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Hydroxamic Acids Derived from 2-Hydroxy-2*H*-1,4-Benzoxazin-3(4*H*)-one: Key Defense Chemicals of Cereals

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Many cereals accumulate hydroxamic acids derived from 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one. These benzoxazinoid hydroxamic acids are involved in defense of maize against various lepidopteran pests, most notably the European corn borer, in defense of cereals against various aphid species, and in allelopathy affecting the growth of weeds associated with rye and wheat crops. The role of benzoxazinoid hydroxamic acids in defense against fungal infection is less clear and seems to depend on the nature of the interactions at the plant−fungus interface. Efficient use of benzoxazinoid hydroxamic acids as resistance factors has been limited by the inability to selectively increase their levels at the plant growth stage and the plant tissues where they are mostly needed for a given pest. Although the biosynthesis of benzoxazinoid hydroxamic acids has been elucidated, the genes and mechanisms controlling their differential expression in different plant tissues and along plant ontogeny remain to be unraveled.

KEYWORDS: Hydroxamic acids; benzoxazin-3-ones; benzoxazolinones; cereals; allelopathy; defense; European corn borer; cereal aphids; cereals; Gramineae; Poaceae; secondary metabolites

INTRODUCTION

Cereals are the most important crops worldwide. The study of their natural defense systems against pests, diseases and weeds has been the subject of numerous studies. Many cereals such as maize, wheat, and rye (but not rice, oat, barley, and sorghum) produce secondary metabolites containing the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton (**Figure 1**), the most active of which occur as hydroxamic acids, i.e., they possess a hydroxyl group bound to the heterocyclic nitrogen atom. Since their discovery over 50 years ago, some 550 papers have been published on different aspects of their chemistry and biology and the rate of publication has increased continuously (**Figure 2**). Benzoxazinoid hydroxamic acids are present in the plant mainly as glucosides which are hydrolyzed to the respective aglucones upon tissue injury, the biological activity of the aglucones being higher than that of glucosides. Benzoxazinoid hydroxamic acids occur in most tissues of the cereal plant, most prominently in younger tissue of younger plants. The biosynthetic pathway leading to them has to a large extent been resolved, although the factors that control their differential expression in different tissues and at different stages of plant ontogeny remain unknown. The involvement of benzoxazinoid hydroxamic acids in plant defense against a wide variety of organisms has been demonstrated, but the molecular mechanisms accounting for the effects have been less explored. Several reviews have appeared on benzoxazinoid hydroxamic acids (*1*−*6*), the latest emphasizing their chemical properties and particularly the synthetic access to them (*3*, *4*, *6*) and their biosynthesis (*5*). The present review succinctly summarizes the chemical and biosynthetic information available, and expands an earlier comprehensive review (*1*) on ecological and agricultural aspects of benzoxazinoid hydroxamic acids research.

BIOSYNTHESIS OF BENZOXAZINOID HYDROXAMIC ACIDS

The elucidation of the benzoxazinoid hydroxamic acids pathway in maize plants resulted from extensive isotope incorporation experiments starting in the 1960s (*7*) and continuing until the early 2000s (*8*−*15*), from the isolation and characterization of some of the enzymes involved (*16*−*18*), and from sophisticated genetic work (*14*). Most enzymes involved in the process have been expressed in microbial systems and characterized (*19*), or have been characterized directly in tissues of Poaceae (*19*−*24*). The biosynthesis of benzoxazinoid hydroxamic acids branches off from primary metabolism at indole-3-glycerol phosphate (*14*, *25*−*27*), an immediate precursor in the biosynthesis of tryptophan (**Figure 3**). The first step involves an indole-glycerolphosphate lyase in the chloroplast and produces indole. Thereafter, four successive oxidation steps taking place in the endoplasmatic reticulum and involving cytochrome P450 monooxygenases lead to the simplest benzoxazinoid hydroxamic acid, DIBOA. Cytosolic UDP-glucosyl-transferases produce DIBOA-Glc. The biosynthesis of DIMBOA-Glc in-

