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Yamada, Naotaka
Faculty of Agriculture, Kyushu University

Hong, Soonsung
Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University

Kuwano, Eiichi
Faculty of Agriculture, Kyushu University

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Novel Inhibitors of Phenylalanine Ammonia–lyase: 5–Aryl–1,3,4–oxathiazol–2–ones

Naotaka YAMADA, Soonsung HONG[1], and Eiichi KUWANO*

Laboratory of Pesticide Chemistry, Division of Plant Protection, Department of Applied Genetics and Pest Management, Faculty of Agriculture, Kyushu University, Fukuoka 812–8581, Japan

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A series of 5–aryl–1,3,4–oxathiazol–2–ones was synthesized and tested for inhibition against phenylalanine ammonia–lyase (PAL) derived from the yeast *Rhodotorula glutinis*. All compounds inhibited PAL at 100 μM. Of the compounds tested, 5–(4–nitrophenyl)–1,3,4–oxathiazol–2–one (**19**) was the most effective, showing IC_{50} value of 2.5 μM, which was 2 times stronger than that of *N*–(aminooxy) acetyl–2,5–dichloroaniline (Z302), a known PAL inhibitor. Compound **19** behaved as a noncompetitive inhibitor of PAL. When potato tuber disks were treated with **19** in the presence of laminarin, a β–1,3–glucooligosaccharide elicitor, the amount of *trans*–cinnamic acid diminished after 48 hr, being consistent with an effective inhibition of PAL. Most of the compounds inhibited the growth of lettuce seedlings at 100–500 μM. However, no correlation was observed between the ability of 5–aryl–1,3,4–oxathiazol–2–ones to inhibit PAL derived from *R. glutinis* and growth inhibitory activity against lettuce seedlings.

INTRODUCTION

Phenylalanine ammonia–lyase (PAL), which catalyzes the formation of *trans*–cinnamic acid (*t*–CA) from L–phenylalanine, plays a central role in plant secondary metabolism (Hohlbrock and Scheel, 1989). *t*–CA is the important precursor for the biosynthesis of a large number of phenylpropanoids such as lignins, lignans, flavonoids, isoflavonoids and coumarins, which are essential for plant development and defense against ultraviolet light, predators and pathogens. Specific inhibitors of PAL are useful as a biochemical probe in the study of the phenylpropanoid pathway and its functions (Zon *et al*., 2002). In addition, since PAL has not been found to date either in bacterial or animal tissues, PAL inhibitors might be relatively non–toxic to these organisms and represent reasonable leads for development of a novel herbicide.

Several kinds of PAL inhibitors have been reported so far. Amrheim and Godeke (1977) have described the hydroxylamine analog of phenylalanine, 2–aminooxy–3–phenylpropanoic acid, as a powerful inhibitor of PAL under both *in vitro* and *in vivo* conditions. A number of *t*–CA derivatives were found to inhibit PAL derived from plants and yeast (Sato *et al*., 1982). (Aminooxy) acetic acid (AOA), an inhibitor of pyridoxal phosphate–dependent enzymes, is known to inhibit PAL (Hoagland, 1985). Ogawa and Amagasa (1998) have prepared *N*–(aminooxy)acetyl–2,5–dichloroaniline (Z302) as a potential PAL inhibitor. Recently, Zon *et al*. (2002) have reported that 1–amino–3',4'–dichlorobenzylphosponic acid strongly inhibited PAL. However, none of these compounds has been developed for practical use in weed control. Most of the PAL inhibitors found so far have a structural similarity to phenylalanine or *t*–CA. We therefore screened heterocycles possessing a partially structural resemblance to *t*–CA in order to discover PAL inhibitors of novel structure. In the present paper we report the synthesis and the evaluation of a series of 5–aryl–1,3,4–oxathiazol–2–ones as PAL inhibitors.

