Relationships of Molecular Structure of 1,4-Oxathiin Fungicides to Chemotherapeutic Activity Against Rust and Smut Fungi in Grasses

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Cooperative investigations of the Crops Research Division and the Oregon Agricultural Experiment Station. Published with approval of the Director as Technical Paper No. 2935, Oregon Agricultural Experiment Station.

Acknowledgment is made to the UniRoyal Corporation, to the Penncross Bentgrass Growers Association, and to the Merion Bluegrass Association for their support of this research through Oregon State University.

Accepted for publication 29 January 1971.

ABSTRACT

Twelve chemicals, including 5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (carboxin), its dioxide (sulfone) form (oxycarboxin), and 10 other substituted analogs of carboxin, from UniRoyal Chemical Corp., Bethany, Conn., were evaluated for systemic fungicidal activity against stripe rust, *Puccinia striiformis;* stripe smut, *Ustilago striiformis;* and flag smut, *Urocystis agropyri;* after soil application and root uptake in *Poa pratensis*. Activity of carboxin was poor on rust, fair on flag smut, and poor on stripe smut. Oxycarboxin was excellent on rust and good on stripe smut; it eradicated *U. agropyri*. The monoxide form (F831) was superior to carboxin for rust but inferior to oxycarboxin for all three diseases. Oxycarboxin plus a 4′-methoxy substitution to the phenyl ring (F837) had poor activity against *U. striiformis* and reduced activity against *U. agropyri,* but maintained good rust control as compared to oxycarboxin. Serious reduction or loss of activity against all three diseases was apparent in most nonoxidized analogs with substitutions to the phenyl ring, including: 2′-phenyl (F427), 2′,6′-diethyl (F829), 2′-methyl, 3′-chloro (F861), and 4′-methoxy (F934). A 2′,3′-dimethyl derivative (F827) with a nonoxidized heterocycle impaired rust control but had much better activity against *U. striiformis* and *U. agropyri* than carboxin and less phytotoxicity than oxycarboxin. F872, which combines active substitutions of F827 and oxycarboxin, maintained strong activity against all three diseases with somewhat less plant injury. Phytopathology 61:731-735.

Discovery of unusual fungicidal activity of 1,4-oxathiin compounds against Basidiomycetes (10) represented a major breakthrough in chemotherapy of plant diseases. Oxathiin fungicides have shown promising activity on a variety of important pathogens (1, 2, 3, 8, 9, 10, 11). Evaluations of a number of oxathiin derivatives tested mainly in vitro against a variety of fungi were reported recently (9), but only three of those derivatives are represented in the present study.

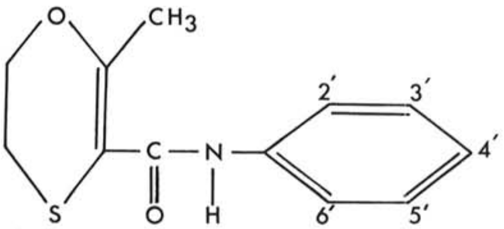
Eradication of *Ustilago striiformis* (Westend.) Niessl (stripe smut) in plants of *Agrostis palustris* Huds. 'Pennlu', *Poa pratensis* L., 'Merion', and *Dactylis glomerata* L., eradication of *Urocystis agropyri* (Preuss) Schroet. (flag smut) in *P. pratensis* 'Merion', and control of *Puccinia striiformis* West. (stripe rust) in *P. pratensis* by soil application and root uptake of oxycarboxin (Table 1) have been recently reported (5, 6, 7), but phytotoxicity was troublesome.

Practical chemical control of *P. striiformis* in grasses has been obtained with nickel-maneb sprays (4), and nickel fungicides are the only feasible chemicals available. The chemicals most likely to replace nickel will be systemic fungicides.

Oxathiin fungicides approach the ideal rust chemical and offer promise for control of stripe and flag smut. The oxathiins, however, at dosages necessary for eradication of *U. striiformis* or *U. agropyri* in grass plants, have been phytotoxic and probably would be too expensive for use on grass fields. The objective of this study was to evaluate analogs of carboxin (Table 1) in an effort to find 1,4-oxathiin derivatives that would control stripe rust and the two smuts at lower dosages that would minimize phytotoxicity and reduce cost.

