Chapter 8

Herbicidal 1-(2,4-Dihalo-5-phenoxyphenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-1,2,4-triazolin-5(1*H*)-one Derivatives

Synthesis and Structure–Activity Relationships

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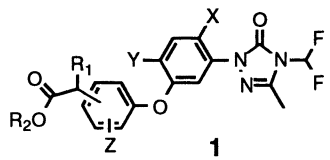
1-(2,4-Dihalo-5-phenoxyphenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-1,2,4-triazolin-5(1H)-ones **1** are a new class of highly active postemergence herbicides. The mechanism of action was found to involve inhibition of the enzyme protoporphyrinogen oxidase which results in the buildup of a photodynamic toxicant, protoporphyrin IX. When compounds **1** were applied postemergence they provided excellent weed control at 7-15 grams/hectare. These herbicides were designed to act as substrate inhibitors of tetrapyrrole-handling enzymes in the chlorophyll synthesis pathway by mimicking the three ring-propionate portion of the tetrapyrrole molecule. Synthesis, biological properties, and SAR are discussed.



1

We have been interested for over a decade in the herbicidal properties of a variety of chemistries that share a common site of action, inhibition of protoporphyrinogen oxidase (Protox)(*1*). Even though several light dependent peroxidizing herbicides such as Ronstar® herbicide and several diphenyl ether herbicides such as Blazer® and Goal® brands have been in commercial use for several decades it was not till recently that their mechanism of action was elucidated (*2,3,4*).

When initial findings suggested that these herbicides acted by inhibiting an enzyme in the chlorophyll synthesis pathway, which in turn led to the accumulation of protoporphyrin IX, it was thought that the inhibited enzyme was magnesium chelatase, which is responsible for the insertion of magnesium into the tetrapyrrole ring during chlorophyll synthesis (*5,6*).

In 1987 we concluded that protoporphyrin IX buildup was a result of the ability of peroxidizing herbicides to mimic the tetrapyrrole substrate and to competitively bind at the same site as the tetrapyrrole molecule. Close examination of the molecular shape of the peroxidizing herbicides and the tetrapyrrole ring soon pointed out the strong similarities between the two molecules. To test this hypothesis we

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proposed that if the two ring molecule from a peroxidizing herbicide such as the diphenyl ethers and the aryl triazolinones (*7*) were mimicking two of the pyrrole rings of the tertrapyrrole molecule, then a three ring molecule with a propionate side chain would more closely resemble the tetrapyrrole ring substrate as shown in Figure 1(*8*).

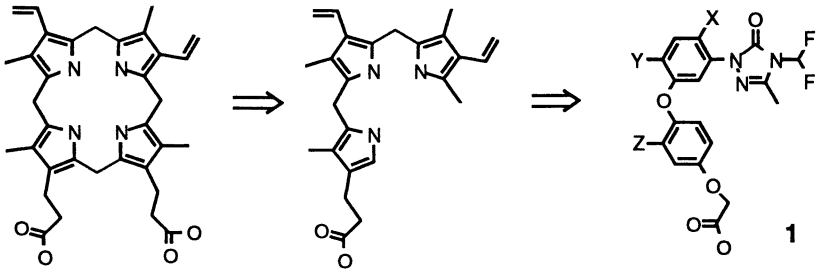


Figure 1. Phenoxyphenoxy propionates **1** as three ring mimics of tetrapyrroles.

We found that compounds with the general chemical structure **1** were among the most active peroxidizing herbicides tested in our laboratories and, as we will be discussing later, the oxypropionate moiety was essential for optimum activity. Subsequently, Matringe et al (*2,3*) and Witkowski and Halling (*4*) showed that peroxidizing herbicides inhibit protoporphyrinogen oxidase and not Mg chelatase as was initially thought. These findings led to further refinements of this model, which will be presented later.