MATERIALS AND METHODS

Chemicals

(Aminooxy)acetic acid (AOA) was purchased from Kanto Co. *N*–(Aminooxy)acetyl–2,5–dichloroaniline (Z302) was a gift from Sankyo Co. All melting points are uncorrected. The ^{1}H–NMR spectra were determined with JEOL EX–400 (400 MHz) spectrometer, using tetramethylsilane as an internal standard, and all samples were prepared in deuterochloroform. 5–Aryl–1,3,4–oxathiazol–2–ones were prepared according to the methods described by Brownsort and Paton (1987) (Fig. 1). The following procedure for the preparation of 5–phenyl–1,3,4–oxathiazol–2–one (**1**) is typical.

A solution of benzamide (0.61 g, 5 mmol) and chlorocarbonylsulfenyl chloride (0.98 g, 7.5 mmol) in 15 ml of dry tetrahydrofuran was stirred for 12hr at room temperature. To the mixture was added 20 ml of 5% $NaHCO_3$ solution. After stirring for 5 minutes at room temperature, the product was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by recrystallization from diisopropyl ether to give 0.51 g (57%) of **1**, mp 62 °C. ^{1}H–NMR δ: 7.47–7.59 (3H, m, phenyl), 7.96–7.98 (2H, m, phenyl).

Compounds **2**–**22** were prepared in the same manner as compound **1** with use of the corresponding substituted benzamide instead of benzamide. The yields were calculated based on the starting substituted benzamides.

[1] Laboratory of Pesticide Chemistry, Division of Plant Protection, Department of Applied Genetics and Pest Management, Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University

* Corresponding author (E–mail: ekuwano@agr.kyushu–u.ac.jp)

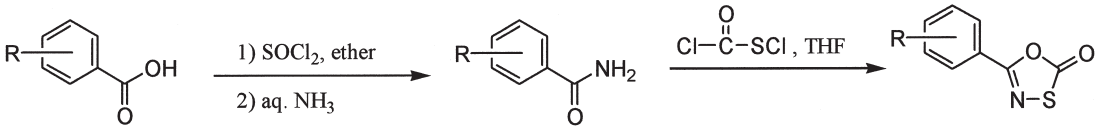


Fig. 1. Synthetic scheme for preparation of 5–aryl–1,3,4–oxathiazol–2–ones.

5–(2–Fluorophenyl)–1,3,4–oxathiazol–2–one (**2**)

Yield 46%; mp 53 °C. ^{1}H–NMR δ : 7.21–7.30 (2H, m, phenyl), 7.53–7.59 (1H, m, phenyl), 7.89–7.93 (1H, m, phenyl). Anal. Found: C, 49.31; H, 2.27; N, 7.03%. Calcd. for $C_8H_4NO_2FS$: C, 48.73; H, 2.04; N; 7.10%.

5–(3–Fluorophenyl)–1,3,4–oxathiazol–2–one (**3**)

Yield 59%; mp 54 °C. ^{1}H–NMR δ : 7.25–7.29 (1H, m, phenyl), 7.45–7.51 (1H, m, phenyl), 7.65–7.69 (1H, m, phenyl), 7.75–7.77 (1H, m, phenyl). Anal. Found: C, 48.19; H, 2.15; N, 7.09%. Calcd. For $C_8H_4NO_2FS$: C, 48.73; H, 2.04; N, 7. 10%.

5–(4–Fluorophenyl)–1,3,4–oxathiazol–2–one (**4**)

Yield 12%; mp 92 °C. ^{1}H–NMR δ : 7.16–7.20 (2H, m, phenyl), 7.97–8.00 (2H, m, phenyl). Anal. Found: C, 48.80; H, 2.10; N, 7.21%. Calcd. For $C_8H_4NO_2FS$: C, 48.73; H, 2.04; N, 7.10%.

5–(2–Chlorophenyl)–1,3,4–oxathiazol–2–one (**5**)

Yield 35%; mp 54 °C. ^{1}H–NMR δ : 7.38–7.42 (1H, m, phenyl), 7.46–7.54 (2H, m, phenyl), 7.84–7.86 (1H, m, phenyl).