Materials and Methods.—Tests were conducted in a greenhouse with small plants of *P. pratensis* L. 'Merion', each infected with either *U. striiformis* or *U. agropyri* in every shoot, or with healthy Merion plants used for inoculations with *P. striiformis*. Smut-infected plants were separated into segments, and each segment was transplanted in 150-ml sandy loam soil in a plastic cup with four drainage holes. After good root development and just before treatment, the plants and soil were transferred to cups or pots without drainage holes to prevent loss of chemical. Stripe rust inoculations were performed by dusting abundant urediospores on healthy plants 7 days after application of chemicals to soil. The inoculated plants were then placed in a moist chamber for 12 hr on each of 3 successive nights.

The basic molecule, carboxin, considered herein as the parent compound, contains a 1,4-oxathiin heterocycle joined at the 3-carbon to a carboxanilide arm, and additions or substitutions to either or both of these moieties created the various analogs as shown in Table 1. The structure of the basic molecule (carboxin) is as follows:



The only change in the heterocycle involves oxidation of the oxathiin S, and, e.g., the dioxide becomes oxycarboxin. The chemical names for carboxin and oxycarboxin have been changed recently from those originally used, resulting primarily from newer clockwise numbering of the carbon atoms in the oxathiin heterocycle.

The substituted carboxanilide moiety is listed as *m*-toluidide when a methyl is substituted at the phenyl 3-carbon (UniRoyal code F306) and *o*-toluidide for methyl substituted to the 2-phenyl position (F813). Regardless of the names used, these and other chemicals in Table 1 all have the same basic structure as the carboxin molecule and contain the same carboxanilide arm. The designations, DCMO for carboxin and DCMOD for oxycarboxin, as formerly used (5, 6, 7), are now antiquated by the new chemical names.

Carboxin, oxycarboxin, and F827 were tested as wettable powder formulations. The other analogs were tested as technical grade and were dissolved in acetone, mixed with small quantities of surfactant, Tween 20 (polyoxyethylene sorbitan monolaurate), and dispersed in water. Desired quantities of the suspended chemicals were placed into 2-cm deep holes in the soil surface at four locations surrounding each plant.

TABLE 1. Identity of 1,4-oxathiin derivatives studied

Code no. or common name	Chemical identity
Parent compound	
Carboxin (=Vitavax or D735)	5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide
Nonoxidized analogs with substitutions to the phenyl	
F306	5,6-Dihydro-2-methyl-1,4-oxathiin-3-carbox-*m*-toluidide
F427	5,6-Dihydro-2-methyl-*N*-(2-biphenyl)-1,4-oxathiin-3-carboxamide
F827	5,6-Dihydro-2,2′,3′-trimethyl-1,4-oxathiin-3-carboxanilide
F829	2′,6′-Diethyl-5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide
F861	3′-Chloro-5,6-dihydro-2,2′-dimethyl-1,4-oxathiin-3-carboxanilide
F934	5,6-Dihydro-4′-methoxy-2,2′-dimethyl-1,4-oxathiin-3-carboxanilide
Oxidized analogs with or without substitutions to the phenyl	
Oxycarboxin (=Plantvax or F461)	5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide-4,4-dioxide
F831	5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide-4-oxide
F837	5,6-Dihydro-4′-methoxy-2-methyl-1,4-oxathiin-3-carboxanilide-4,4-dioxide
F813	5,6-Dihydro-2-methyl-1,4-oxathiin-3-carbox-*o*-toluidide-4,4-dioxide
F872	5,6-Dihydro-2,2′,3′-trimethyl-1,4-oxathiin-3-carboxanilide-4,4-dioxide

Fungicide activities against stripe smut and flag smut were noted by appearance of smut-free leaf tissue. The healthy and smutted shoots were counted periodically. Stripe rust control was evaluated at 14 and 18 days after inoculation by noting the presence or absence and type of rust infections.

RESULTS.—*Ustilago striiformis*.—The parent compound, carboxin, applied to soil around infected plants of *P. pratensis* 'Merion', gave fair control of *U. striiformis* (6, 7), and the chemical was mildly phytotoxic at relatively high dosages. Most nonoxidized analogs gave either no control or only partial and/or temporary control of stripe smut (Table 2); however, the 2′,3′-dimethyl substitution (F827) displayed promising activity. The 3′-methyl substitution (F306) produced fungistatic control by preventing sporulation and visible symptoms for 8 to 12 weeks, but this effect was gradually lost. The other substitutions yielded inactive molecular forms.