More recently, Duke et al. proposed that peroxidizing herbicides were competitive inhibitors of Protox, requiring a bicyclic ring system and mimicking one half of the protogen molecule for a good fit into the active site (*9,10*). Our early appreciation of the structural similarities between the tetrapyrrole ring substrate and the peroxidizing herbicides allowed us to design a new class of herbicide chemistry, as well as to demonstrate that polycyclic molecules, such as compounds of general structure **1**, are inhibitors of Protox. When applied postemergence, compound **6** (Z=H, R_1,R_2=CH_3) causes rapid desiccation of sensitive weed species at application rates as low as 7.8 g/ha.

Synthesis

The synthesis of the majority of the compounds described in this work involves the derivatization of the key anilino intermediate **4**, which is prepared in good yields in two steps from the reaction of the appropriately substituted phenol **2** with a halonitrobenzene, followed by catalytic hydrogenation with PtO_2 catalyst in ethanol. The synthesis of the phenol intermediate **2** has been previously described (*7*).

The p-aminophenoxyphenyl compound **4** can be converted to the corresponding p-hydroxyphenoxyphenyl derivative **5** by the diazotization of compound **4** with $NaNO_2$ in sulfuric acid, followed by hydrolysis with $CuSO_4$ in refluxing water/xylene. Treatment of the p-hydroxyphenoxyphenyl derivative **5** with K_2CO_3 and 1-halo esters or alkyl halides resulted in good yields of the desired product **6** (Figure 2). This approach was used to obtain the para substituted phenoxyphenoxy oxypropionates, as well as other para substituted alkoxy derivatives.