5–(3–Chlorophenyl)–1,3,4–oxathiazol–2–one (**6**)

Yield 22%; mp 76 °C. ^{1}H–NMR δ : 7.42–7.46 (1H, m, phenyl), 7.53–7.54 (1H, d, J=6.8 Hz, phenyl), 7.84–7.86 (1H, d, J=7.8 Hz, phenyl), 7.97 (1H, s, phenyl).

5–(4–Chlorophenyl)–1,3,4–oxathiazol–2–one (**7**)

Yield 49%; mp 128 °C. ^{1}H–NMR δ : 7.47 (2H, d, J= 8.3, phenyl), 7.91 (2H, d, J=8.3 Hz, phenyl).

5–(2–Bromophenyl)–1,3,4–oxathiazol–2–one (**8**)

Yield 63%; mp 60 °C. ^{1}H–NMR δ : 7.37–7.46 (2H, m, phenyl), 7.72–7.74 (1H, m, phenyl), 7.78–7.81 (1H, m, phenyl).

5–(3–Bromophenyl)–1,3,4–oxathiazol–2–one (**9**)

Yield 49%; mp 79 °C. ^{1}H–NMR δ : 7.36–7.38 (1H, m, phenyl), 7.68–7.70 (1H, m, phenyl), 7.89–7.91 (1H, m, phenyl), 8.12 (1H, m, phenyl).

5–(4–Bromophenyl)–1,3,4–oxathiazol–2–one (**10**)

Yield 59%; mp 145 °C. ^{1}H–NMR δ : 7.62–7.65 (2H, m, phenyl), 7.81–7.84 (2H, m, phenyl).

5–(2–Methylphenyl)–1,3,4–oxathiazol–2–one (**11**)

Yield 80%; oil. ^{1}H–NMR δ : 2.64 (3H, s, CH_3), 7.29–7.32 (2H, m, phenyl), 7.41–7.43 (1H, m, phenyl), 7.85–7.87 (1H, m, phenyl).

5–(3–Methylphenyl)–1,3,4–oxathiazol–2–one (**12**)

Yield 64%; mp 80 °C. ^{1}H–NMR δ : 2.42 (3H, s, CH_3), 7.37–7.38 (2H, m, phenyl), 7.76–7.79 (2H, m, phenyl).

5–(4–Methylphenyl)–1,3,4–oxathiazol–2–one (**13**)

Yield 46%; mp 83 °C. ^{1}H–NMR δ : 2.42 (3H, s, CH_3), 7.29 (2H, d, J=8.3 Hz, phenyl), 7.85 (2H, d, J=8.3 Hz, phenyl).

5–(2–Methoxyphenyl)–1,3,4–oxathiazol–2–one (**14**)

Yield 79%; mp 69 °C. ^{1}H–NMR δ : 3.95 (3H, s, OCH_3), 7.03–7.07 (2H, m, phenyl), 7.50–7.54 (1H, m, phenyl), 7.79–7.81 (1H, m, phenyl).

5–(3–Methoxyphenyl)–1,3,4–oxathiazol–2–one (**15**)

Yield 60%; mp 87 °C. ^{1}H–NMR δ : 3.86 (3H, s, OCH_3), 7.09–7.12 (1H, m, phenyl), 7.37–7.41 (1H, m, phenyl), 7.47 (1H, m, phenyl), 7.55–7.57 (1H, m, phenyl). Anal. Found: C, 51.80; H, 3.41; N, 6.75%. Calcd. For $C_9H_7O_3NS$: C, 51.67; H, 3.37; N, 6.69%.

5–(4–Methoxyphenyl)–1,3,4–oxathiazol–2–one (**16**)

Yield 69%; mp 114 °C. ^{1}H–NMR δ : 3.88 (3H, s, OCH_3), 6.96–6.99 (2H, m, phenyl), 7.89–7.92 (2H, m, phenyl).

5–(2–Nitrophenyl)–1,3,4–oxathiazol–2–one (**17**)

Yield 68%; mp 91 °C. ^{1}H–NMR δ : 7.72–7.76 (1H, m, phenyl), 8.29–8.32 (1H, m, phenyl), 8.42–8.45 (1H, m, phenyl), 8.83–8.84 (1H, m, phenyl).