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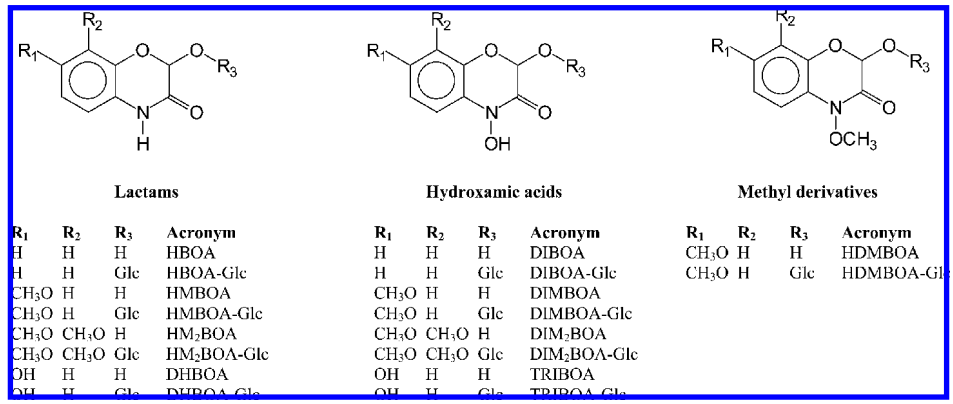

Lactams

R_1	R_2	R_3	Acronym
H	H	H	HBOA
H	H	Glc	HBOA-Glc
CH_3O	H	H	HMBOA
CH_3O	H	Glc	HMBOA-Glc
CH_3O	CH_3O	H	HM_2BOA
CH_3O	CH_3O	Glc	HM_2BOA-Glc
OH	H	H	DHBOA
OH	H	Glc	DHBOA-Glc

Hydroxamic acids

R_1	R_2	R_3	Acronym
H	H	H	DIBOA
H	H	Glc	DIBOA-Glc
CH_3O	H	H	DIMBOA
CH_3O	H	Glc	DIMBOA-Glc
CH_3O	CH_3O	H	DIM_2BOA
CH_3O	CH_3O	Glc	DIM_2BOA-Glc
OH	H	H	TRIBOA
OH	H	Glc	TRIBOA-Glc

Methyl derivatives

R_1	R_2	R_3	Acronym
CH_3O	H	H	HDMBOA
CH_3O	H	Glc	HDMBOA-Glc

Figure 1. The family of 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones (benzoxazinoids) from cereals and other plants. Stereochemistry at C-2 has not been indicated in glucosides.

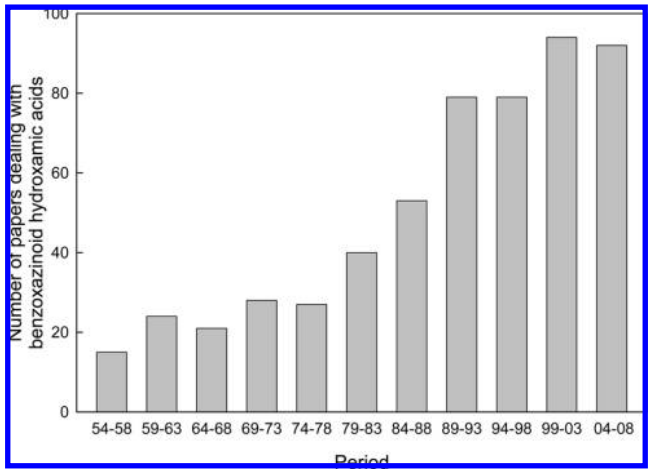

Figure 2. Time dependence of publications dealing with 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one-derived hydroxamic acids from cereals and other species.

volves the oxidation of DIBOA-Glc by a 2-oxoglutarate-dependent dioxygenase present in the cytosol (*24*, *28*), followed by methylation by a methyltransferase (*28*). Glucosides of benzoxazinoid hydroxamic acids are stored in the vacuoles. Upon tissue damage, specific glucosidases (*29*−*31*) present in the plastids (*32*) come into contact with the glucosides and bioactive aglucones are produced (*33*) (**Figure 4**).

