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Synthesis and Structure−Activity Relationships of Substituted Cinnamic Acids and Amide Analogues: A New Class of Herbicides

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In the present investigation, substituted cinnamic acids (3-hydroxy, 4-hydroxy, 2-nitro, 3-nitro, 4-nitro, 3-chloro, and 4-methoxy) and their amide analogues with four different types of substituted anilines have been synthesized. The synthesized compounds have been screened for their germination inhibition activity on radish (*Raphanus sativus* L. var. Japanese White) seeds at 50, 100, and 200 ppm concentrations, and the activity was compared with standard herbicide, metribuzin formulation (sencor). Significant activity was exhibited by all of the compounds. It was observed that with the increase in concentration of the test solution, the activity also increased. All of the compounds showed more than 70% inhibition at 100 ppm concentration except 4-hydroxy cinnamanilide. The compound, 2-chloro (4′-hydroxy) cinnamanilide was the best among the tested compounds, and it was found to be at par with the standard, metribuzin at all concentrations. Thus, it can be concluded that substituted cinnamic acids and their amide analogues may be developed as potential herbicides.

KEYWORDS: Substituted cinnamic acids; cinnamic acid amide analogues; radish (*Raphanus sativus* L.); metribuzin; germination inhibition activity

INTRODUCTION

Substituted cinnamic acids are widely distributed in the plant kingdom and are found in coffee beans, olives, propolis, fruits, and vegetables. They are found usually as simple derivatives including amide, esters, sugar esters, and glycosides (*1*). Hydroxycinnamic acid esters are widely distributed in the plant kingdom and are reported as cellular antioxidants, anti-inflammatory agents, or inhibitors of enzymes involved in cell proliferation, and some biological activities (*2–4*).

Weeds compete with crops for sunshine, water, nutrients, and space and thus influence the growth of crops and undermine both crop quality and yield. Since the discovery of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) by Zimerman and Hithcock, the agrochemical industry has successfully developed a wide range of herbicides with various chemical structures and modes of actions (*5*). But the main problem associated with the use of herbicides is the occurrence of herbicide resistant weeds. According to one estimate, worldwide at least 315 weed biotypes, 183 weed species including 110 dicots and 73 monocots have been reported to have acquired resistance to important herbicides (*6*). Therefore, it is necessary to develop efficient herbicides with novel structures and modes of actions to overcome the resistance of weeds. During the past three decades, efforts have been focused on discovering new allelochemicals with potential application in weed management (*7*). The biocides developed from allelochemicals have important advantages with respect to traditional herbicides, fungicides, or insecticides since they have novel modes of action, high biodegradability, and low environmental impact (*8*). The three main groups of allelochemicals that have been identified in wheat are phenolic acids (*9, 10*), hydroxamic acids (*11−14*), and short chain fatty acids (*15, 16*). Phenolic acids and hydroxamic acids are produced by living wheat plants and either exuded by the plants or released following the degradation of plant material, whereas short chain fatty acids are secondary products produced by anaerobic fermentation of polysaccharides.

The two hydroxamic acids found most abundantly in wheat, 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA) and 2,4-dihydroxy-1,4-benzoxazin-3-one (DIBOA), have been studied extensively ranging from their isolation to synthetic analogues (*17−21*), whereas phenolic acids have been studied either for their joint allelochemical effects with hydroxamic acids (*22*) or for joint action of their mixtures. Studies show contrasting results. Reigosa et al. (*23*) reported additive effects of phenolic acids, whereas Inderjit et al. (*24*) have found mostly antagonistic interactions between phenolic acids. In contrast, Einhellig et al. (*25−27*) have reported synergistic effects with a mixture of phenolic acids. This discrepancy in results may be due to the use of different statistical methods or allelochemicals actually exhibiting variable activity.

The mode of action of wheat alleochemicals is not fully understood. Einhellig (*28*) and Blum et al. (*29*) have suggested that phenolic acids depolarized the cell membrane, affecting membrane ATPase activity and ion flux.

