Fungitoxicity and Structure-Activity Relationships of Some Oxathiin and Thiazole Derivatives

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ABSTRACT

ED_{50} values of carboxin (5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide), its sulfone analog, oxycarboxin (both systemic fungicides used for control of diseases caused by Basidiomycetes), and 13 related, substituted oxathiin and thiazole compounds were determined to a selected number of Basidiomycetes, Deuteromycetes, and a Zygomycete. Eradicant activity of these compounds was determined against bean rust, *Uromyces phaseoli typica*. Substitutions in the carboxin molecule studied do not increase the spectrum of fungi to which the oxathiins are toxic. A number of yeastlike lower Basidiomycetes belonging to the Tremellales (jelly fungi) proved to be insensitive to oxathiins. The only Deuteromycete in this study sensitive to oxathiins was *Monilia cinerea* f. *americana*. The 3′-methyl-analog of carboxin is the only compound surpassing the fungitoxicity of carboxin. Electron withdrawing groups (—Cl and $—NO_2$) substituted in the aniline ring markedly reduce fungitoxicity. Replacement of the 2-methyl-oxathiin moiety by an *o*-tolyl,2,4-dimethylthiazolyl, 2-amino-4-methyl-thiazolyl, or even to some extent by a butyryl group, results in compounds retaining the original biological activity. Benzanilide is significantly less toxic to *Rhizoctonia solani* than *o*-toluanilide, indicating that a methyl group in position 2 is necessary for good toxicity.

Results of evaluation of the eradicant activity of oxathiins against bean rust correlate very well with those of in vitro fungitoxicity tests, suggesting that oxathiin systemic fungicides act by virtue of their fungitoxicity, rather than by altering host metabolism. Phytopathology 60:1164-1169.

Additional key words: Systemic fungicides, chemotaxonomy, bean rust.

Systemic fungicidal activity of carboxin (5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide) and oxycarboxin (5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilido-4,4-dioxide) against *Uromyces phaseoli typica* Arth. and *Ustilago nuda* was first reported in 1966 by von Schmeling & Kulka (14). Since then the oxathiins have been found to be effective chemotherapeutants for many smut and rust diseases. As a rule, oxycarboxin, the sulfone analog, will give better results than carboxin in instances where a long-lasting chemotherapeutic activity is required, e.g., in the control of cereal rusts (9) and bean rust. Snel & Edgington (12) attribute the better protection against bean rust with oxycarboxin to greater stability within the plant, even though carboxin has a higher toxicity to uredospores of *Uromyces phaseoli* than oxycarboxin (11).

Except for a report that carboxin effectively controls barley leaf stripe (6), oxathiins have been reported to control exclusively diseases caused by Basidiomycetes. These in vivo findings correlate well with work of Edgington et al. (4) showing oxathiins to be selective to Basidiomycetes in in vitro tests. In a further study of the fungitoxic spectrum of oxathiin compounds, Edgington & Barron (3) reported that 2′-phenyl-5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide has a wider fungitoxic spectrum than carboxin. The fact that a number of Zygomycetes and Fungi Imperfecti belonging to the Porosporae, Phialosporae, and Blastosporae proved to be sensitive to the 2′-phenyl substituted form of carboxin (3) although quite insensitive to carboxin, led us to investigate the fungitoxic spectrum and to determine the toxicity of 16 derivatives of oxathiins and related compounds, viz, thiazoles. The purpose of the present investigation is to determine some structural requisites for fungitoxicity to Basidiomycetes. An attempt will be made to correlate these in vitro data with studies on chemotherapeutic activity against bean rust.

MATERIALS AND METHODS.—*Chemicals.*—Chemicals tested were synthesized at UniRoyal Research Laboratory Ltd., Guelph, Ontario, Canada, by M. Kulka and co-workers. Chemicals were technical grade.