The benzoxazinoid hydroxamic acids pathway is found in maize *Zea mays* (*14*), wheat *Triticum aestivum* (*34*), in rye *Secale cereale* (*19*), and in the wild barley *Hordeum lechleri* (*35*), but not in cultivated barley (*19*, *36*). Genes encoding the oxidative enzymes (*ZmBx1*−*ZmBx6*) as well as the methyltransferase (*ZmBx7*) are found clustered in the short arm of chromosome 4 of maize (*14*, *28*, *37*). In rye, orthologous genes involved in the biosynthesis of benzoxazinoid hydroxamic acids are divided between chromosomes 7R (*ScBx1* and *ScBx2*) and 5R (*ScBx3*−*ScBx5*) (*38*), while in hexaploid wheat the *Bx* gene cluster is divided between group 4 (*TaBx1* and *TaBx2*) and group 5 (*TaBx3*−*TaBx5*) homeologous chromosomes (*34*, *38*). This confirms earlier work using wheat aneuploids and wheat substitution lines which suggested chromosomes 4 and 5 as the location of genes involved in benzoxazinoid hydroxamic acids accumulation (*39*), and monosomic and B−A translocational analyses on maize locating the *bx* locus in chromosome 4 (*40*). Interestingly, the short arm of chromosome 4 of maize has been suggested to have a broad synteny with wheat group-5 chromosomes (*41*), and there is a degree of sinteny between rye chromosomes 7R and 5R and group-4 and group-5 chromosomes of wheat, respectively (*42*, *43*). Genes encoding for UDP-glucosyl-transferases have been found near the gene cluster for oxidative enzymes of the biosynthesis of benzoxazinoid hy-

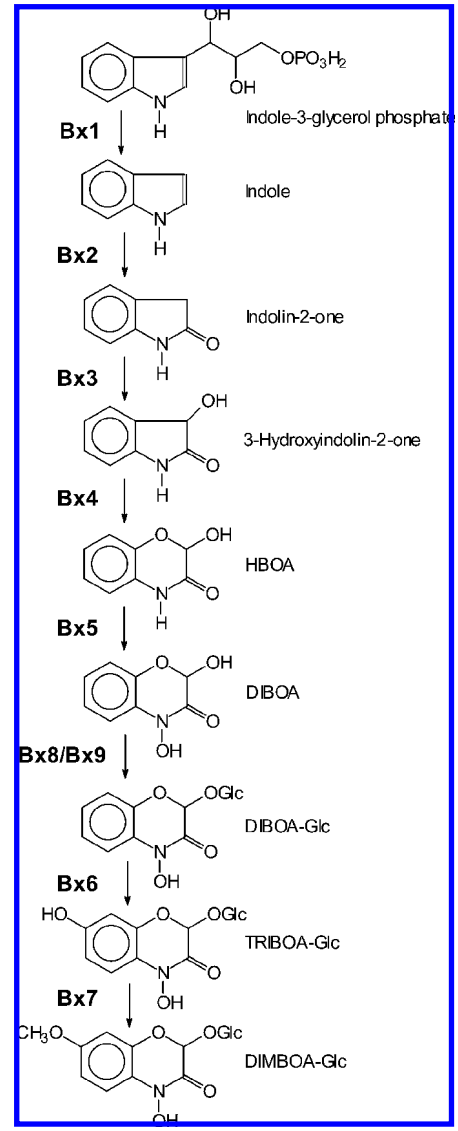

Figure 3. Biosynthetic pathway to benzoxazinoid hydroxamic acids. Each enzyme (Bxn) is associated with a gene (*Bxn*) which, depending on the plant from which it was isolated, is denominated *ZmBxn* (maize), *TaBxn* (hexaploid wheat), *ScBxn* (rye), *TbBxn* (*Triticum boeoticum*) or *HlBxn* (*Hordeum lechleri*). Stereochemistry at C-2 has not been indicated in glucosides.