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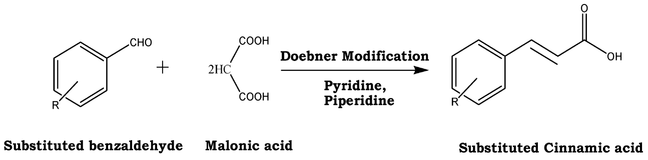
Scheme 1. Synthesis of Substituted Cinnamic Acids



Substituents-

a. R = 3-hydroxy
b. R = 4-hydroxy
c. R = 2-nitro
d. R = 3-nitro
e. R = 4-nitro
f. R = 3-chloro
g. R = 4-methoxy

A literature survey shows that phenolics, specificially having the cinnamic acid moiety, have not been studied extensively by synthesizing their analogues and determining the activity. To the best of our knowledge, we are the first to report the herbicidal activity in cinnamic acid derivatives. Therefore, the objectives of the present study were to synthesize some substituted cinnamic acids and their amide analogues to determine their activity. This work is in continuation of our program to search potential and novel compounds with promising herbicidal activity.

EXPERIMENTAL PROCEDURES

General. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. UV spectra were taken on a Genesys 10 UV−vis spectrophotometer, ^{1}H NMR spectra were recorded on a Bruker Avance 400 NMR spectrophotometer, and IR spectra were recorded on a Bruker IR spectrophotometer. The chemicals used in the present study, 3-hydroxy benzaldehyde, 4-hydroxy benzaldehyde, 2-nitro benzaldehyde, 3-nitrobenzaldehyde, 4-nitro benzaldehyde, 3-chlorobenzaldehyde, 4-methoxy benzaldehyde, malonic acid, piperidine, aniline, 2-chloro aniline, 4-nitro aniline, and 4-methyl aniline, were purchased from M/S Sigma-Aldrich Chemical Co. (USA), and pyridine, triethylamine, and phosphorus oxychloride were purchased from M/S Merck India Chemicals Company. Metribuzin (Sencor 70 WP) was obtained from M/S Bayer AG, Germany. All of the chemicals were of AR grade. The radish (*R. sativus* L. var. Japanese White) seeds were obtained from Vegetable Research Centre, G. B. Pant University of Agriculture and Technology, Pantnagar, India.

Preparation of Substituted Cinnamic Acids. The substituted cinnamic acids were synthesized using Doebner−Knoevenagel modification (*30*). Cinnamic acids were prepared by mixing substituted benzaldehydes (60 mM), malonic acid (100 mM), pyridine (20 mL), and piperidine (0.8 mL) together and stirring on a magnetic stirrer for 4 days (**Scheme 1**). The reaction progress was monitored over silica gel TLC plates. The reaction mixture was then poured in excess of diluted HCI. Precipitates obtained were filtered, washed with cold water repeatedly, and dried. The yields were between 70−98% (Chart 1, Supporting Information).

Preparation of Substituted Cinnamic Acid Amide Analogues. All of the amides were synthesized using the method described by Greenstein and Winitz (*31*). To a solution of acid (1.0 mM) in chloroform containing triethylamine (0.1 mL) and amino compound (1.2 mM) was added dropwise $POC1_3$ (2.0 mM) at 0 °C with constant stirring. Triethylamine (0.2 mM) was then added in one portion. The reaction mixture was stirred for another 30 min at low temperature and then poured into crushed ice; the organic phase separates out. The aqueous phase was extracted with dichloromethane, and combined layers were washed successively with diluted HC1, aqueous $NaHCO_3$, water and dried over anhydrous $CaCl_2$ (**Scheme 2**). Evaporation of solvent gave residues of varying colors, which were recrystallized from ethanol/chloroform (80:20). The yields were between 48−92% (Charts 2−5, Supporting Information).

Scheme 2. Synthesis of Amides of Substituted Cinnamic Acids

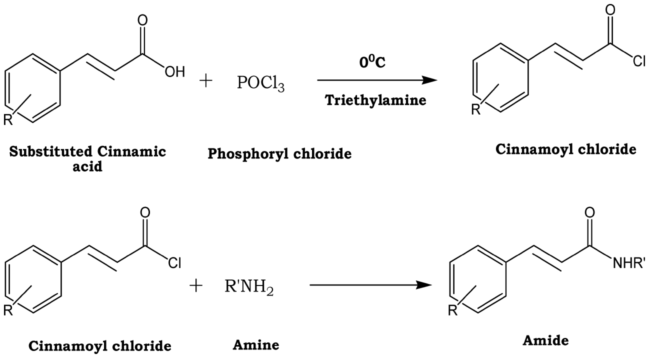


Table 1. Mean Percent Seed Germination Inhibition Values of Substituted Cinnamic Acids