5–(3–Nitrophenyl)–1,3,4–oxathiazol–2–one (**18**)

Yield 62%; mp 103 °C. ^{1}H–NMR δ : 7.74–7.80 (2H, m, phenyl), 7.82–7.86 (2H, m, phenyl), 8.02–8.04 (1H, m, phenyl).

5–(4–Nitrophenyl)–1,3,4–oxathiazol–2–one (**19**)

Yield 53%; mp 168 °C. ^{1}H–NMR δ : 8.16–8.19 (2H, m, phenyl), 8.35–8.38 (2H, m, phenyl).

5–(2–Trifluoromethylphenyl)–1,3,4–oxathiazol–2–one (**20**)

Yield 75%; mp 49 °C. ^{1}H–NMR δ : 7.64–7.75 (2H, m, phenyl), 7.82–7.87 (2H, m, phenyl).

5–(3–Trifluoromethylphenyl)–1,3,4–oxathiazol–2–one (**21**)

Yield 49%; mp 82 °C. ^{1}H–NMR δ : 7.66 (1H, t, J=7.8 Hz, phenyl), 7.83 (1H, d, J=7.8 Hz, phenyl), 8.16 (1H d, J=7.8 Hz, phenyl), 8.24–8.26 (1H, m, phenyl).

Enzymatic assays and HPLC analysis

Yeast PAL originating from *Rhodotorula glutinis* was purchased from Sigma–Aldrich Co. Enzyme assay was conducted by the procedure modified from that described in the literature (Matsuda *et al.*, 2000). One enzyme unit was defined as the amount of protein catalyzing the appearance of 1 μmole of *t*–CA per minute at 30 °C. The reaction mixture containing 0.0005 unit of PAL, 5 μl of test compound and 420 μl of tris–HCl buffer (0.1 M, pH 8.0) was preincubated for 1 hr at 30 °C. After addition of 50 μl of 20 mM phenylalanine, the mixture was incubated for 30 min at 30 °C. The reaction was stopped by adding 30 μl of 2 M HCl. The reaction mixture (20 μl) was taken for HPLC analysis.

The amount of *t*–CA was determined using reverse phase HPLC (Shimadzu LC–10A) equipped with a Shimadzu UV–VIS diode array. Separations were performed on a 4.6×250 mm Shimadzu ODS–Ⅱ (5 μm) column at 40 °C. The elution program consisted of a linear gradient of a mixture of phosphoric acid buffer (pH 3.0)/methanol/2–propanol (75:20:5, v/v/v) and methanol delivered at a flow rate of 1 ml/min. The deaminated

product of phenylalanine by PAL, *t*–CA, was monitored at 280 nm, and compared with authentic *t*–CA in both retention time (13.9 min) and the UV spectra of the peak. *t*–CA was not detectable in the incubation mixture without substrate. The potency of inhibitory activity was represented by the IC_{50} value, which was defined as the concentration of the test compound that resulted in 50% inhibition of the peak areas of *t*–CA produced by PAL.

Treatment of potato tubers and determination of *t*–CA

Tubers of potato (*Solanum tuberosum*) were used as described by Matsuda *et al*. (2000). The tuber was cut into disks (8 mm in diameter and 2 mm thick), and washed with deionized water for 30 min. Five disks were treated with each amount of compound **19** dissolved in acetone (40 μl). After evaporation of the solvent at room temperature, 1 ml of a laminarin solution (1 mg/ml) was applied to the tuber disks in a Petri dish. The disks were incubated at 25˚C under wet and dark conditions for 24 and 48 hr. Five disks were combined and homogenized with 5 ml of methanol. After filtration of the homogenate, the filtrate was concentrated under reduced pressure, and saturated $NaHCO_3$ solution was added to the residue. The aqueous solution was washed twice with 8 ml of ethyl acetate and acidified by adding 10 ml of 2 M HCl. *t*–CA was extracted twice with ethyl acetate. The combined ethyl acetate solution was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in 1 ml of methanol and the amount of *t*–CA was determined by HPLC according to the method used in enzyme assays.