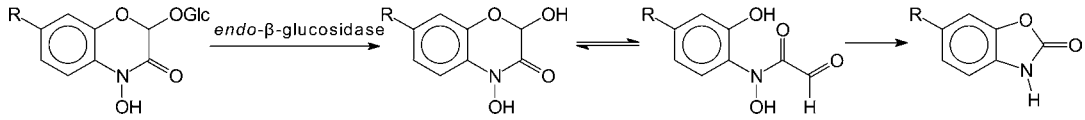

Figure 4. Enzymatic and chemical transformations of a benzoxazinoid hydroxamic acid glucoside.

droxamic acids (*ZmBx8*) and also in chromosome 1 of maize (*ZmBx9*) (*23*).

Genes *Bx1* to *Bx5* are present in the three diploid progenitors of hexaploid wheat *T. aestivum* (*44*). The three genomes of hexaploid wheat contribute to the biosynthesis of benzoxazinoid hydroxamic acids, but the B genome contributes the most (*44*). This supports earlier predictions that the progenitors of the B genome should exhibit the highest concentrations of benzoxazinoid hydroxamic acids (*39*). Some accessions of *Triticum boeoticum*, a wild diploid species containing the A genome of hexaploid wheat, were shown not to accumulate benzoxazinoid hydroxamic acids. The loss of biosynthetic capability was attributed to disintegration of the *TbBx1* coding sequence which triggered loss of transcriptional activity followed by elimination of the *TbBx1*−*TbBx5* genes (*45*). On the other hand, the inability of cultivated barley to biosynthesize benzoxazinoid hydroxamic acids has been suggested to have occurred by elimination of the *Bx* gene cluster from a wild *Hordeum* progenitor (*27, 38*).

As described below, benzoxazinoid hydroxamic acids are heterogeneously accumulated within the plant and their concentrations vary considerably with tissue age. Knowledge of factors affecting gene expression of *Bx* genes is of paramount importance for the efficient use of benzoxazinoid hydroxamic acids in pest and disease control. Some progress has recently been made in this area: the stage specific transcription of *Bx3* and *Bx4* genes in hexaploid wheat and its diploid progenitors was found not to be controlled by global sequence similarity of their promoters but by some essential *cis*-regulatory elements in the promoter region (*46*).

ANALYSIS AND SYNTHESIS OF BENZOXAZINOID HYDROXAMIC ACIDS

Biological and ecological methodologies for measuring the effect of plant secondary metabolites on interacting organisms have reached a high level of sophistication. Concomitantly, a need has arisen to determine the precise composition of the chemical mixtures in the plant, to isolate major compounds and synthesize minor compounds efficiently and in high purity, and to enable the study of the effects of each component individually and in mixtures to assess potential synergisms.

Numerous analytical approaches have been developed for the quantitation of benzoxazinoids in plants (*47*). Early methods which relied on the quantitation of benzoxazolinones produced from hydrolysis of the glucosides and decomposition of the aglucones have been superseded by fast, accurate, specific, and sensitive high performance liquid chromatography (HPLC) and gas−liquid chromatography (GLC) methods for direct analysis of the benzoxazinoids. Most frequently, plant extracts are produced in such way that a major portion of the naturally occurring glucosides are hydrolyzed by plant glucosidases and aglucones are separated and quantitated by HPLC coupled to UV detection (HPLC−UV) (*48*−*52*), electrospray ionization mass spectrometry (HPLC−ESI-MS) (*53*) or electrospray ionization tandem mass spectrometry (HPLC−ESI-MS−MS) (*54*), GLC−MS−MS (*55*), or thin layer chromatography (TLC) (*56*). Alternatively, glucosidases have been heat inactivated when preparing the extracts, and naturally present glucosides analyzed by HPLC coupled to atmospheric pressure chemical ionization-MS−MS (*57*). Interlaboratory comparison of methods based on HPLC coupled to diode array detector, MS, and tandem MS revealed low variability in the analyses of standard solutions but high variability in the analysis of purified root extracts (*58*). Extensive analyses of mass spectral fragments derived from benzoxazinoids (*59*) and from their chemical and microbial transformation products (*60*) have been achieved with ESI and ESI time-of-flight mass spectrometry (*61*). Specific methods have been developed which allow the quantitation of benzoxazinoids together with allelopathic plant phenolics (*55*) and organic acids (*62*), and of products from the degradation of benzoxazinoid hydroxamic acids in the soil (*60, 63*).