	mean percent inhibition values			
name of the compounds	50 ppm	100 ppm	200 ppm	CD at 5%
metribuzin (standard)	80.00	93.33	100.00	13.30
3-hydroxy cinnamic acid	56.66	86.66	100.00	9.40
4-hydroxy cinnamic acid	53.33	73.33	100.00	9.40
2-nitro cinnamic acid	70.00	86.66	100.00	6.65
3-nitro cinnamic acid	70.33	80.00	100.00	6.65
4-nitro cinnamic acid	70.00	93.33	96.66	6.65
3-chloro cinnamic acid	53.33	76.66	93.33	11.51
4-methoxy cinnamic acid	56.66	66.66	93.33	11.51
CD at 5%	10.59	9.34	4.99	

Bioassay. A bioassay based on seed germination was used to study seed germination inhibition activity of the synthesized compounds. Test solutions of concentration 50 ppm, 100 ppm, and 200 ppm were prepared by serial dilution of stock solution of 500 ppm of the compounds in ethanol. The test solutions of standard metribuzin (sencor) were also prepared by serial dilution in distilled water. Each compound was dissolved in a minimum amount of ethanol, which was suspended in distilled water with Tween-20 (3 mL/l). Seeds of radish (*R. sativus* L.) prior to sowing in Petri dishes (9 cm diameter) were surface sterilized with distilled water followed by 95% ethanol for 15 s and finally with distilled water. Ten seeds were taken in each Petri dish. Double layered filter paper was placed in the Petri dishes on which 7 mL of each test solution was poured. A mixture of distilled water/ethyl alcohol/Tween-20 (97: 2.5: 0.5) was taken as the control. All treatments were replicated three times with CRD fashion. The radish seeds were allowed to germinate at 25 ± 2 °C in an incubator with 12 h of photoperiod. The seed germination process was observed after five days of incubation and seeds were considered to be germinated when the protrusion of radical was evident (*32*). After 120 h, the number of seeds germinated in each Petri dish was counted, and percent seed germination inhibition values were calculated.

Statistical Analysis. The percent seed germination inhibition values were determined and subjected to analysis of variance (ANOVA). Critical differences (CDs) were calculated at $p \leq 0.05$.

RESULTS AND DISCUSSION

Synthesis. Spectral analysis of two cinnamic acid intermediates (3-chloro and 4-methoxy cinnamic acid) and one of the amides (3-chloro cinnamanilide) was carried out. The structure of substituted cinnamic acids and their amides are displayed in Figures 1 and 2 in Supporting Information.

Seed Germinatin Inhibition Activity. Percent seed germination inhibition values of compounds at different concentrations are given in **Tables 1** and **2**. Perusal of **Table 1** clearly indicates that there is significant increase in mean percent inhibition values with increasing concentrations. Activities of 2-nitro cinnamic acid, 3-nitro cinnamic acid, and 4-nitro cinnamic acid are at par with the standard at all concentrations, whereas 4-hydroxy cinnamic acid was found at par with the standard only at 200 ppm.

Table 2. Mean Percent Seed Germination Inhibition Values of Substituted Cinnamanilides

	mean percent inhibition values			
name of the compounds	50 ppm	100 ppm	200 ppm	CD at 5%
metribuzin (standard)	80.00	93.33	100.00	13.30
3-hydroxy cinnamanilide	53.33	86.66	100.00	9.40
4-hydroxy cinnamanilide	50.00	63.33	96.66	14.87
2-nitro cinnamanilide	73.33	86.66	100.00	9.40
3-nitro cinnamanilide	70.00	73.33	100.00	6.65
4-nitro cinnamanilide	83.33	90.00	100.00	6.65
3-chloro cinnamanilide	70.00	93.33	100.00	6.65
4-methoxy cinnamanilide	53.33	76.66	93.33	11.51
CD at 5%	9.34	11.17	4.99	