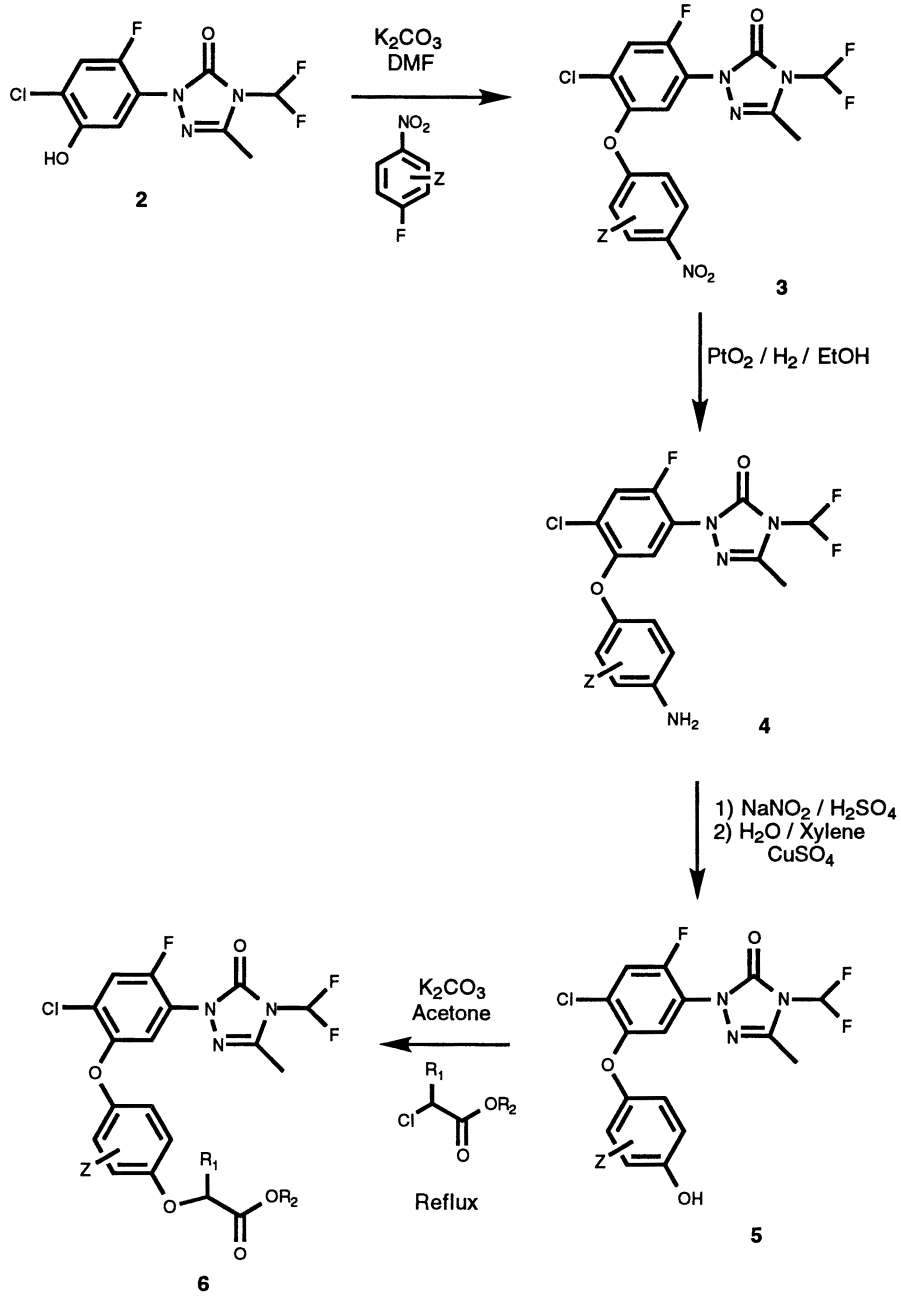


Figure 2. Synthesis of para-substituted phenoxyphenoxy derivatives.

When the substituent Z = 2-OCH_3, as in the intermediate **7**, the diazotization of the amino group followed by treatment with ethanol/toluene resulted in the meta-substituted methoxyphenoxy derivative **8**. Demethylation of compound **8** with BBr_3 gave quantitative yields of the meta-substituted phenol **9**, which in turn becomes the starting material for the synthesis of the meta-substituted oxypropionate **10** (Figure 3).

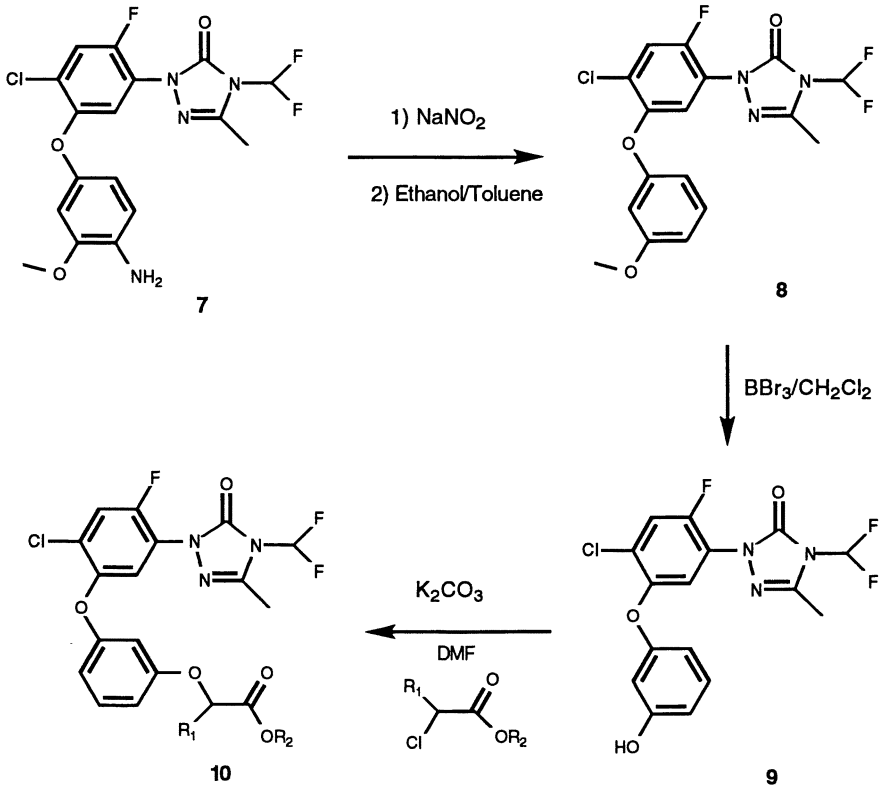


Figure 3. Synthesis of meta-substituted phenoxyphenoxy derivatives.

