

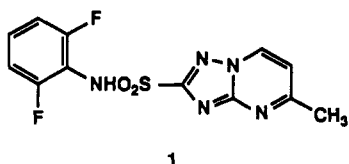
DE-498, a New Acetolactate Synthase Inhibiting Herbicide with Multicrop Selectivity

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DE-498 is a member of a new structural class of highly active herbicides, the triazolopyrimidine sulfonanilides, which act by inhibiting acetolactate synthase (EC 4.1.3.18). DE-498 exhibits broad spectrum activity on broad-leaved weed species with selectivity to several major agronomic crops in soil and foliar applications. The toxicological profile of DE-498 to mammals, fish, and wildlife is favorable. The moderate soil half-life and patterns of crop selectivity of DE-498 eliminate the potential for carryover injury to crops grown in corn/soybean/wheat rotations.

The triazolopyrimidine sulfonanilides represent a new class of highly active, broad spectrum herbicides (Kleschick and Gerwick, 1989; Kleschick et al., 1990). These herbicides act by disrupting branched-chain amino acid biosynthesis through inhibition of the enzyme acetolactate synthase (ALS, EC 4.1.3.18) (Gerwick et al., 1990). Members of this class of compounds exhibit selectivity to several major crop species. In many instances crop selectivity is a result of metabolic detoxification (Hodges et al., 1989). One of the members of this class, *N*-(2,6-difluorophenyl)-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonamide (DE-498, 1), is a highly active herbicide with selectivity to several major crops. Herein, we report the chemical and biological properties of DE-498 (proposed common name flumetsulam).



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MATERIALS AND METHODS

General Chemical Methods. Starting materials and reagents were purchased from commercial suppliers and were used without further purification unless otherwise noted. NMR chemical shifts are expressed as δ values (ppm) relative to Me_4Si internal standard. Significant NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; m, multiplet; br, broad), coupling constant(s) in hertz.

Preparation of 5-Methyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonyl chloride. Chlorine gas (22 g, 0.31 mol) was added over 50 min to a suspension of 25.6 g (0.100 mol) of 2-(benzylthio)-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine (Monte et al., 1989; Kleschick et al., 1990) in 75 mL of acetic acid-water (1:1 v/v) maintained at a temperature between -5 and 3 °C. After the addition was complete, the reaction mixture was stirred for 15 min and filtered. The solid which was collected was washed with water and dried under vacuum to afford 14.7 g (63%) of crude

Table I. Physical Properties of DE-498

melting point, °C	251-253	soil absorption	5-182
vapor pressure at 25 °C, mmHg	2.8×10^{-15}	constant (K_{oc})	
octanol water distribution (K_{ow})	0.21	water solubility at pH 2.5, ^b mg/L	49
		pK_a	4.6

^a Extrapolated value. ^b Solubility is higher at higher pH.

Table II. Mammalian Toxicity of DE-498

test (species or assay)	result
acute oral (male rat)	LD ₅₀ > 5000 mg/kg
acute oral (female rat)	LD ₅₀ > 5000 mg/kg
acute dermal (rabbit)	LD ₅₀ > 2000 mg/kg
dermal sensitization (guinea pig)	negative
eye irritation (rabbit)	slight irritation at 24 h with recovery by 48 h
mutagenicity (Ames <i>Salmonella</i> /mammalian microsomal assay)	negative
mutagenicity (rat hepatocyte unscheduled DNA synthesis assay)	negative
mutagenicity (Chinese hamster ovary cell/hypoxanthine-HGPRT assay)	negative
mutagenicity (mouse bone marrow micronucleus test)	negative
dietary teratology (rat)	NOEL 1000 mg/kg/day (highest dose tested) for embryo/fetotoxic or teratogenic effects

sulfonyl chloride as a tan solid which was used without further purification: ¹H NMR (CDCl₃) δ 8.90 (1 H, d), 7.33 (1 H, d), 2.80 (3 H, s); IR (CHCl₃) 1629, 1524, 1392, 1172 cm⁻¹.