Efficient methods have been described for the large scale isolation of benzoxazinoid hydroxamic acids from cereals, in both the glucosidic (*64*−*66*) and agluconic forms (*67, 68*). The synthesis of benzoxazinoid hydroxamic acid has proved challenging, that of aglucones due to their instability in solution (**Figure 4**) and the presence of two main functional groups—hemiacetal and hydroxamic acid—at intermediate oxidation levels, and that of glucosides due to the need to connect two stereogenic centers with only one of the four possible configurations of the product being the desired one. Efficient methods have been reported for the syntheses of DIBOA (*69*), DIMBOA (*70*) and their glucosides (*71*).

OCCURRENCE AND DISTRIBUTION OF BENZOXAZINOID HYDROXAMIC ACIDS

Benzoxazinoid hydroxamic acids occur mainly in wild (*72*−*77*) and cultivated (*78*−*86*) Poaceae. Concentrations reported in wild Poaceae are as high as 44 mmol/kg fresh weight (*73*); in cultivated cereals maximum concentrations found are lower, 13 mmol/kg fresh weight in wheat (*87*), 8 in maize (*88*), and 19 in rye (*89*). Benzoxazinoids have also been found in other plant families: Acanthaceae (*90*−*100*), Ranunculaceae (*101*), Scrophulariaceae (*94, 102, 103*) and Lamiaceae (*104*). It may be speculated that acquisition of the benzoxazinoid hydroxamic acids pathway occurred early in the evolution of the Poaceae, before monocots and dicots diverged, or that independent convergent evolution has taken place. Recent evidence from studies of the biosynthesis of benzoxazinoids in dicots suggests that benzoxazinoid hydroxamic acids in *Consolida orientalis* (Ranunculaceae) and in members of the Poaceae may have arisen through the latter mechanism (*105*). The isolation of gene homologues as well as knowledge of the architecture of gene clusters from dicots should provide a deeper insight into the evolution of the gene cluster responsible for the biosynthesis of benzoxazinoid hydroxamic acids.

Benzoxazinoid hydroxamic acids are absent from the dry seed (*106*−*108*), but become detectable when the seed germinates (*106, 108*). They are distributed in most plant parts, including shoots and roots (*79, 85, 86, 89, 105, 106, 109*−*113*). Their concentration increases upon germination up to a maximum and then decreases (*44, 89, 106, 107, 109*−*111, 114, 115*). However, relatively high benzoxazinoid hydroxamic acids concentrations are found in young and highly exposed tissues of old plants (*109, 116*−*118*), particularly the flag leaf (*116*); interestingly, a recent cDNA microarray analysis has shown that four genes involved in the biosynthesis of benzoxazinoid