Determination of the fungitoxic spectrum and ED_{50} *values.*—Stock solutions of the chemicals were prepared in 95% ethanol at 100 times the desired concn in test media. Aliquots of 1 ml were dispensed in 100 ml of malt extract (Difco) agar medium held at 50 C. Plates containing 15 ml of medium were poured. Initially the chemicals were tested at the following concn: 50, 20, and 5 μM. Seven-mm discs of agar with mycelial growth of test fungi were placed on three plates of each chemical at each concn. The fungi were incubated at 25 C with the exception of the coprophilous fungus *Coprinus lagopus* Fr., which was incubated at 37 C. The classification of the Agaricales was based on Singer (10), while for the classification of the Deuteromycetes we followed Barron (1). ED_{50} (50% inhibition of mycelial growth) values were calculated

by plotting the percentage inhibition of mycelial growth on log-probability graph paper. If the ED_{50} value of a certain chemical/fungus combination proved to be lower than 5 μM, the test would be repeated using the following concn: 0.32, 0.8, 2.0, and 5.0 μM. The latter concn was used in order to obtain a value used in both tests, allowing correlation of the results.

Spore germination tests of bean rust.—A suspension of uredospores was prepared in a 0.1% Tween 20 (polyoxyethylene sorbitan monolaurate) solution in glass distilled water (v/v). Aliquots of 0.15 ml of this spore suspension were pipetted into deep-well slides. An equal volume of an aqueous solution of the chemical at 2 times the final concn was added, and the slides were incubated for 24 hr at room temp in containers with a high relative humidity. Germination was determined at 8 concn of the chemical with two replicate slides/concn. As a criterion for germination, a germ-tube length 2 times the length of the spore was used.

Evaluation of eradicant activity against bean rust.—The ability to control bean rust already established in snap bean (*Phaseolus vulgaris* L.) was evaluated by employing the following technique. A 2,000-ppm solution of the chemical was prepared by dissolving 200 mg of chemical in 20 ml of acetone containing 60 mg of Tween 20. To this solution 80 ml of distilled water was added, giving the desired 2,000-ppm solution. By serial dilution, solutions of 500 and 125 ppm, respectively, were prepared. Duplicate pots, each containing three bean plants, were sprayed on a turntable until run-off with the aid of a gun-type sprayer. The plants had been inoculated with bean rust, *Uromyces phaseoli typica,* 48 hr prior to application of the chemical. At time of spraying, the plants were just expanding the first trifoliate leaves. In order to obtain adequate penetration of the chemicals, test plants were then placed in a controlled environment room at 23 C and a 95-100% relative humidity for 24 hr. About 10 days later, the plants were scored for disease severity. Evaluation of eradicant activity was carried out at UniRoyal's Agricultural Chemical Research Station, Bethany, Connecticut.

RESULTS.—*Spectrum of fungi sensitive to oxathiins.*—The results presented in Tables 1 and 2 show that the substitutions in the carboxin molecule do not alter the fungitoxic spectrum. Although oxathiins display selectivity to Basidiomycetes, a number of exceptions should be noted; e.g., the higher Basidiomycete *Schizophyllum commune* Fr. is highly insensitive to these compounds. Of the lower Basidiomycetes, the Tremellales (the jelly fungi) prove to be rather insensitive to oxathiins. However, two species within the Tremellales were very sensitive to oxathiins. These species were *Dacrymyces palmatus* (Schw.) Bres. (Dacrymycetaceae) and *Itersonilia perplexans* Derx. in the Sporobolomycetaceae. *Tremella encephala* Pers. was tested against all compounds, while four other *Tremella* species were only evaluated against carboxin and showed no inhibition of growth at the highest concn. Among the four fungi tested from the Fungi Imperfecti, each from a different group, only *Monilia cinerea* f. *americana* Wormald (Blastosporae) was sensitive to oxathiins.

Monilia cinerea f. *americana* was not sensitive, however, to substituted thiazoles. Growth of the Zygomycete *Thamnidium elegans* Link ex Fries was not inhibited by any of the compounds tested.