The 5-oxypropionate-2-pyridyloxy derivative **14** was prepared in a similar way as previously described for the synthesis of the para-substituted phenoxyphenoxy analogs **6** (Figure 2), with the exception of the step where the amino group is converted to the hydroxy group. Attempts to apply the same diazotization conditions resulted in poor yields of the phenol intermediate **13**. A better synthesis of the required hydroxy intermediate **13** involved the initial diazotization of the 5-amino-2-pyridyloxy intermediate **11** with aqueous HCl followed by the addition of tetrafluoroboric acid to give the corresponding tetrafluoroborate salt **12** in good yields. Treatment of compound **12** with potassium carbonate and trifluoroacetic acid gave the desired product **13** in good yields(*11*), which could then be further derivatized by following standard procedures as shown in Figure 4.

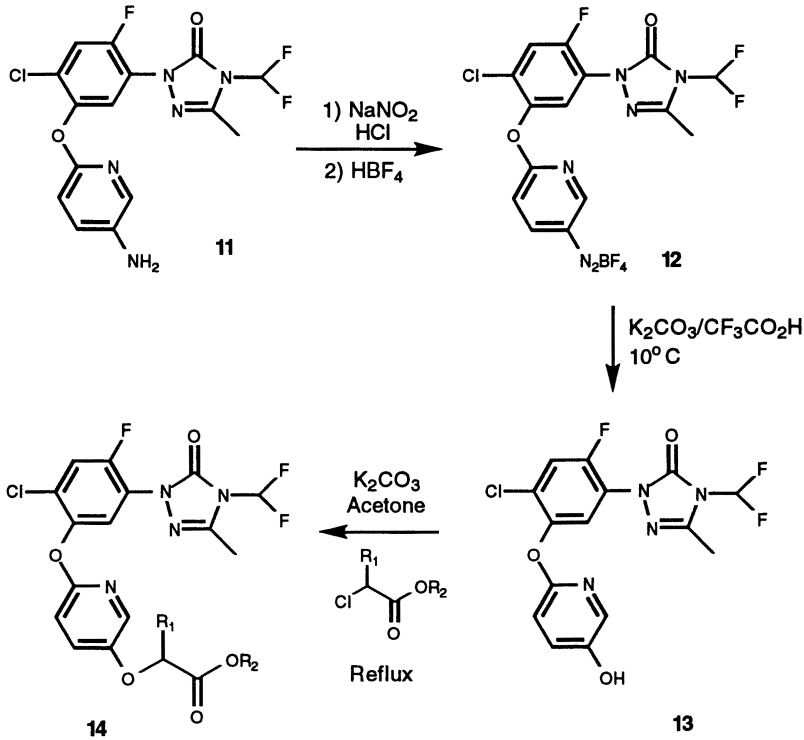


Figure 4. Synthesis of phenoxy-2-pyridyloxy -5-oxypropionates.

The synthesis of the propionate derivatives **15**, where the oxygen from the oxypropionate moity has been replaced with a methylene group, was accomplished by using the Meerwein reaction. Diazotization of the amino group of compound **4** with sodium nitrite and concentrated hydrochloric acid in acetone as a solvent followed by the addition of excess alkyl acrylate and cuprous chloride gave the desired product **15** in excellent yields (Figure 5).

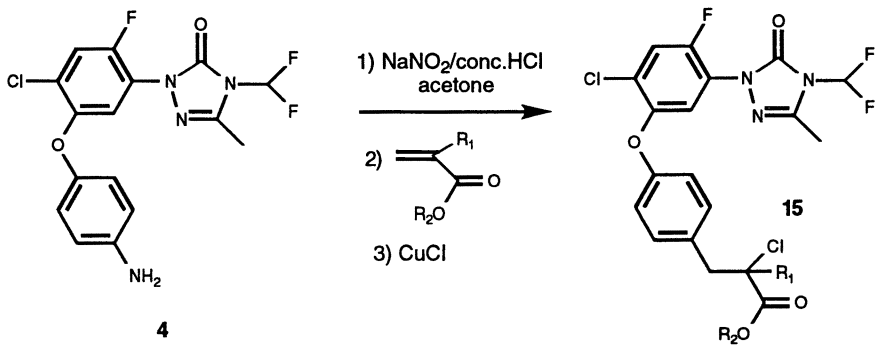


Figure 5. Synthesis of para-phenoxyphenyl-alpha-chloropropionates.