Preparation of *N*-(2,6-Difluorophenyl)-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonamide (1, DE-498). 5-Methyl[1,2,4]triazolo[1,5-*a*]pyrimidine-2-sulfonyl chloride (36.1 g, 0.155 mol) was added to a solution of 18.1 g (0.140 mol) of 2,6-difluoroaniline in 45 mL of dry pyridine. After an initial exothermic reaction subsided, the reaction mixture was stirred at ambient temperature for 15.5 h. The pyridine was removed by evaporation at reduced pressure, and the residue was treated with 600 mL of 0.5 N NaOH(aq). The mixture was stirred to dissolve all soluble material and filtered through Celite. The filtrate was acidified by cautious addition of 3 N HCl(aq). The solid which separated was collected by filtration and dried to yield 33.0 g (73%) of DE-498 as a pale red solid: mp 245-247 °C; ¹H NMR (DMSO-*d*₆) δ 10.8 (1 H, br), 9.36 (1 H, d), 6.8-7.6 (4 H, m), 2.70 (3 H, s); ¹⁹F NMR (DMSO-*d*₆) 45.6 ppm upfield from C₆F₆ (m); IR (KBr) 3230, 1611, 1477, 1416, 1358, 1163, 1153, 998 cm⁻¹. Anal. Calcd for C₁₂H₉F₂N₆O₂S: C, 44.31; H, 2.79; N, 21.53. Found: C, 44.69; H, 2.80; N, 21.85.

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Scheme I

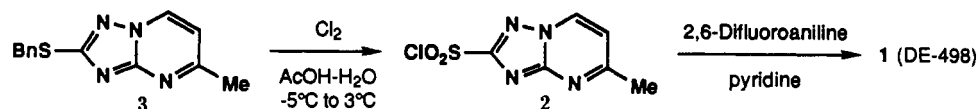


Table III. Fish and Wildlife Toxicity of DE-498

species	result	species	result
quail	LC ₅₀ > 5620 ppm	rainbow trout	practically nontoxic
mallard duck	LC ₅₀ > 5620 ppm	silverside minnow	LC ₅₀ > 379 mg/L
bluegill/fathead minnow	practically nontoxic	shrimp	LC ₅₀ > 349 mg/L
daphnia	practically nontoxic	oyster (new shell growth)	EC ₅₀ > 173 mg/L

Table IV. Weed Control Spectrum of DE-498

weed	true leaves present at post-emergence application	post-emergence GR ₈₀ value, g/ha	pre-emergence GR ₈₀ value, g/ha
broadleaves			
<i>A. theophrasti</i>	2	9	20
<i>C. album</i>	4	17	15
<i>Xanthium strumarium</i>	2	40	60
<i>Ipomoea hederaceae</i>	1	50	40
<i>Ipomoea lacunosa</i>	1	>140	>140
<i>Amaranthus hybridus</i>	4	4	10
<i>S. spinosa</i>	1	4	14
<i>Polygonum scabrum</i>	2	100	65
<i>Datura stramonium</i>	2	10	25
<i>Solanum</i> spp.	4	10	20
<i>Stellaria media</i>	4	9	18
<i>Matricaria matricariodes</i>	2	2	15
<i>Convolvulus arvensis</i>	2	>140	>140
grasses			
<i>Echinochloa crus-galli</i>	2	>140	40
<i>Digitaria sanguinalis</i>	3-4	140	>140
<i>Setaria lutescens</i>	4	70	35
<i>Sorghum halapense</i>	2	34	>140
<i>Avena fatua</i>	2	>140	>140
sedge			
<i>Cyperus esculentus</i>	2	70	40

Physical Property, Mammalian Toxicology, and Ecotoxicology Methods. Physical property, mammalian toxicology, and ecotoxicology studies were conducted by DowElanco Laboratories based on standard protocols required by Environmental Protection Agency guidelines. The results are listed in Tables I-III.