hydroxamic acids (*Bx2*, *Bx4*, *Bx6* and *Bx9*) were upregulated during senescence of wheat flag leaves (*119*). While the concentration of benzoxazinoid hydroxamic acids in wheat (*106, 109, 110*), maize (*107, 118*) and rye (*31*) plants peaks a few days after germination, a peak in concentration was reported in greenhouse-grown rye plants at a much later stage (*111*). Older wheat plants of some cultivars show a higher concentration of benzoxazinoid hydroxamic acids in the roots than younger plants (*52, 112*), while in other cultivars older plants showed higher benzoxazinoid hydroxamic acids concentrations in the foliage than in the root but higher root/foliage ratios of benzoxazinoid hydroxamic acids concentrations than younger ones (*52, 115*). Benzoxazinoid hydroxamic acids are present in undifferentiated tissues (*120, 121*) and callus tissue (*121*) of wheat. Benzoxazinoid hydroxamic acids are present in the phloem of wheat seedlings (*122, 123*), in root exudates of various cereals (*85, 112, 113, 124, 125*), in the essential oil of maize leaves (*126*), in the pollen of rye plants (*127*), and in flowers of *Acanthus mollis* (*128*) and *Consolida orientalis* (*105*). As mentioned earlier, the genetic mechanisms determining the concentration of benzoxazinoid hydroxamic acids along the development of the plant have recently been addressed (*46*).

The most abundant benzoxazinoid hydroxamic acid aglucone in wheat and maize extracts is DIMBOA while in rye it is DIBOA. DIMBOA is accompanied by DIBOA in wheat extracts (*106*) and by DIBOA and DIM_2BOA in maize extracts (*117*). In rye extracts, DIBOA may be accompanied by DIMBOA (*54, 89, 129*), particularly in root extracts (*54, 89*). The ratio between concentrations of different benzoxazinoid hydroxamic acids depends on the tissue analyzed and plant age, both in cereals (*106, 107, 109, 110*) and in dicots (*105, 128*). Analysis of extracts of numerous wild Poaceae shows that DIBOA and DIMBOA may occur alone (*76, 130, 131*) or in mixtures (*73, 132, 133*).

Many studies have suggested that benzoxazinoids are naturally present in the plant as glucosides which are hydrolyzed to the respective aglucones upon tissue injury (*57, 134, 135*). However, the issue can not be considered settled since both glucosides and aglucones have been found under conditions which supposedly avoid the enzymatic hydrolysis of the glucosides (*106, 108, 115, 136, 137*). Moreover, aglucones appear to be the preferential form in which benzoxazinoid hydroxamic acids are found in root exudates (*85, 124, 138*) as well as in undifferentiated tissues such as meristem cells (*120*) and callus (*121*). Aglucones have also been found in young seedlings before they begin autotrophic growth (*137*). Hence, the finding of glucosides or aglucones in a particular cereal extract should depend not only on the activity of the plant β-glucosidases in the extract and the sensitivity of the analytical method used but also on the tissues processed in the extract analyzed. The question of how the plant avoids the toxic effects of the aglucones remains to be unraveled.

Accumulation of benzoxazinoid hydroxamic acids can be affected by environmental factors, the effects depending not only on the plant species but also on the cultivar studied. Among the factors assessed are temperature (*139*), water and nitrogen stress (*140−142*), photoperiod (*139*), light intensity (*143, 144*), and exposure to UV radiation (*145−147*). Detailed studies on temperature effects on concentrations of benzoxazinoid hydroxamic acids in wheat showed they arise from changes in plant growth rate (*148, 149*). Concentration of benzoxazinoid hydroxamic acids in wheat plants was not affected by the farming system used, suggesting that the use of pesticides and fertilizers does not affect their accumulation (*52, 115*); however, they did show seasonal variations (*52*).

The concentration of benzoxazinoids in plants can also be altered by treatment with plant activators. Maize plants treated with jasmonic acid and methyl jasmonate showed increased accumulation of the methyl derivative, HDMBOA-Glc in leaves (*150*). Treatment of wheat plants with jasmonic acid and methyl salicylate increased the concentration of DIMBOA in the seedlings (*151*) and in the roots (*152*), and treatment with *cis*-jasmone increased accumulation of DIMBOA in aerial parts (*153*). Study of gene expression following treatment of maize plants with methyl jasmonate showed an initial increase of the *Bx1* gene expression followed by an increase of the *Bx9* gene expression (*154*). Jasmonic acid treatment of wheat and Job's tears, *Coix lachryma-jobi*, showed an increased accumulation of HDMBOA-Glc at the expense of DIMBOA-Glc, and the concomitant induction of the methyltransferase responsible for the methylation of DIMBOA-Glc (*155*).