Biological Testing

The compounds described were tested preemergence and postemergence on various weeds and crops in the greenhouse The seeds of the plant test species were planted in furrows in steam-sterilized sandy loam soil contained in disposable fiber flats. A topping soil of equal portions of sand and sandy loam soil was placed uniformly on top of each flat to a depth of approximately 0.5 cm.

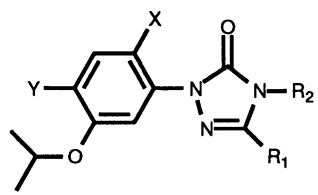
The flats were placed in a greenhouse and watered for 8-10 days, then the foliage of the emerged test plants was sprayed with a solution of the test compound in acetone-water containing up to 5 ml liter $^{-1}$ sorbitan monolaurate emulsifier/solubilizer. The concentration of the test compound in solution was varied to give a range of application rates.

Phytotoxicity data were taken as percentage control, determined by a method similar to the 0-100 rating system described previously (*12*), with 0% control of crops or weeds showing no effect relative to controls, and 100% control indicating complete crop or weed destruction. Biological data in Tables I-VI are presented as the postemergence application rate required to give 90% control as compared with untreated plants. In general, the 95% confidence interval for individual ED_{90} values in these tests is $ED_{90}/2$ to $ED_{90}x2$ (e.g., the CI for an ED_{90} of 30 g ha^{-1} is 15-60). The weeds species used in this study were morningglory, velvetleaf, johnsongrass, green foxtail, and barnyardgrass.

Structure-Activity Relationships

Aromatic substitution

Structure-activity studies were directed towards the optimization of the phenoxypropionate ring and the propionate group. We have previously discussed the structure-activity relationship of both the triazolinone ring and the aromatic ring of related herbicides **16**. The conclusion from that study was that the following chemical groups X=F, Y=Cl, R_1=CH_3 and R_2=CHF_2 were required for optimum biological activity(*7*).



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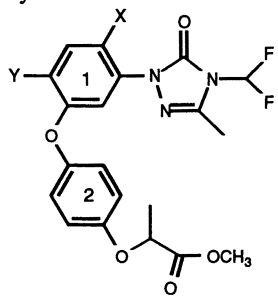
Representative examples with different X and Y groups were prepared in the phenoxyphenoxy propionate chemistry, and it was found that the same structure-activity relationship rules that applied to the molecule shown above also applied to the phenoxyphenoxy propionate chemistry. The most active compounds had X=F and Y=Cl (Table I).

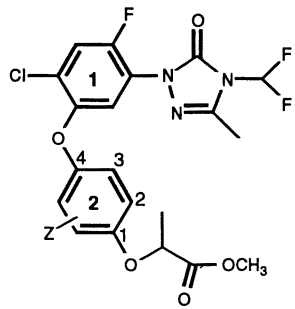
Table I. Effect of Groups at Positions 2(X) and 4(Y) of Aromatic Ring 1 on Biological Activity



X	Y	Rate required to provide 90% control of both morningglory and velvetleaf when applied postemergence (grams/ha)
F	Cl	7.8
Cl	Cl	31.3
H	Cl	1000
Cl	H	2000
H	H	2000

Halogens at position 3 of the aromatic ring 2 resulted in compounds with biological activity comparable to that of the parent compound. This is particularly true when Z=3-chlorine and 3-fluorine. Substitution at the 2 position of ring 2 resulted in a dramatic reduction of biological activity (Table II).