General Biology Test Methods. Seeds of broad-leaved, grass, and sedge weeds along with crops were obtained from commercial seed suppliers and planted in pots containing a sandy loam soil (1% organic matter, pH 7.1) for preemergence treatments or directly in sand (<0.1% organic matter, pH 7.3) for postemergence treatments. The postemergence treatments were thinned prior to application to 2-10 plants per pot depending on species. The leaf stage was noted at postemergence treatment and is listed in Table IV.

All applications were made with a belt-driven tracksprayer (E. Allen Instruments, Midland, MI) through a 8002E nozzle at 4.9 kph, 265 kPa, and 188 L/ha. DE-498 was formulated as a flowable formulation containing 12.5% ai and diluted with 0.1% Ortho X-77 nonionic surfactant prior to spraying. Following application the preemergence treatments received top-watering to move the chemical into the soil and initiate seed germination. The postemergence treatments received watering and nutrient additions through subirrigation. Treated plants were maintained along with untreated controls under greenhouse conditions for the duration of the test. Greenhouse temperature ranges were 25-28 (daytime) and 20-21 °C (nighttime). The photoperiod was extended to 14.5 h through the use of 1000-W multivapor lights positioned to provide 150-200 μEinstein m⁻² s⁻¹ PAR at plant heights.

Applications were made to two pot replicates over a rate range encompassing six serial dilutions (140-4 g/ha for weed control determinations, 70-2 g/ha for crop injury assessments). Injury

Table V. Crop Tolerance to DE-498

crop	postemergence GR ₁₀ value, g/ha	preemergence GR ₁₀ value, g/ha
corn	>70	50
wheat	>70	>70
barley	>70	>70
soybean	20	>70
rice	15	22
sunflower	12	11
cotton	7	4
sugar beet	3	5
rape	3	4

Table VI. Soil Mobility of DE-498 Relative to That of Chlorimuron and Imazaquin

compd	soil type ^a	R _f max
chlorimuron	A	0.79
chlorimuron	B	0.49
imazaquin	A	0.81
imazaquin	B	0.79
DE-498	A	0.85
DE-498	B	0.63

^a Soil type A, sandy loam (pH 7.1, OM = 1%); soil type B, silt loam (pH 6.0, OM = 3.5%).

was assessed visually 14 days after postemergence treatments and 21 days after preemergence treatments on a scale of 0-100, where 0 represents no effect and 100 complete plant death. The data were subjected to log-linear regression with the aid of a SAS computer program and application rates producing 80% growth reduction (GR₈₀) of weeds and 10% growth reduction of crops (GR₁₀) interpolated. The results are listed in Tables IV and V.

Soil Mobility Test Methods. Soil mobility was evaluated by bioassay in soil leaching columns. Columns were prepared for all treatments by packing 3 cm diameter plastic tubes to a height of 43 cm with either a sandy loam (1% organic matter, pH 7.1) or a catlin silt loam (3% organic matter, pH 6.0). The columns were allowed to preequilibrate by adding 2 acre in. of water to the surface 24 h prior to chemical application. DE-498 was added to the top of the column at an application rate of 30 g/ha. The columns were then leached with 2 acre in. of water for 24 h, oriented horizontally, and seeded with oilseed rape. The rape was allowed to grow for 3 weeks under growth chamber conditions (21 °C, 30-90% relative humidity, 14-h day length), after which time the distance of growth inhibition was measured and expressed as an R_f. The results are given in Table VI.

RESULTS AND DISCUSSION

DE-498 is prepared by the reaction of the 5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-sulfonyl chloride (2) with 2,6-difluoroaniline in pyridine (Scheme I). The sulfonyl chloride (2) is obtained from 2-(benzylthio)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine (3) (Monte et al., 1989; Kleschick et al., 1990) by reaction with chlorine in aqueous acid.