Maize plants with Bt (*Bacillus thuringiensis*) genes accumulated lower concentrations of benzoxazinoid hydroxamic acids in their leaves than the corresponding near-isogenic nontransgenic lines (*142*).

Further studies on the genes and gene products which regulate the differential accumulation of benzoxazinoid hydroxamic acids and its interaction with environmental factors would be desirable, particularly in rye. This would open possibilities for producing cereals with increased concentration of benzoxazinoid hydroxamic acids until later growth stages, and consequently enhanced pest resistance and allelopathic capabilities.

CHEMICAL PROPERTIES OF BENZOXAZINOID HYDROXAMIC ACIDS

Aglucones of benzoxazinoid hydroxamic acids are cyclic hemiacetals which upon ring opening generate the highly reactive α-oxo-aldehyde intermediate derived from *N*-(2-hydroxy-phenyl)-glyoxylo-hydroxamic acid (*156*) (**Figure 4**). The intermediate exists in small quantities in solution (*157*), and is responsible for many of the observed reactions of benzoxazinoid hydroxamic acids. Thus, reclosure of the intermediate produces a benzoxazolinone, at rates which depend on a variety of factors, most importantly pH (*158*), solvent (*159, 160*) and substitutions in the aromatic ring (*161, 162*). The intermediate reacts with a range of nucleophiles present in amino acid residues of proteins, particularly thiols (*161, 163−165*) and amines (*166*), and also with nucleophilic residues in enzymes which are important for catalytic activity (*167−169*). These reactions may account for the inhibition by benzoxazinoid hydroxamic acids of various metabolic processes, such as electron transport in mitochondria and chloroplasts (*170−172*), NADH oxidation by oat cell wall peroxidases (*173*) and aphid cholinesterases (*169*).

Metabolic activation of the hydroxamic acid function produces a hydroxamate ester which may react with nucleophilic moieties present in nucleic acids (*174*); these reactions may account for the formation of adducts of DNA of cells exposed to wheat extracts (*175*), binding to DNA molecules (*174*), mutagenic activity of cereal extracts (*174, 176, 177*), genotoxic properties of benzoxazinoid hydroxamic acids on human-derived liver cells (*177*) and induction of new genotypes in aphids fed with seedlings with high concentrations of benzoxazinoid hydroxamic acids (*178*).

BENZOXAZINOID HYDROXAMIC ACIDS AS DEFENSE COMPOUNDS

Allelopathy. Allelopathy has received considerable attention ever since varietal differences in the effects of crops on

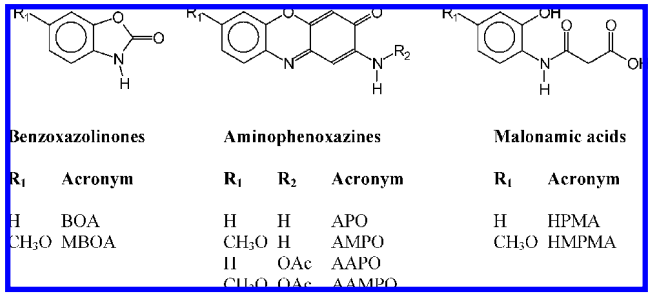

Figure 5. Products of transformations of benzoxazinoid hydroxamic acids in the soil.