Table II. Effect of Position 2 and 3 of Aromatic Ring 2 on Biological Activity

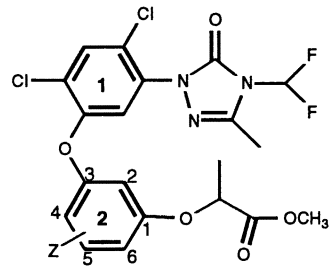


Z	Rate required to provide 90% control of morningglory, velvetleaf, johnsongrass and barnyardgrass when applied postemergence (grams/ha)
H	31.3
3-F	31.3
3-Cl	31.3
2-Cl	125

When the oxypropionate group was in the meta position, the resulting compounds were found to have comparable biological activity to that of the corresponding para- phenoxyphenoxy propionate analog. Analogs with a halogen in position 4 of ring 2 retained biological activity, while introducing halogens at both positions 4 and 6 resulted in loss of biological activity. When groups such as NO_2 and NH_2 were introduced at position 4 of ring 2, the resulting compounds were significantly less active (Table III).

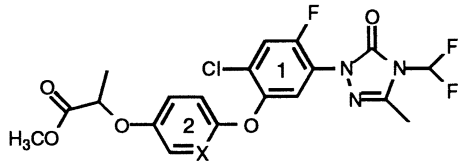
Replacing the aromatic ring 2 in compound **6** with a 2-pyridine group resulted in a somewhat less active molecule (Table IV).

Table III. Meta Substituted Phenoxyphenoxy Propionate Derivatives



Z	Rate required to provide 90% control of morningglory, velvetleaf, johnsongrass and green foxtail when applied postemergence (grams/ha)
H	62.5
4-F	62.5
4-F,6-Cl	125
4-NO_2	250
4-NH_2	>500

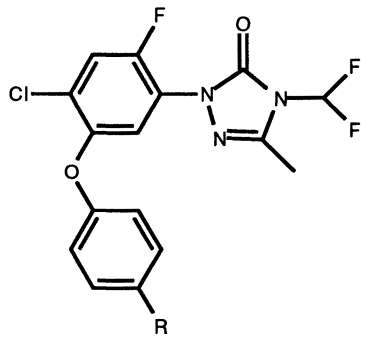
Table IV. Effect of Pyridine Ring 2 on Biological Activity



X	Rate required to provide 90% control of morningglory, velvetleaf, johnsongrass and barnyardgrass when applied postemergence (grams/ha)
CH	31.3
N	62.5

We have previously mentioned the importance of the presence of the ester side chain on phenyl ring 2 in our original design of the phenoxyphenoxy herbicides. Several other R groups were investigated and they resulted in compounds with significantly less biological activity. It is interesting to note that the compound where R=CO_2CH_3 is significantly less active than the compound where R=$OCH(CH_3)CO_2CH_3$, pointing out the need for the two atom linkage between the ester and the aromatic ring for optimum biological activity (Table V).

Table V. Effect of Phenyl Ring 2 Substituents on Biological Activity

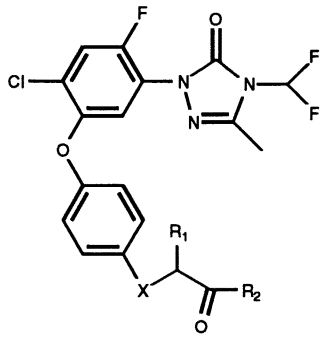


R	Rate required to provide 90% control of morningglory, velvetleaf, johnsongrass and barnyardgrass when applied postemergence (grams/ha)
$OCH(CH_3)CO_2CH_3$	31.3
OCH_3	500
CO_2CH_3	500
H	1000
NH_2	4000
NO_2	>4000

Effect of X, R_1 and R_2 groups of the ester side chain on biological activity

Several acid derivatives of the ester side chain in ring 2 were prepared, including amides, acids and their salts. The best control of both broadleaf and grass weeds was obtained with the ester derivatives, particularly when X=O, R_1=CH_3 and R_2=OCH_3. The amides and acids, though highly active, were not as effective in controlling grass weeds. It is interesting to note that replacing oxygen with a methylene group, to give R=$CH_2CH_2CO_2CH_3$, resulted in excellent broadleaf weed control with a significant decrease in grass weed control. Replacement of the oxygen atom with an NH group, X=NH, resulted in a dramatic loss of biological activity. The broadleaf weeds morningglory and velvetleaf, and the grass weeds barnyardgrass and johnsongrass, were used for Table VI.