The dioxide (sulfone) form, oxycarboxin, has shown much stronger activity than the parent compound in many previous trials (6, 7) and in present tests (Table 2). The monoxide form, F831, was inactive. The dioxide form with a 2′-methyl substitution was reasonably active but fairly toxic. The dioxide with a 4′-methoxy substitution, F837, was systemically fungistatic and prevented sporulation and other symptoms for 12 weeks. An analog, F872, containing two effective molecular forms, was only slightly more active than either "parent" (F827 and oxycarboxin) alone. F872 was less phytotoxic than oxycarboxin, but caused more injury than F827. F872 was not active enough to provide control at the low dosages desired. F827 is considered a promising candidate for field testing, because it causes less plant injury than either oxycarboxin or F872 with nearly the same activity.

Urocystis agropyri.—The parent compound, carboxin, applied to soil around infected plants of *P. pratensis* 'Merion', showed only weak activity against *U. agropyri* in previous trials (5, 6) and in present tests (Table 3). Compared with carboxin, a wide range of activity was noted among the six analogs with a nonoxidized heterocycle but with substitutions to the phenyl. Addition of ethyl to both the phenyl 2 and 6 carbons (F829) destroyed all activity of the parent molecule. At the lower dosages when compared to carboxin, only slight to moderate improvement in activity was obtained with compounds F427, F861, and F934. Enhanced fungicidal activity resulted from 3′-methyl (F306) and 2′,3′-dimethyl (F827) substitutions.

In previous (5, 6) and present tests (Table 3), oxycarboxin readily eradicated *U. agropyri*, demonstrating a great increase in activity over the parent compound. The monoxide form (F831) was superior to the parent compound but inferior to oxycarboxin. Strong activity superior to the parent compound but slightly inferior to oxycarboxin resulted from 4′-methoxy (F837) and

TABLE 2. Control of *Ustilago striiformis* in *Poa pratensis* 'Merion' by soil application of systemic fungicides

Chemical	Mg/150 ml soil	Smutted shoots/total shoots					
		Weeks after chemical application					
		0	4	8	12	16	32
Parent compound							
Carboxin	5	13/13	15/23	25/25	25/25		
	10	10/10	2/14	9/12	10/13		
	15	15/15	0/12	0/10	2/11		
	20	10/10	0/13	1/13	7/16		
	25	13/13	0/16	8/12	9/13		
Nonoxidized heterocycle with substitutions to the phenyl							
F306	5	8/8	7/8	7/9	7/7	0/3	42/42
	10	8/8	6/9	5/10	6/9	6/11	42/42
	15	8/8	6/10	0/10	0/10	3/31	19/103
	20	8/8	2/7	0/7	Dead		
F427	2.5	8/8	10/10				
	5	8/8	16/16				
	10	8/8	11/11				
	20	8/8	14/14				
F827	5	8/8	0/11	5/38	14/67	41/111	55/110
	10	8/8	0/15	0/44	2/78	10/128	17/134
	15	8/8	0/8	1/29	3/55	17/98	45/122
	20	8/8	0/15	0/41	0/78	0/168	2/150
F829	5	8/8	8/8	8/8	7/7		
	10	8/8	7/7	7/7	5/5		
	15	8/8	6/6	6/7	6/6		
	20	8/8	7/7	7/7	7/7		
F861	5	8/8	8/8	13/13	15/15		
	10	8/8	2/8	10/11	17/17		
	15	8/8	7/8	8/8	8/8		
	20	8/8	8/8	11/11	12/12		
F934	5	8/8	8/8	10/10	13/13		
	10	8/8	7/7	13/13	17/17		
	15	8/8	8/8	9/9	15/15		
	20	8/8	6/6	8/15	15/19		
Oxidized heterocycle with or without substitutions to the phenyl							
Oxycarboxin	2.5	11/11	21/21	28/28	26/26		
	5	14/14	26/26	29/29	30/30		
	10	14/14	0/21	2/14	10/25		
	15	13/13	0/19	0/13	3/17		
	20	13/13	0/18	0/8	0/13		
F831	5	8/8	8/8	6/6	8/8		
	10	8/8	8/8	7/7	4/4		
	15	8/8	7/7	5/5	Dead		
	20	8/8	4/4	2/3	Dead		
F837	5	8/8	7/7	11/18	43/44	49/53	
	10	8/8	8/8	15/20	38/41	51/53	
	15	8/8	0/10	9/21	38/51	59/79	
	20	8/8	0/8	1/24	24/49	50/92	
F813	2.5	12/12	29/29	34/34	33/34		
	5	12/12	11/19	15/17	21/22		
	10	14/14	0/18	6/14	7/16		
	20	12/12	0/8	0/9	0/10		
F872	2.5	11/11	1/19	8/17	14/19		
	5	13/13	7/23	14/19	18/23		
	10	15/15	0/24	1/20	1/23		
	20	16/16	0/20	0/19	0/21		
	None	8/8	8/8	17/17	28/28	34/34	83/83
	None	8/8	9/9	9/9	15/15	35/35	92/92