Table 3. Mean Percent Seed Germination Inhibition Values of Substituted 2-Chloro Cinnamanilides

	mean percent inhibition values			
name of the compounds	50 ppm	100 ppm	200 ppm	CD at 5%
metribuzin (standard)	80.00	93.33	100.00	13.30
2-chloro-(3′-hydroxy) cinnamanilide	56.66	80.00	93.33	9.40
2-chloro-(4′-hydroxy) cinnamanilide	86.66	96.66	100.00	9.40
2-chloro-(2′-nitro) cinnamanilide	86.66	93.33	100.00	9.40
2-chloro-(3′-nitro) cinnamanilide	83.33	93.33	100.00	9.40
2-chloro-(4′-nitro) cinnamanilide	80.00	86.66	100.00	13.30
2-chloro-(3′-chloro) cinnamanilide	33.33	53.33	76.66	11.51
2-chloro-(4′-methoxy) cinnamanilide	76.66	83.33	96.66	11.51
CD at 5%	12.23	9.34	6.11	

Table 4. Mean Percent Seed Germination Inhibition Values of Substituted 4-Nitro Cinnamanilides

	mean percent inhibition values			
name of the compounds	50 ppm	100 ppm	200 ppm	CD at 5%
metribuzin (standard)	80.00	93.33	100.00	13.30
4-nitro-(3′-hydroxy) cinnamanilide	80.00	83.33	96.66	9.40
4-nitro-(4′-hydroxy) cinnamanilide	86.66	96.66	100.00	9.40
4-nitro-(2′-nitro) cinnamanilide	73.33	86.66	96.66	11.51
4-nitro-(3′-nitro) cinnamanilide	73.33	96.66	100.00	9.40
4-nitro-(4′-nitro) cinnamanilide	60.00	66.66	93.33	9.40
4-nitro-(3′-chloro) cinnamanilide	76.66	83.33	96.66	16.29
4-nitro-(4′-methoxy) cinnamanilide	76.66	96.66	100.00	9.40
CD at 5%	9.99	11.71	7.06	

Table 5. Mean Percent Seed Germination Inhibition Values of Substituted 4-Methyl Cinnamanilides

	mean percent inhibition values			
name of the compounds	50 ppm	100 ppm	200 ppm	CD at 5%
metribuzin (standard)	80.00	93.33	100.00	13.30
4-methyl-(3′-hydroxy) cinnamanilide	80.00	86.66	100.00	13.30
4-methyl-(4′-hydroxy) cinnamanilide	70.00	86.66	100.00	6.65
4-methyl-(2′-nitro) cinnamanilide	63.33	80.00	93.33	9.40
4-methyl-(3′-nitro) cinnamanilide	73.33	86.66	96.66	11.51
4-methyl-(4′-nitro) cinnamanilide	83.33	90.00	100.00	6.65
4-methyl-(3′-chloro) cinnamanilide	70.00	83.33	93.33	9.40
4-methyl-(4′-methoxy) cinnamanilide	70.00	93.33	100.00	6.65
CD at 5%	10.59	8.65	6.11	

Electron withdrawing groups on the benzene ring of acids tend to increase the activity as is evident from the higher values exhibited by 2-nitro cinnamic acid, 3-nitro cinnamic acid, and 4-nitro cinnamic acid, whereas electron donating groups (-OH and -OCH_3) on the benzene ring decrease the activity. This trend is more prominent at lower concentrations, i.e., 50 ppm. At higher concentration, there is no correlation between the presence of electron withdrawing/electron donating groups and activity.

In **Table 2**, seed germination inhibition values of amide derivatives prepared by aniline and substituted cinnamic acids are given. The seed germination inhibition values are found to increase significantly with increasing concentrations, except for 3-nitro cinnamanilide for which activity at 50 ppm and 100 ppm is at par. At 50 ppm concentration, 2-nitro cinnamanilide and 4-nitro cinnamanilide exhibit activity at par with standard metribuzin. At 50 ppm concentration, higher values of activity are observed in the case of amide derivatives having $-NO_2$ and $-$Cl group substituents at the benzene ring of the acid moiety, and lower values are observed for amide derivatives containing substituents -OH and -OCH_3 on the benzene ring of the acid moiety.