The physical properties of DE-498 are listed in Table I. DE-498 is a high melting solid with a very low vapor pressure. The soil absorption constant of DE-498 varies

as a function of soil pH. Water solubility is also impacted by pH. This is attributed to the weakly acidic nature of the compound.

The toxicity of DE-498 to mammals and fish and wildlife is summarized in Tables II and III, respectively. The acute toxicity of DE-498 is very low. No dermal sensitization was observed with DE-498. Slight eye irritation was observed. No mutagenic or teratogenic effects have been observed with DE-498.

DE-498, like other triazolopyrimidine sulfonanilides, is an inhibitor of ALS (Kleschick et al., 1990). The I_{50} measured against the enzyme isolated from tobacco cultures is 0.02 ppm.

The foliar and soil activity of DE-498 on a range of broad-leaved, grass, and sedge weeds is illustrated in Table IV. A broad range of susceptibility is observed in these weeds as GR₅₀ values vary from 2 g/ha for *Matricaria* to greater than 140 g/ha for several weed species. Among the highly sensitive weed species, and of particular importance to corn and soybean production, is *Abutilon theophrasti* (velvetleaf). Velvetleaf is recognized as a serious problem in both of these crops, as a weed with substantial economic impact, and as a weed not adequately controlled by existing measures (Spencer, 1984). As little as 9 g/ha postemergence or 20 g/ha preemergence of DE-498 is sufficient for 80% control. Other difficult to control weeds demonstrating high sensitivity include *Amaranthus hybridus* (smooth pigweed), *Chenopodium album* (lambsquarters), *Sida spinosa* (teaweed), and *Solanum* spp. (nightshade). The variation among species in response to DE-498 is lower following soil applications than foliar. This suggests greater opportunity for broad spectrum control following this method of application. Indeed, at the anticipated preemergence use rate of 70 g/ha, control at greater than 80% is obtained for the vast majority of broad-leaved weeds as well as several grasses and sedge.

The tolerance of major agronomic crops to DE-498 is illustrated in Table V. Barley, wheat, and corn all demonstrate high levels of tolerance to soil and foliar applications. Additionally, soybean shows high tolerance to soil applications. Oilseed rape, cotton, and sugar beets all appear quite sensitive following either method of application. The spectrum of weeds sensitive to DE-498, coupled to the tolerance of corn, soybean, wheat, and barley, suggests a multitude of opportunities for selective weed control with DE-498. The basis for the selectivity of DE-498 to corn and soybean is metabolic detoxification (Swisher et al., 1991).

The soil half-life of DE-498 is between 30 and 60 days (2–4% organic matter, soil pH 6–7), suggesting minimal chemical carryover to subsequent growing seasons (Gerwick and Kleschick, 1991). Variations in soil moisture and temperature can impact the decomposition rates of all herbicides. The high sensitivity of cotton, sugar beet, and oilseed rape to DE-498 will prohibit rotation to these crops for 22 months. However, in view of the potential for environmental variability, the multicrop selectivity of DE-

498 provides additional insurance of safety to crops commonly rotated with corn, including soybean and wheat.

The mobility of DE-498 in soil is illustrated by data presented in Table VI. DE-498 was compared to two commercial ALS inhibitor herbicides, chlorimuron and imazaquin, in a greenhouse bioassay with oilseed rape. The mobility of DE-498 is comparable to that of both standards in the slightly alkaline soil (soil type A). DE-498 is more mobile than chlorimuron but less mobile than imazaquin in the acid soil (soil type B).

CONCLUSION

DE-498 is a highly active broad spectrum, ALS inhibitor herbicide with utility in a number of major agronomic crops. DE-498 offers the flexibility of application timings from preemergence to early postemergence. DE-498 has a very favorable profile of mammalian toxicology and does not pose a significant threat to fish and wildlife. DE-498 poses no threat to injuring crops in the corn/soybean/wheat rotation by virtue of the moderate soil half-life and crop selectivity.

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