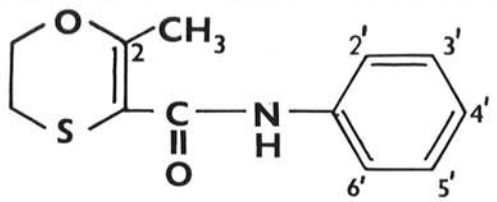
Structure-activity relationships.—The only compound significantly more toxic than carboxin is the 3′-(meta-) methyl substituted analog of carboxin. Substitution of chlorine in the anilino moiety of the carboxin molecule decreases fungitoxicity, although it should be observed that the 3′-substituted analog is 0.5 times less toxic than carboxin. All fungi studied are insensitive to oxathiins with a NO_2-group substituted in the anilino moiety, irrespective of the position in the ring. Replacement of the oxathiin ring by a substituted thiazole ring does not reduce fungitoxicity significantly. If an *o*-toluene ring (Table 2) is substituted in place of the 2-methyl-oxathiin ring, fungitoxicity is reduced 5 to 10 times, with an exception in the case of *Rhizoctonia solani* Kühn to which the ED_{50} of *o*-toluanilide is 0.83 μM as compared to 0.4 μM for carboxin.

Replacing the methyl group in the 2-position of the oxathiin ring with an *n*-propyl group leads to a 30-fold reduction of fungitoxicity (Table 2). It is especially interesting to note that the factorial differences in toxicity of oxathiin and thiazole analogs apply to all fungi studied. Bearing this in mind, and considering that the spectrum of fungi sensitive to oxathiins was not altered by the substitutions in a second experiment evaluating structural requisites for fungitoxicity, we subsequently used only *R. solani* as an assay organism (Table 3). The product resulting from hydrolytic cleavage of the 1,2 linkage of the oxathiin ring; α-(β-hydroxy-ethylmercapto)acetoacetanilide has a very low toxicity (ED_{50}: 450 μM). Crotonanilide, a product which can be formed from carboxin by reductive cleavage of linkages 1,2 and 3,4 of the oxathiin ring, likewise has a low toxicity to *R. solani.* Butyranilide, however, is fairly toxic to *R. solani* (ED_{50}: 20 μM). A product which we could imagine to be formed after hydrolysis of carboxin resulting in cleavage of the amide bond, 5,6-dihydro-3-carboxy-2-methyl-1,4-oxathiin, is nontoxic at a concentration of 800 μM.

Evaluation of eradicant activity of oxathiins and thiazoles against bean rust.—Results of the evaluation of eradicant activity of oxathiins and thiazoles against bean rust are summarized in Table 4. The most striking feature of these results is total lack of eradicant activity of oxathiins with a NO_2-group substitution in the aniline ring. Substitution of chlorine, especially in the ortho and para position of the aniline ring, also reduced chemotherapeutic activity significantly. Both thiazoles are nearly as active as carboxin. An *n*-propyl group rather than methyl group in the oxathiin ring renders the compound inactive. Excellent eradicant properties are displayed by 5,6-dihydro-2-methyl-1,4-oxathiin-3-*N*-cyclohexylcarboxamide, indicating that the aniline ring can be replaced by a cyclohexyl ring.

DISCUSSION.—*Spectrum of fungi sensitive to oxathiins.*—Although oxathiins are selective to Basidio-

TABLE 1. Fungitoxic spectrum and ED_{50} value[a] (50% inhibition of mycelial growth) of carboxin and analogs substituted in the anilino moiety