In **Table 3**, the data of seed germination inhibition activity of amide derivatives of substituted cinnamic acids with *o*-chloro aniline are presented. The seed germination inhibition values of all of the compounds increase significantly with increase in concentration. The activities of 2-chloro-(4′-hydroxy) cinnamanilide, 2-chloro-(2′-nitro) cinnamanilide, 2-chloro-(3′-nitro) cinnamanilide, 2-chloro-(4′-nitro) cinnamanilide, and 2-chloro-(4′-methoxy) cinnamanilide are at par with that of standard metribuzin at all concentrations. Here, the effect of the presence of the electron withdrawing group ($-NO_2$ and $-$Cl) and electron donating groups (-OH and -OCH_3) on the benzene ring of the acid moiety cannot be correlated with the activity. Here, the effect of electron withdrawing group $-$Cl on the benzene ring of the amine moiety seems to have an overriding electronic effect that decides the activity.

The seed germination inhibition activity data of amide derivatives of substituted cinnamic acids with *p*-nitro aniline is displayed in **Table 4**. At 50 ppm concentration, 4-nitro-(3′-hydroxy) cinnamanilide, 4-nitro-(4′-hydroxy) cinnamanilide, 4-nitro-(3′-chloro) cinnamanilide, and 4-nitro-(4′-methoxy) cinnamanilide exhibit seed germination inhibition activity at par with the standard. The 4-nitro-(2′-nitro) cinnamanilide, 4-nitro-(3′-nitro) cinnamanilide, and 4-nitro-(4′-nitro) cinnamanilide are showing less activity due to the presence of the $-NO_2$ group on the benzene ring of the amine moiety. We have already discussed that the presence of different substituents on the benzene ring of the amine moiety increases the activity, but in this class of amides, the trend is reversed. The reversal in trend may be due to the presence of the $-NO_2$ group at fourth position in the benzene ring of the amine moiety. It seems that the presence of the electron withdrawing group on the benzene ring of the amine moiety is the overriding factor in deciding the electronic effect that is responsible for the activity.

In **Table 5**, seed germination inhibition values of substituted cinnamic acids with *p*-methyl aniline are recorded. Perusal of the table reveals that at 50 ppm concentration only 4-methyl-(3′-hydroxy) cinnamanilide, 4-methyl-(3′-nitro)cinnamanilide, and 4-methyl-(4′-nitro) cinnamanilide are at par with the standard. There is no definite trend observed in activity.

Higher values are attributed to the presence of electron withdrawing groups, and lower values due to presence of electron donating groups. It is clear from these results that activity is considerably affected by electronic effects. At higher (100 and 200 ppm) concentration, these electronic effects do not give a clear trend of activity. This may be due to the fact that most of the compounds of these two bear limiting activity; therefore, differentiation in activity cannot be established on the basis of electronic effects. But this does not mean that the electronic effect is not playing its role in deciding the activity.

Comparison of activity of the compounds with the standard clearly indicates that all of the compounds except 4-methoxy cinnamanilide are at par with the standard metribuzin at 200 ppm concentration, while at 100 ppm concentration, 3-hydroxy cinnamanilide, 2-nitro cinnamanilide, 4-nitro cinnamanilide, and 3-chloro cinnamanilide are at par with the standard, and at 50 ppm, only 2-nitro cinnamanilide and 4-nitro cinnamanilide are at par with the standard herbicide.

Omokawa et al. (*33*) have tried to establish the structure–herbicidal activity relationship of α-phenylsulfonyl propanamide. Effect of substituents at the aromatic moiety of the compounds was studied in which the compounds substituted with the alkyl group (electron donating group) were found to remarkably increase the activity. In pyrazole-4-carboxamide derivatives, Ohno et al. (*34*) have correlated the effect of substituents on the benzene moiety of the compound with herbicidal activity. Some substituents (alkyl and halogens) have been found to increase activity, but a clear trend was not observed.

Kawamura et al. (*35*) investigated that in 2,4-diarylpyrimidines, substituents in two phenyl rings are very important for activity. For one phenyl ring at the pyrimidine 4-position, a meta substituent enhanced herbicidal activity, while ortho or para substituents gave a reduction or complete loss of activity.