Lettuce seedling test

Onto two sheets of filter paper placed on the bottom of a Petri dish of 6 cm in diameter was poured 1 ml of acetone solution of the test compound. After evaporation of the solvent, 5 ml of deionized water was poured into the dish, and 10 seeds of the lettuce (*Lactuca sativa* cv Sacramento) were placed in it. Plants were maintained at 25˚C in 12 hr photoperiod for 4 days. Inhibitory activity of compounds was evaluated by inspecting the rate of growth of the hypocotyls and radicles. The activity rates was expressed as symbols of – to +++, corresponding to 0–24, 25–49, 50–74 and over 75% growth inhibition.

RESULTS AND DISCUSSION

We first examined inhibitory activity of known PAL inhibitors such as *p*–coumaric acid, AOA and Z302 against PAL derived from *R. glutinis* under experimental conditions used in this study (Table 1). Z302 significantly inhibited this PAL with an IC_{50} value of 4.8 μM, which was similar to that reported by Ogawa and Amagasa (1998). *p*–Coumaric acid and AOA did not show strong inhibitory activity. Sato *et al*. (1982) have reported that *p*–coumaric acid inhibited *R. glutinis* PAL by 87% at 1 mM, which was the same order of magnitude as that obtained in this study.

Table 1. PAL inhibitory activity of *p*–coumaric acid, AOA and Z302

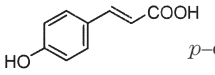
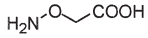
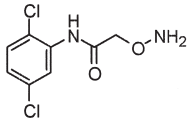
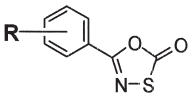
Compound		IC_{50} (μM)
	*p*–coumaric acid	240
	AOA	330
	Z302	4.8

Table 2. Biological activity of 5–aryl–1,3,4–oxathiazol–2–ones

		PAL inhibition *in vitro*	Growth inhibition against lettuce seedlings		
No	**R**	IC_{50} (μM)	500	250	100 (μM)
1	H	8.0	+++	++	–
2	2–F	6.5	X	+++	++
3	3–F	8.5	+	–	–
4	4–F	8.7	X	+	–
5	2–Cl	6.2	X	X	+++
6	3–Cl	9.5	+++	++	+
7	4–Cl	4.9	++	–	–
8	2–Br	7.3	X	X	+++
9	3–Br	7.2	++	++	+
10	4–Br	6.0	–	–	–
11	2–CH_3	13.0	+++	+++	–
12	3–CH_3	12.6	X	X	++
13	4–CH_3	11.8	X	+++	+
14	2–OCH_3	12.4	+++	++	–
15	3–OCH_3	10.3	++	++	+
16	4–OCH_3	8.7	+	+	–
17	2–NO_2	3.5	+++	+++	++
18	3–NO_2	3.6	+++	+++	++
19	4–NO_2	2.5	+++	+++	++
20	2–CF_3	8.1	+++	+	–
21	3–CF_3	8.1	+++	+++	+++
22	4-CF_3	10.1	+++	+++	++

Growth inhibition: X; no germination, +++; over 75%, ++; 74–50%, +; 49–25%, –; below 24%.

Table 2 shows inhibitory activity of 5–aryl–1,3,4–oxathiazol–2–ones against PAL from *R. glutinis*. All of the synthesized compounds showed much stronger inhibitory activity than *p*–coumaric acid and AOA. The phenyl analog **1** was about 2–fold less active than Z302. The fluorophenyl analogs (**2**–**4**) had the almost same activity as that of **1**. Introducing a chloro substituent at the *meta* position (**6**) decreased the inhibitory activity, while the 4–chlorophenyl analog **7** showed activity comparable to Z302. The inhibitory activity of the bromophenyl analogs (**8**–**10**) was found to slightly increase