Carboxin

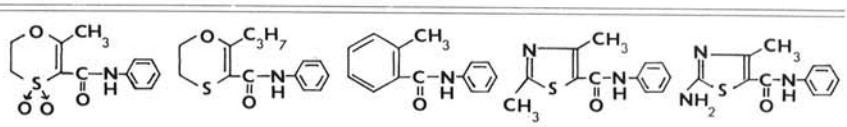
Substituted group, position	—	—CH_3 2'—	—CH_3 3'—	—Cl 2'—	—Cl 3'—	—Cl 4'—	—NO_2 2'—	—NO_2 3'—	—NO_2 4'—
BASIDIOMYCETES									
HETEROBASIDIAE									
Ustilaginales									
Ustilago maydis	1.0	1.2	0.5	16	4.2	14.4	54	20	50
Uredinales									
Uromyces phaseoli[b]	2.8		1.5					10.0	
Tremellales									
Auriculariaceae									
Auricularia auricularis	4.8	16	4.0	30	5.5	22	>50	>50	>50
Tremellaceae									
Tremella encephala	>50	>50	>50	>50	>50	>50	>50	>50	>50
Dacrymycetaceae									
Dacrymyces palmatus	0.7	0.6	0.5	7.0	2.6	20	25	23	50
Sporobolomycetaceae									
Sporobolomyces roseus[c]	>50								
Tilletiopsis washingtonensis	18								
Itersonilia perplexans	0.2	0.75	0.14	2.7	0.6	0.2	3.4	14	20
EUBASIDIAE									
Polyporales									
Polyporaceae									
Fomes annosus (Fr.) Cooke	1.8	2.2	0.8	21.8	3.2	8.4	31	>50	>50
Thelephoraceae									
Corticium vellereum	0.45	1.2	0.22	1.6	0.8	0.3	>50	22.5	>50
Rhizoctonia solani	0.4	0.36	0.3	4.8	33	22	4.8	21	28
Agaricales									
Polyporaceae									
Schizophyllum commune	50	>50	37	>50	>50	>50	>50	>50	>50
Coprinaceae									
Coprinus lagopus	1.1	3.2	1.1	21	4.5	13	>50	>50	>50
HYPHOMYCETES									
POROSPORAE									
Drechslera sp. (ex *Portulaea*)	>50	>50	>50	>50	>50	>50	>50	>50	>50
PHIALOSPORAE									
Fusarium oxysporum lycopersici	>50	>50	>50	>50	>50	>50	>50	>50	>50
SYMPODULOSPORAE									
Graphium ulmi	>50	>50	>50	>50	>50	>50	>50	>50	>50
BLASTOSPORAE									
Monilia cinerea f. *americana*	7.4	25	5.0	70	7.4	24	6.6	34	>50
PHYCOMYCETES									
ZYGOMYCETES									
Thamnidium elegans	>50	>50	>50	>50	>50	>50	>50	>50	>50

[a] ED_{50} values represent the mean of 3 replicates. Maximum variation between replicates was never greater than 5% of the mean.

[b] Figures based on spore germination tests. Germination of controls 80 to 86%.

[c] Two isolates tested.

TABLE 2. Fungitoxic spectrum and ED_{50} value[a] (50% inhibition of mycelial growth) of substituted oxathiin and thiazole fungicides



Substituted group, position	oxycarboxin —	oxycarboxin —CH_3 4′—	5,6-dihydro-2-n-propyl-1,4-oxathiin-3-carboxanilide	*o*-toluanilide	2,4-dimethyl-thiazole-5-carboxanilide	2-amino-4-methyl-thiazole-5-carboxanilide
BASIDIOMYCETES						
HETEROBASIDIAE						
Ustilaginales						
Ustilago maydis	30	>50	36.0	8.8	5.6	3.5
Uredinales						
Uromyces phaseoli[b]	12.8		12.0	11.0	6.4	
Tremellales						
Auriculariaceae						
Auricularia auricularis	50	24	24	22.5	4.5	3.0
Tremellaceae						
Tremella encephala	>50	>50	>50	>50	>50	>50
Dacrymycetaceae						
Dacrymyces palmatus	35.5	110		48	50	5
Sporobolomycetaceae						
Sporobolomyces roseus[c]	>50				>50	>50
Tilletiopsis washingtonensis	>50				58	
Itersonilia perplexans	4.4	10.5	12.0	10.8	2.0	2.7
EUBASIDIAE						
Polyporales						
Polyporaceae						
Fomes annosus (Fr.) Cooke	32.5	120	60	13.0	10	9.4
Thelephoraceae						
Corticium vellereum	6.1	29	17.5	12.8	4.0	3.0
Rhizoctonia solani	13.6	3.8	3.8	0.83	2.4	3.2
Agaricales						
Polyporaceae						
Schizophyllum commune	>50	>50	>50	>50	>50	>50
Coprinaceae						
Coprinus lagopus	31	46	60	10.5	8	5
HYPHOMYCETES						
POROSPORAE						
Drechslera sp. (ex *Portulaea*)	>50	>50	>50	>50	>50	>50
PHIALOSPORAE						
Fusarium oxysporum lycopersici	>50	>50	>50	>50	>50	>50
SYMPODULOSPORAE						
Graphium ulmi	>50	>50	>50	>50	>50	>50
BLASTOSPORAE						
Monilia cinerea f. *americana*	>50	>50	68	48	>50	>50
PHYCOMYCETES						
ZYGOMYCETES						
Thamnidium elegans	>50	>50	>50	>50	>50	>50

[a] ED_{50} values represent the mean of 3 replicates. Maximum variation between replicates was never greater than 5% of the mean.