All of the tested compounds have been found to exhibit promising seed germination inhibition activity. The compound 2-chloro (4′-hydroxy) cinnamanilide was found to have excellent activity, which is at par with the standard, metribuzin. The compounds, 2-chloro (3′-nitro) cinnamanilide, 2-chloro (2′-nitro) cinnamanilide, and 4- nitro cinnamanilide, have also been shown promising herbicidal activity. Therefore, we can conclude that substituted cinnamic acids and their amide analogues can be developed as a new class of herbicides.

Analytical and Spectral Characterization Data. *3-Chloro Cinnamic Acid.* M.P. 191 °C; yield 95.2%. λ_{max} (nm)/DCM, 274. IR υ_{max} (cm^{-1}, KBr): 3075.4, 2881.7, 1696.9, 1638, 1596, 1476.4, 1303.7, 980.8, 749.8. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.43 (1H, d, $J = 16$ Hz, -CH=CH-), 7.64 (1H, d, $J = 16$ Hz, -CH=CH-), 7.94 (1H, s, H-2), 7.35 (m, benzene ring).

4-Methoxy Cinnamic Acid. M.P. 174 °C; yield 78.4%. λ_{max} (nm)/DCM, 304. IR υ_{max} (cm^{-1}, KBr): 3400–3300, 3110–3075, 2937, 1686.9, 1622.8, 1596, 1476.5, 1414.6, 1315.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.28 (1H, d, $J = 16$ Hz, -CH=CH-), 7.57 (1H, d, $J = 16$ Hz, -CH=CH-), 3.81 (3H, s), 7.48 (2H, Ar, d, $J = 13$ Hz, H-3, H-5), 6.90 (2H, Ar, d, $J = 14.5$ Hz, H-2, H-6).

3-Chloro Cinnamanilide. M.P. 110 °C; yield 81.2%. λ_{max} (nm)/DCM, 283. IR υ_{max} (cm^{-1}, KBr): 3289.6, 3125.4, 3058.6, 1657.4, 1627, 1565, 1472, 1441.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.45 (1H, d, $J = 16$ Hz, -CH=CH-), 7.64 (1H, d, $J = 16$ Hz, -CH=CH-), 7.97 (1H, s br, -NH), 7.6 (m, benzene ring).

4-Nitro-(3′-chloro) Cinnamanilide. M.P. 168 °C; yield 87.8%. λ_{max} (nm)/DCM, 265. IR υ_{max} (cm^{-1}, KBr): 3356.6, 2984.7, 1696.4, 16321.7, 1475.7, 1401, 1304. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.45 (1H, d, $J = 16$ Hz, -CH=CH-), 7.68 (1H, d, $J = 16$ Hz, -CH=CH-), 5.52 (1H, s br, -NH), 6–8 (m, benzene ring).

4-Methyl-(3′-chloro) Cinnamanilde. M.P. 194 °C; yield 89.4%. λ_{max} (nm)/DCM, 253. IR υ_{max} (cm^{-1}, KBr): 3236, 2938.7, 1664, 1550, 1402, 1343. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.75 (1H, d, $J = 16$ Hz, -CH=CH-), 7.64 (1H, d, $J = 16$ Hz, -CH=CH-), 6.30 (3H, s, $-CH_3$).

2-Chloro-(3′-chloro) Cinnamanilide. M.P. 119 °C; yield 68.6%. λ_{max} (nm)/DCM, 274. IR υ_{max} (cm^{-1}, KBr): 3287, 2987.7, 1758, 1660.6, 1589, 1536, 1439.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.6 (1H, d, $J = 16$ Hz, -CH=CH-), 7.7 (1H, d, $J = 16$ Hz, -CH=CH-), 6.19 (1H, s br, -NH).

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Supporting Information Available: Synthesis of substituted cinnamic acids, substituted cinnamic acids with aniline, substituted cinnamic acids with *o*-chloro aniline, substituted cinnamic acids with *p*-nitro aniline, substituted cinnamic acids with *p*-methyl aniline, and structures of substituted cinnamic acids, substituted cinnamanilides, substituted 2-chloro cinnamanilides, substituted 4-nitro cinnamanilides, and substituted 4-methyl cinnamanilides. This material is available free of charge via the Internet at http://pubs.acs.org.