in comparison with that of the phenyl analog **1**, but less active than Z302. The introduction of a methyl (**11**–**13**) or a methoxy (**14**–**16**) substituent on the benzene ring irrespective of its position resulted in decrease of activity, indicating that an electron–donating group is unfavorable for activity. Strong inhibitory activity was exhibited by the nitrophenyl analogs (**17**–**19**), which showed stronger activity than Z302. In particular, the 4–nitrophenyl analog **19** was the most active of the compounds tested on PAL from *R. glutinis*, showing 2 times stronger activity than Z302. It is noteworthy that a nitro group on the benzene ring irrespective of its position enhanced the activity compared with unsubstituted phenyl analog **1**. The introduction of a strong electron–withdrawing trifluoromethyl group on the benzene ring (**20**–**22**) did not lead to an enhancement of inhibitory activity. These results suggest that PAL inhibitory activity of 5–aryl–1,3,4–oxathiazol–2–ones is not significantly influenced by the electron distribution on the benzene ring.

The Lineweaver–Burk plots for the inhibition of PAL by compound **19** showed that it was a noncompetitive inhibitor (Fig. 2), suggesting that **19** binds to a site distinct from the phenylalanine binding site.

Since compound **19** was found to strongly inhibit PAL from *R. glutinis in vitro*, we examined the effect of **19** on plants. The expected impact of the inhibition of PAL *in vivo* is a decrease in the formation of downstream metabolites in the phenylpropanoid pathway such as *t*–CA or *p*–coumaric acid. To see whether compound **19** decreased *t*–CA, we conducted experiments using potato tubers, in which the phenylpropanoid pathway is known to be activated by an oligosaccharide elicitor (Matsuda *et al*., 2000). No significant accumulation of *t*–CA was observed in potato tuber disks immediately after treatment. In the presence of the elicitor, laminarin, the level of *t*–CA in the acetone–treated control increased to about 0.2 μg per potato tuber disk 24 hr after treatment (Fig. 3). The amount of *t*–CA decreased in control disks after 48 hr. When compound

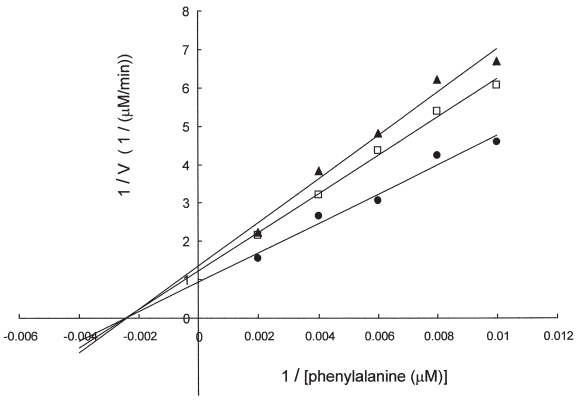


Fig. 2. Lineweaver–Burk plots for the inhibition of PAL by compound **19**. The substrate concentrations were 100, 125, 167, and 500 μM. The concentrations of inhibitor were 0 (●), 10 (□), and 20 μM (▲). Values are expressed as the means of triplicate experiments.

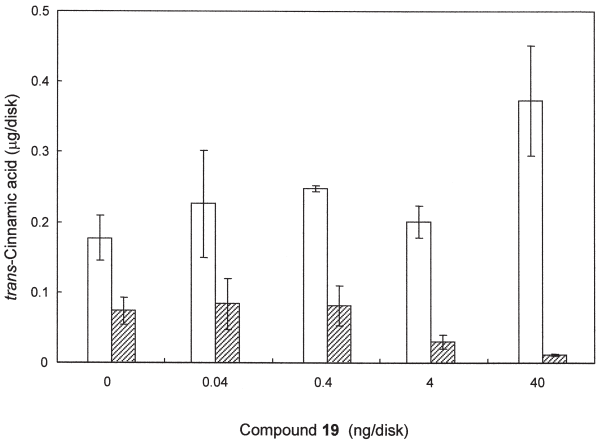


Fig. 3. Effect of compound **19** on the *t*–CA content of potato tuber disks. The applied doses of the inhibitor were 0.04, 0.4, 4 and 40 ng/disk. *t*–CA was extracted after 24 (white bars) and 48 hr (hatched bars) of incubation. Data represent the averages of three experiments.