[b] Figures based on spore germination tests. Germination of controls 80 to 86%.

[c] Two isolates tested.

mycetes as originally proposed by Edgington et al. (4), a number of exceptions occur. In the case of *Schizophyllum commune,* it may be possible that we are dealing with a highly insensitive isolate. This is obviously a danger inherent to studies of this nature, where each species is represented by only a single isolate. However, the insensitivity of a number of Heterobasidiomycetes to oxathiins is well-documented. All five members of the Tremellaceae tested displayed pronounced insensitivity. Carboxin is approximately 5 times less toxic to the representative of the Auriculariaceae than to *Ustilago maydis* (DC.) Corda. With the exception of the plant pathogen *Itersonilia perplexans,* the Sporobolomycetaceae tested were very

TABLE 3. Toxicity of cleavage products of carboxin to *Rhizoctonia solani*

	ED_{50} value[a] (μM)
α-(β-hydroxy-ethylmercapto) acetoacetanilide	450
Crotonanilide	320
Butyranilide	34
5,6-dihydro-3-carboxy-2-methyl-1,4-oxathiin	> 800
Benzanilide	20

[a] 50% inhibition of mycelial growth.

insensitive to oxathiins. *Sporobolomyces roseus* Kluyv. & v. Niel is a yeastlike fungus, which some mycologists place in the Deuteromycetes rather than in the Basidiomycetes. On the basis of the "behavior" of *S. roseus* in the presence of oxathiins, we would support this classification. Similarly, we doubt that *I. perplexans*, which displays great sensitivity to oxathiins, should be classified in the Sporobolomycetaceae. The *Tremella* species used in this study are haploid strains which display a budding-type rather than mycelial growth. Edgington & Barron (2, 3) showed that the 2′-phenyl substituted analog of carboxin (UniRoyal Code: F427) proved to be highly toxic to Blastosporae, however, with exception of two yeastlike forms, *Rhodotorula aurantiaco* and *Candida humicola*. Therefore, it seems feasible that, with exception of the smuts, oxathiins are less toxic to Basidiomycetes with budding-type growth rather than hyphal growth. Interestingly, none of the 2′-substituted forms (—CH_3, —Cl, or —NO_2) of carboxin influence selectivity of the compounds. A 2′-phenyl substitution resulted in the extended selectivity of F427 which includes a number of Zygomycetes; e.g., *Thamnidium elegans* (2, 3). *Thamnidium elegans* was insensitive to the 2′-methyl analog of carboxin. Thus, it seems reasonable to assume that in order to achieve an increased selectivity of oxathiins substitution of a more lipophilic group in the aniline ring is a requisite.

TABLE 4. Evaluation of eradicant activity of oxathiins and thiazoles against bean rust (*Uromyces phaseoli typica*)

	Control of bean rust[a,b]		
	Spray concn (ppm)		
Name of chemical	2,000	500	125
5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide (=carboxin)	100	100	100
2′-methyl—substitution	100	100	100
3′-methyl—substitution	100	100	100
4′-methyl—substitution	100	90	40
2′-chloro—substitution	100	75	75
3′-chloro—substitution	*phytotoxic*	100	80
4′-chloro—substitution	45	0	
2′-nitro—substitution	0	0	0
3′-nitro—substitution	0	0	
4′-nitro—substitution	0	0	0
5,6-dihydro-2-*n*-propyl-1,4-oxathiin-3-carboxanilide	*phytotoxic*	0	0
o-toluanilide	100[c]	95	10
5,6-dihydro-2-methyl-1,4-oxathiin-3-*N*-cyclohexyl-carboxamide	*phytotoxic*	100	100
5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxanilide-4,4-dioxide (=oxycarboxin)	100	100	95
4′-methyl—substitution	85	20	15
2,4-dimethylthiazole-5-carboxanilide	100	97	
2-amino-4-methylthiazole-5-carboxanilide	100	100	98

[a] Per cent control as compared to untreated checks.
[b] Untreated checks had severe rust averaging from 10 to 15 pustules/cm^2.
[c] Moderate chlorosis on trifoliates.