LITERATURE CITED

(1) Kavitha, J.; Vanisree, M.; Subbaraju, G. V. Synthesis of O-geranylconiferyl alcohol, a metabolite of *Fagara rhetza*. *Indian J. Chem.* **2000**, *40*, 522–523.

(2) Chan, R. I.; San, R. H.; Stich, H. F. Mechanisim of inhibition of N-methyl-N′-nitro-N-nitrosoguanidine-induced mutagenesis by phenolic compounds. *Cancer Lett.* **1986**, *31* (1), 27–34.

(3) Chen, H.; Muramato, K.; Yamauchi, F.; Nokihara, K. Antioxidant activity of designed peptides based on the antioxidative peptides isolated from digests of a soybean protein. *J. Agric. Food Chem.* **1996**, *44* (9), 2619–2623.

(4) Laranjinha, J.; Vierira, O.; Almeida, L.; Madeira, V. Inhibition of metmyoglobin/H_2O_2-dependent low density lipoprotein lipid peroxidation by naturally occurring phenolic acids. *Biochem. Pharmacol.* **1996**, *51* (4), 395–402.

(5) Böger, P.; Wakabayashi, K.; Hirai, K. Herbicide Class. In *Development, Mode of Action, Targets, Genetic Engineering, Chemistry*; Springer-Verlag: Berlin, Germany, 2002; pp 364.

(6) Heap, I. International Survey of Herbicide Resistant Weeds. http://www.weedscience.org (accessed Nov 29, 2007).

(7) Macias, F. A. In *Allelopathy: Organism, Processes and Applications*; Dakshini, K. M. M., Einhellig, F. A., Eds.; ACS Symposium Series 582; American Chemical Society: Washington, DC, 1995.

(8) Rice, E. L. *Biological Control of Weeds and Plant Diseases*, University of Oklahoma Press: Norman, U.K., 1995.

(9) Blum, U.; Wentworh, T. R.; Klein, K.; Worsham, A. D.; King, L. D.; Gerig, T. M.; Lyu, S. W. Phenolic acid content of soils from wheat-no till, wheat-conventional till and fallow-conventional till soybean cropping systems. *J. Chem. Ecol.* **1991**, *17*, 1045–1068.

(10) Wu, H.; Haig, T.; Pratley, J.; Lemerle, D.; An, M. Allelochemicals in wheat (*Triticum aestivum* L.): Variation in phenolic acids in short tissues. *J. Chem. Ecol.* **2001**, *27*, 125–135.

(11) Wu, H.; Haig, T.; Pratley, J.; Lemerle, D.; An, M. Distribution and exudation of allelochemicals in wheat *Triticum aestivumJ. Chem. Ecol.* **2000**, *26*, 2141–2154.

(12) Niemeyer, H. Hydroxamic acids (4-hydroxy-1, 4-benzoxazin-3-ones) defence. Chemicals in Gramineae. *Phytochemistry* **1988**, *27*, 3349–3358.

(13) Copaja, S. V.; Nicol, D.; Wratten, S. D. Accumulation of hydroxamic acids during wheat germination. *Phytochemistry* **1999**, *50*, 17–24.

(14) Wu, H.; Haig, T.; Pratley, J.; Lemerle, D.; An, M. Allelochemicals in wheat (*Triticum aestivum* L.): production and exudation of 2,4-dihydroxy-7-methoxy-1, 4-benzoxazin-3-one. *J. Chem. Ecol.* **2001**, *27*, 1691–1700.

(15) Lynch, J. M. Production and phytotoxicity of acetic acid in anaerobic soils containing plant residues. *Soil Biol. Biochem.* **1978**, *56*, 503–510.

(16) Tang, C. S.; Waiss, A. C. Short Chain fatty acids as growth inhibitors in decomposing wheat straw. *J. Chem. Ecol.* **1978**, *4*, 225–232.

(17) Regina, G. B.; Karl, H. Differential exudation of two benzoxazinoids: One of the determining factors for seedling allelopathy of triticeae species. *J. Agric. Food Chem.* **2005**, *53*, 250–261.