2′-methyl (F813) substitutions to the dioxide form. The best new analog, dioxide with methyl substitutions at the 2 and 3 phenyl carbons (F872), eradicated *U. agropyri* at dosages equal to oxycarboxin and with less plant injury. Although F872 combines the molecular features of the other two best analogs (dioxide from oxycarboxin and 2′,3′-dimethyl substitutions to the phenyl from F827), only a limited advantage was

TABLE 3. Control of *Urocystis agropyri* in *Poa pratensis* 'Merion' by root uptake after soil application 1,4-oxathiin systemic fungicides

Chemical	Mg/150 ml soil	Smutted shoots/total shoots					
		Weeks after chemical application					
		0	4	12	16	20	28
Parent compound							
Carboxin	2.5	12/12	26/26	34/34	36/36		
	5	13/13	25/27	36/36	43/43		
	10	12/12	18/23	25/28	34/34		
	15	10/10	0/17	5/18	11/23		
Nonoxidized heterocycle with substitutions to the phenyl							
F306	2.5	19/19	4/27	21/48	89/104	89/93	70/81
	5	21/21	0/18	5/50	39/106	42/101	34/92
	10	18/18	0/19	0/24	0/75	0/76	0/97
	20	21/21	0/16	0/11	0/66	0/64	0/79
F427	2.5	10/10	8/35				
	5	10/10	6/25				
	7.5	10/10	2/32				
	10	11/11	7/29				
F827	2.5	15/15	0/31	0/40	0/108	0/107	24/112
	5	21/21	1/30	3/34	22/114	22/118	20/124
	10	20/20	0/31	0/44	0/111	0/119	0/105
	20	21/21	0/26	0/23	0/104	0/108	0/100
F829	2.5	15/15	34/34	43/43			
	5	19/19	45/45	74/74			
	10	18/18	31/31	50/50			
	20	20/20	33/33	73/73			
F861	2.5	12/12	11/26	49/49			
	5	15/15	0/30	5/50			
	10	18/18	7/32	24/43			
	20	19/19	0/29	3/38			
F934	2.5	14/14	16/24	36/36			
	5	16/16	14/39	43/60			
	10	19/19	4/33	22/44			
	20	20/20	0/38	1/53			
Oxidized heterocycle with or without substitutions to the phenyl							
Oxycarboxin	2.5	9/9	0/22	0/19	0/22		
	5	11/11	0/22	0/21	0/25		
	7.5	11/11	0/16	0/14	0/16		
	10	12/12	0/12	0/10	0/14		
F831	2.5	17/17	32/32	52/52			
	5	14/14	24/24	56/56			
	10	16/16	0/14	10/24			
	20	23/23	0/5	Dead			
F837	2.5	11/11	0/30	15/15	94/130	95/127	127/144
	5	17/17	0/33	0/39	0/108	0/111	0/127
	10	22/22	0/27	0/21	0/95	0/90	0/124
	20	19/19	0/29	0/39	0/104	0/120	0/162
F813	2.5	15/15	0/29	6/35			
	5	13/13	0/19	0/20			
	10	15/15	0/25	0/24			
	20	16/16	0/19	0/18			
F872	2.5	12/12	0/22	0/21			
	5	13/13	0/21	0/24			
	10	17/17	0/27	0/25			
	20	13/13	0/18	0/15			
	None	22/22	42/42	57/57	133/133	123/123	125/125
	None	16/16	31/31	40/40	127/127	123/123	126/126

gained by a slight reduction in phytotoxicity. No significant gain in activity at lower dosages was found for F872 in several separate tests.