Structure activity relationships.—Somers (13), in a recent review on selectivity and specificity of fungicides, points out that selectivity can often be explained on the basis of selective accumulation. Evidence that this could explain the selectivity of oxathiins for Basidiomycetes has been gathered for *Rhizoctonia solani* and *U. maydis* by Mathre (7). It was found that carboxin accumulates more readily than oxycarboxin in ribosomes of the fungal cells (7). Since uptake by fungal cells of the oxathiins appears to be a passive process (7), it is reasonable to assume that lipid solubility plays an important role. Horsfall & Lukens (5) and many other workers have presented evidence that in many instances the more lipid soluble compound is the more fungitoxic. Carboxin which is more fungitoxic than oxycarboxin is also more lipid soluble. In Table 1, we note that substitutions which increase lipid solubility of the oxathiins, i.e., —CH_3 and —Cl substitutions in the anilino moiety, do not aid toxicity of the compounds with exception of the 3′-methyl substitution which results in a compound which surpasses carboxin in toxicity. Therefore, we assume that besides influencing solubility, these substitutions alter the reactivity of the site of fungitoxic action in the carboxin molecule. In all instances, substitutions of electron-withdrawing groups reduce toxicity. Methyl groups in the ortho and para positions in the anilino moiety also decrease toxicity.

Interestingly, replacement of the methyl group in the 2-position of the oxathiin ring by an *n*-propyl group reduces toxicity. In order to get more information on the role of this methyl group in the fungitoxicity, we determined the toxicity of benzanilide. Comparing the toxicity of benzanilide (Table 3) to that of *o*-toluanilide, which is benzanilide with a methyl group in the 2-position, we demonstrated that this methyl group significantly increases toxicity. Assuming that *o*-toluanilide has a similar mode of action as carboxin, it can be reasoned that a small lipophilic group, viz, a methyl or ethyl group in the 2-position, is necessary for good toxicity. It does not seem important whether this group has an electron-donating or electron-withdrawing character, since Pommer & Osieka (8) reported that 2-chlorobenzanilide has a fungitoxicity to *R. solani, Sclerotium rolfsii,* and *Coniophora cerebella* almost identical to the toxicity of *o*-toluanilide. The steric effect of the group in the 2-position of the oxathiin ring may therefore be of key importance for fungitoxicity.

Butyranilide, which was reported by Wallnofer (15) as a breakdown product of carboxin formed by the

Zygomycete *Rhizopus japonicus* in soil, has some toxicity to *R. solani* (Table 3). The acid formed after hydrolytic cleavage of the carboxin molecule is absolutely nontoxic, so we conclude that the carboxamide moiety is integral for fungitoxicity. However, since the 2-methyl-oxathiin ring of carboxin can be replaced by a 2,4-dimethylthiazolyl, 2-amino-4-methylthiazolyl, *o*-tolyl, 2-chlorophenyl ring, or even possibly a butyryl group, it is hard to determine its role in fungitoxicity, although as a rule compounds with 2-methyl-oxathiin rings prove to be definitely more fungitoxic than these substituted compounds.

Eradicant activity of oxathiins and thiazoles against bean rust.—The most striking feature of this part of our investigation is that eradicant activity correlates very well with fungitoxicity in vitro. One of the two exceptions we should discuss is the lack of eradicant activity of oxathiins with $-NO_2$ groups substituted in the aniline ring, notwithstanding the fact that the 3′-nitro analog is fungitoxic. The absence of eradicant activity may be due to a decrease in lipid solubility of NO_2-substituted oxathiins as compared to carboxin. Poor lipid solubility would prevent penetration of the cuticle. The second exception, 5,6-dihydro-2-*n*-propyl-1, 4-oxathiin-3-carboxanilide, has no eradicant properties, which, however, cannot be attributed to lack of penetration, since at 2,000 ppm, the chemical is phytotoxic. Considering the excellent general agreement between in vitro and in vivo data, we believe that the oxathiins act as systemic fungicides by virtue of their fungitoxic properties, rather than by altering the metabolism of the host.

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