(18) Macias, F. A.; Marin, D.; Alberto, O. P.; Castellano, D.; Simonet, A. M.; Jose, M. G. M. Structure-activity relationship (SAR) studies of Benzoxazinones, their degradation products and analogues. Phytotoxicity on problematic weeds *Avena fatua* L. and *Lolium rigidum* Gaud. *J. Agric. Food Chem.* **2006**, *54*, 1040–1048.

(19) Hansen, L. M. Effect of 6-methoxy benzoxazolin-2-one (MBOA) on the reproduction rate of the grain aphid (*Sitobion avenae* F.). *J. Agric. Food Chem.* **2006**, *54*, 1031–1035.

(20) Macias, F. A.; Marin, D.; Bastidas, A. O.; Chinchilla, D.; Simonet, A. M.; Jose, M. G. M. Isolation and synthesis of allelochemicals from Gramineae: Benzoxazinones and related compounds. *J. Agric. Food Chem.* **2006**, *54*, 991–1000.

(21) Villagrasa, M.; Guillamon, M.; Labandeira, A.; Taberner, A.; Eljarrat, E.; Barcelo, D. Benzoxazinoid allelochemicals in wheat: Distribution among foliage, roots and seeds. *J. Agric. Food Chem.* **2006**, *54*, 1009–1015.

(22) Jia, C.; Kudsk, P.; Mathiassen, S. K. Joint action of benzoxazinone derivatives and phenolic acids. *J. Agric. Food Chem.* **2006**, *54*, 1049–1057.

(23) Reigosa, M. J.; Sonto, X. C.; Gonzales, L. Effect of phenolic compounds on the germination of six weed species. *Plant Growth Regul.* **1999**, *28*, 83–88.

(24) Inderjit; Streibig, J. C.; Olofrdotter, M. Joint action of phenolic acid mixtures and its significance in allelopathy research. *Physiol. Plant* **2002**, *114*, 422–428.

(25) Einhellig, F. A.; Rasmussen, J. A. Synergistic inhibitory effects of vanillic and p-hydroxy benzoic acids on radish and grain sorghum. *J. Chem. Ecol.* **1978**, *4*, 425–436.

(26) Ramussen, J. A.; Einhellig, F. A. Inhibitory effects of combination of three phenolic acids on grain sorghum germination. *Plant Sci. Lett.* **1979**, *14*, 69–74.

(27) Einhellig, F. A.; Schon, M. K.; Rasmussen, J. A. Synergistic effects of four cinnamic acid compounds on grain sorghum. *J. Plant Growth Regul.* **1982**, *1*, 251–258.

(28) Einhellig, F. A. Mechanism of Action of Allelochemicals in Allelopathy. In *Allelopathy. Organism, Processes and Applications*; Dakshini, K. M. M., Einhiellig, F. A., Eds.; American Chemical Society: Washington, DC, 1995; pp 96−116.

(29) Blum, U.; Shafer, S.; Lehman, M. Evidence for inhibitory interaction involving phenolic acids in field soil: concepts vs experimental model. *Crit. Rev. Plant Sci.* **1999**, *18*, 673–693.

(30) Furniss, B. S.; Hannaford, H. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Text Book of Practical Organic Chemistry*, Vth ed.; ELBS; Bath Press Ltd.: U.K., 1989; pp 1040.

(31) Greenstein, J. P.; Winitz, M. In *Chemistry of the Aminoacid*; John Wiley: New York, 1961; Vol. II, pp 1009.

(32) Bewley, D.; Black, M. *Seeds: Physiology of Development and Germination*; Plenum Press: New York, 1985.

(33) Omokawa, H.; Ichizen, N.; Tabogami, S.; Takamatsu, T. Structure-herbicidal activity relationship of α-phenylsulfonyl propanamide. *Agric. Biol. Chem.* **1985**, *49*, 3551–3555.

(34) Ohno, R.; Watanabe, A.; Matsukawa, T.; Ueda, T.; Sakurai, H.; Hori, M.; Hirai, K. Synthesis and herbicidal activity of new pyrazole-4-carboxamide derivatives. *J. Pestic. Sci.* **2004**, *29*, 15–26.

(35) Kawamura, S.; Sato, J.; Hamada, T.; Sakai, M.; Sanemitsu, Y. Synthesis and herbicidal activity of some 2,4-diarylpyrimidines. *J. Agric. Food Chem.* **1993**, *41*, 288–291.

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