19 was applied to the disks at a wide range of doses (0.04–40 ng/disk) in the presence of the elicitor, there was no significant difference between control and treated disks in the *t*–CA content after 24 hr. However, after 48 hr the amount of *t*–CA diminished in potato tuber disks treated with higher doses (4 and 40 ng) of **19**. In this case the accumulation of *t*–CA was inhibited by **19** in a dose dependent manner.

We further examined the effect of 5–aryl–1,3,4–oxathiazol–2–ones on the growth of lettuce seedlings (Table 2). Most of the compounds showed growth inhibitory activity at 100–500 μM. In halogen–substituted phenyl analogs, the activity increased by the introduction at the *ortho* position. Especially, the 2–chlorophenyl (**5**) and 2–bromophenyl (**8**) analogs completely inhibited germination at 250 μM and exhibited the most potent activity. Compound **12** with a methyl substituent at the *meta* position of phenyl group showed activity comparable to compounds **5** and **8**, while the 2–methylphenyl analog **11** was less active. Although there was no apparent correlation between PAL inhibitory activity of 5–aryl–1,3,4–oxathiazol–2–ones and growth inhibitory activity against lettuce seedlings, the nitrophenyl analogs (**17**–**19**), which strongly inhibited PAL from *R. glutinis*, caused more than 50% inhibition of seedling growth at 100 μM.

In conclusion, 5–aryl–1,3,4–oxathiazol–2–ones represent a structurally novel class of potent PAL inhibitors and this series of compounds is worthy of further investigation for development of new plant growth regulators or herbicides.

REFERENCES

Amrhein, N. and K.–H. Godeke 1977 α–Aminooxy– β–phenylpropionic acid – A potent inhibitor of L–phenylalanine ammonia–lyase *in vitro* and *in vivo*. *Plant Sci. Lett*., **8**: 313–317

Brownsort, P. A. and R. M. Paton 1987 Nitrile Sulphides. Part 7. Synthesis of [1]benzopyrano[4,3–c]isothiazoles and isothiazolo [4,3–c]quinolines. *J. Chem. Soc. Perkin Trans. 1*, 2339–2344

Hoagland, R. E. 1985 *O*–Benzylhydroxylamine: An inhibitor of phenylpropanoid metabolism in plants. *Plant Cell Physiol*., **26**: 1353–1359

Hohlbrock, K. and D. Scheel 1989 Physiology and molecular biology of phenylpropanoid metabolism. *Annu. Rev. Plant Physiol. Plant Mol. Biol*., **40**: 347–369

Howe, R. K., T. A. Gruner, L. G. Carter, L. L. Black and J. E. Franz 1978 Cycloaddition reactions of nitrile sulfides with acetylenic esters. Synthesis of isothiazolecarboxylates. *J. Org. Chem*., **43**: 3736–3742

Matsuda, F., H. Miyagawa and T. Ueno 2000 β –1,3–Glucooligosaccharide induced activation of four enzymes responsible for *N*–*p*–coumaroyloctopamine biosynthesis in potato (*Solanum tuberosum* cv.) tuber tissue. *Z. Naturforsch*., **55c**: 373–382

Ogawa, M. and T. Amagasa 1998 Plant growth–regulating activities of aminooxyacetate derivatives. *Chemical Regulation of Plants (in Japanese)*, **33**: 62–72

Sato, T., F. Kiuchi and U. Sankawa 1982 Inhibition of phenylalanine ammonia–lyase by cinnamic acid derivatives and related compounds. *Phytochemistry*, **21**: 845–850

Zon, J., N. Amrhein and R. Grancarz 2002 Inhibitors of phenylalanine ammonia–lyase: 1–aminobenzylphosphonic acids substituted in the benzene ring. *Phytochemistry*, **59**: 9–21