Table VI. Effect of X, R_1 and R_2 Groups of the Ester Side Chain on Biological Activity



			Rate required to provide 90% control of weeds tested (grams/ha)	
X	R_1	R_2	Broadleaf	Grass
O	CH_3	OCH_3	7.8	31.3
O	CH_3	NH_2	15.6	62.5
O	CH_3	OH	7.8	62.5
O	H	OCH_3	7.8	62.5
CH_2	Cl	OCH_3	3.9	>125
NH	CH_3	OCH_2CH_3	4000	>4000

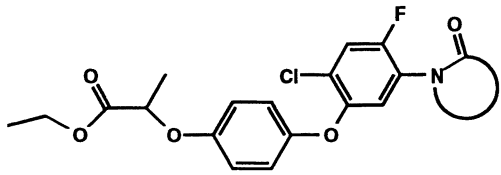
Effect of heterocyclic ring on biological activity

In addition to the triazolin-5-one, we investigated a number of other heterocyclic rings. In general the triazolin-5-one gave the best overall activity, providing good control of both broadleaf and grass weeds. The tetrahydrophtalimide and the hydantoin heterocycles required higher application rates than the triazolin-5-one for broadleaf weed control, while grass weed control for these two rings was in general poor (Table VII).

Potential of heteroaryl phenoxyphenoxy oxypropionates as rice herbicides

Several compounds in this new class of postemergence herbicides have shown promise as potential rice herbicides. Compound **17** provided excellent control of a number of weeds when applied postemergence at rates as low as 3.9 g/ha in greenhouse tests. Rice was tolerant at this rate (Table VIII).

Table VII. Effect of Heterocyclic Ring on Biological Activity



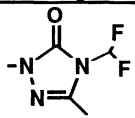
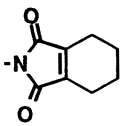
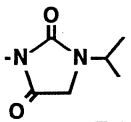
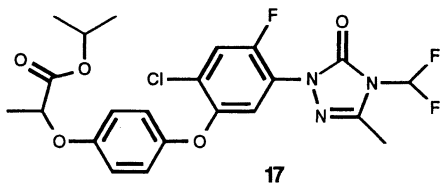
Heterocyclic ring	Rate grams a.i./ha	Greenhouse postemergence activity phytotoxicity(% control) Velvetleaf	Morningglory	Barnyard grass	Johnson grass
	7.8	100	100	40	60
	31.3	100	100	90	80
	15.6	90	95	20	20
	62.5	100	100	30	20
	62.5	100	95	40	30
	250	100	100	70	60

Table VIII. Potential of phenoxyphenoxy oxypropionates as rice herbicides



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Rate grams a.i./ha	Rice	Grenhouse postemergence activity phytotoxicity (% control) Cocklebur	Velvetleaf	Morningglory	Barnyard grass	Nightshade
3.9	5	100	100	100	20	100
7.8	5	100	100	100	40	100
15.6	10	100	100	100	50	100
31.3	20	100	100	100	90	100

Summary

The 1-(2,4-dihalo-5-phenoxyphenyl)-4-difluoromethyl-4,5-dihydro-3-methyl-1,2,4-triazolin-5(1H)-ones **1** are a new class of highly active postemergence herbicides providing excellent weed control at rates as low as 7-15 grams/hectare. Crop selectivity was observed in some cases, such as the rice selectivity obtained with compound **17**. The rational design of this novel class of herbicides was based on the assumption that peroxidizing herbicides acted as substrate inhibitors of tetrapyrrole handling enzymes in the chlorophyll synthesis pathway. This approach allowed us to discover not only a highly active class of herbicides but also an area in which chemistry deviated greatly from that of previously known peroxidizing herbicides.

Acknowledgments

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