dihydro-dioxazin Fluoxastrobin (HEC 5725), einem Meilenstein in der jüngeren Geschichte der Strobilurin-Forschung.

Fluoxastrobin zeigt ein Produktprofil, das in idealer Weise eine ausgezeichnete fungizide Performance mit ausserordentlich günstigen toxikologischen und ökotoxikologischen Eigenschaften verbindet.

Die physikalischen und chemischen Eigenschaften des reinen Wirkstoffs, die spektroskopischen Daten (NMR, IR, UV) sowie die Einkristall-Röntgenstrukturanalyse werden ausführlich dargestellt; im weiteren wird die Quantenchemie von Fluoxastrobin beschrieben.

Résumé

Fluoxastrobine – une nouvelle dimension pour les fongicides de la classe des strobilurines

Des strobilurines synthétiques dérivées de la structure de base de la Strobilurine A sont la classe chimique la plus importante de fongicides à usage agricole qui a été découverte au cours de la seconde moitié des années 1980 et pendant les années 1990. De nombreuses variations des chaînes latérales et de toxophores de la structure centrale de la Strobilurine A ont été réalisées et sont, au niveau mondial, protégées par plus de 900 brevets.
L'association totalement innovatrice d'un "toxophore Bayer" et d'une chaîne latérale ajustée de façon optimale a engendré le méthoxyimino-dihydro-dioxazine fluoxastrobine qui représente un événement marquant dans l'histoire récente des strobilurines.
Le profile de produit de la fluoxastrobine associe une excellente performance fongicide à des propriétés toxicologiques et écotoxicologiques remarquables.
Les propriétés physiques et chimiques du principe actif isolé, les données spectroscopiques (RMN, IR, UV), ainsi que l'analyse cristallographique aux rayons X sont présentés. Enfin, les mécanismes chimioquantiques de la fluoxastrobine seront brièvement exposés.

Resumen

Fluoxastrobin – la nueva dimensión en las estrobilurinas fungicidas

Las estrobilurinas sintéticas derivadas de la estructura lider "Strobilurin A", son la clase química más importante de fungicidas agrícolas que se ha descubierto a finales del siglo pasado. Multiples variaciones realizadas en cadenas laterales y en el toxoforo de "Strobilurin A" están recogidas en más de 900 solicitudes de patente en todo el mundo.
La combinación del nuevo "Bayer-Toxophor" con la cadena adecuada llevó al Metoxiimino-dihidro-dioxazino Fluoxastrobin (HEC 5725), uno de los descubrimientos más importantes en la reciente historia de las estrobilurinas.
Fluoxastrobin muestra un perfil ideal ya que posee unas propiedades fungicidas excelentes así como un comportamiento toxicológico y ecotoxicológico ejemplares.
Se describen las propiedades físico-químicas, sus datos espectroscópicos (RMN, IR, UV), su estructura cristalina determinada con difracción de rayos X, así como las consideraciones teóricas y de química cuántica.

Резюме

Флуоксастробин – новое измерение фунгицидов стробилуринового ряда

Синтетические стробилурины, происходящие от основной структуры стробилурина А, образуют важнейший химический класс аграрных фунгицидов, открытых во второй половине 80-х годов и в 90-х годах XX века. Были разработаны многочисленные модификации на боковых цепях и токсофорах основного каркаса стробилурина А, являющиеся предметом более 900 патентных заявок во всем мире.
Сочетание совершенно нового токсофора фирмы Байер с оптимально выбранной боковой цепью привело к метоксиимино-дигидро-диоксазину флуоксастробину (HEC 5725), представляющему собой новую веху в

современной истории стробилуриновых исследований.

Во флуоксастробине идеальным образом сочетаются отличные фунгицидные характеристики с исключительно удачными токсикологическими и экотоксикологическими свойствами.

Детально рассматриваются физические и химические свойства чистого биологически активного вещества, спектроскопические данные (ЯМР, ИК, УФ), а также результаты рентгеноструктурного анализа, описывается квантовая химия флуоксастробина.

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