Puccinia striiformis.—In many tests, the parent compound (carboxin) has shown only mediocre activity against *P. striiformis* by root uptake in *P. pratensis* after application to soil, except at high dosages. In present tests, five of the nonoxidized analogs were decidedly inferior to carboxin. The 3′-methyl substitution (F306) improved activity against rust, but also greatly increased phytotoxicity. The dioxide form, oxycarboxin, has been much superior to the parent compound for stripe rust control. The monoxide form, F831, was inferior to oxycarboxin, although better than carboxin. Among the dioxide analogs, the phenyl substitutions, 2′,3′-dimethyl (F872) and 2′-methyl (F813) were nearly equal to oxycarboxin, and the 4′-methoxy (F837) may be equally promising. F837, the dioxide with a 4′-methoxy substitution, was equal to other analogs for rust control and less phytotoxic than oxycarboxin and other rust-active oxidized derivatives.

DISCUSSION.—In vivo evaluations of 1,4-oxathiin derivatives indicate that substitutions of chlorine, alkyl, or phenyl radicals to various carbons of the phenyl in the carboxanilide moiety of the nonoxidized parent molecule (carboxin) will increase or decrease the systemic fungicidal properties. Poor control of all three diseases resulted from certain substitutions, as follows: 2′-phenyl (F427); 2′,6′-diethyl (F829); 2′-methyl, 4′-methoxy (F934); and 2′-methyl, 3′-chloro (F861). A 3′-methyl substitution (F306) improved activity on all three diseases, but at the expense of increased plant injury. A 2′,3′-dimethyl analog (F827) was poor against rust, but gave improved activity against flag smut.

Addition of the dioxide to the oxathiin S (oxycarboxin) greatly increased fungicidal activity against *U. striiformis, U. agropyri,* and *P. striiformis,* but also increased phytotoxicity. The monoxide form improved activity against *P. striiformis* but quenched activity to both smuts. Among analogs with a dioxide heterocycle, the 4′-methoxy substitution (F837) improved activity on rust and flag smut over the parent but was inferior to the dioxide with no phenyl alteration, and a 2′-methyl substitution (F813) did not improve activity over the dioxide.

Substitutions of methyl at the 2′ and 3′-positions on the phenyl of the nonoxidized form (F827) and dioxide form with unaltered phenyl (oxycarboxin) were individually more active than the parent molecule, but a combination of these two analogs, F872, gave only slightly better activity than either "parent". The phytotoxicity of F872 remained serious.

Phytotoxicity to *P. pratensis* continues to be a characteristic of most oxathiins with strong systemic activity against the three diseases studied, especially to plants infected with stripe smut. At dosages effective for eradication of *U. striiformis,* oxycarboxin kills many leaf blades and retards growth for prolonged periods. Several compounds imparted an intense green color to leaves (F934 and F827) that would not be objectionable on certain grasses in lawns and turf.

In addition to oxycarboxin, two analogs, F827 and F872, showed promising activity against *U. striiformis.* F827 may be superior to oxycarboxin for stripe rust control because of its reduced plant injury at rates effective for eradication of *U. striiformis.* Three analogs, F872, F813, and F837, appear promising for stripe rust control in addition to oxycarboxin. F837 was superior to analogs other than oxycarboxin and was significantly less phytotoxic than other rust-active analogs.

The 3′-methyl substitution and carboxin were both rated as more fungitoxic than oxycarboxin against *Ustilago maydis* (DC.) Cda. in vitro tests and against *Uromyces phaseoli* (Pers.) Wint. var. *typica* Arth. in spore germination and foliar spray tests on bean (9). In contrast, in the present study oxycarboxin was more active chemotherapeutically than the 3′-methyl substitution (F306) and carboxin against *U. striiformis, U. agropyri,* and *P. striiformis* after root uptake in *P. pratensis.*

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