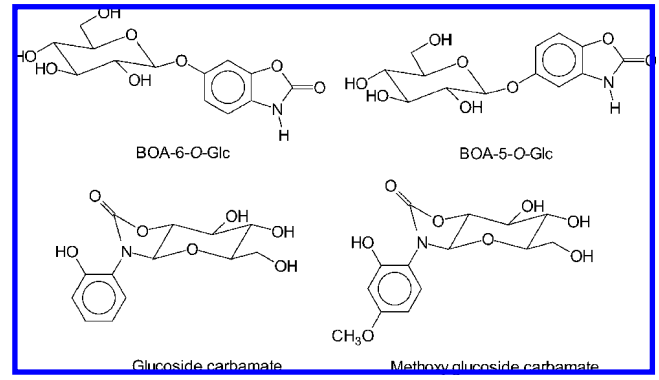

Figure 6. Products of detoxification of benzoxazolinones by plants.

associated weeds were discovered in the 1970s. Weed suppression may be obtained at two stages of the allelopathic crop, i.e. the vegetative stage and the postharvest stage. Allelopathy at the vegetative stage of the crop occurs through the exudation by the roots of phytotoxins which affect the germination and growth of surrounding weeds. At the postharvest stage, allelochemicals in the crop residues may leach into the soil and thus suppress weeds. Research on cereal allelopathy has focused on the description of the chemicals responsible for such property, examining their presence, tissue localization, and variations along the development of the plant in different crop cultivars and related species, studying their effects on the environment and on beneficial organisms, and assessing their potential for use in integrated management of weeds (*179*).

The primary compound responsible for allelopathy of rye residues is DIBOA (*124, 180*−*182*). Thus, DIBOA appeared at the last stages of allelopathy bioassay-guided fractionation of rye tissues (*181*), the allelopathic effect of rye residues disappeared in parallel with the disappearance of DIBOA in them (*183*), tissues with higher DIBOA content were more phytotoxic than tissues with lower DIBOA concentration (*54*), and DIBOA inhibited a wide variety of weed species both in vitro (*184*) and in vivo (*138*).

Analysis of plants of rye cultivars showed that while DIMBOA is generally absent from aerial parts (*86, 89, 111, 182*), it is present in root extracts in concentrations comparable to those of DIBOA (*89*). In rye root exudates, either DIBOA alone (*124*) or DIBOA accompanied by DIMBOA (*125, 138*) has been found. Following the demonstration of the presence of benzoxazinoid hydroxamic acids and related compounds in roots and root exudates of rye, benzoxazinoid hydroxamic acids have been found in root exudates of other Poaceae: wheat (*85, 112, 138, 185, 186*), maize (*125, 187*), *Echinocloa crus-galli* (*132*), *Agropyrens repens* (*130, 133*), triticale (*Triticocereale*) (*129*), and the wheat progenitor *Triticum speltoides* (*87*). Concentration of benzoxazinoid hydroxamic acids in root exudates does not necessarily correlate with concentrations in the roots or in above ground tissues (*112, 185, 186*), and the active release of these compounds is thought to be genetically controlled (*113, 188, 189*).

DIBOA and DIMBOA suffer transformations in the soil which generate compounds with allelopathic activity of their own (**Figure 5**). Some of these transformations and their time course in the soil (*190, 191*) have been studied in great detail (*192*). DIBOA and DIMBOA spontaneously decompose in the soil to produce BOA and MBOA, respectively (**Figure 4**). Microorganisms in the soil induce further transformations of BOA and MBOA. With the intermediacy of 2-aminophenol and 5-methoxy-2-aminophenol, respectively, the corresponding aminophenoxazinones, APO (*193*) and AMPO (*194*−*196*), are produced, the transformation rates being a function of soil type, microbial activity, and also the concentration of the parent chemicals (*190, 191, 197*). Both APO and AMPO show a high degree of stability in the soil (*190, 191, 196*).

This family of allelopathic compounds can be detoxified to various extents by root-infecting microorganisms (*198*) and endophytic fungi asymptomatically associated with Poaceae in the soil (*198*−*200*). Thus, aminophenoxazinones can be acetylated to produce AAPO and AAMPO from APO and AMPO, respectively. BOA and MBOA can also be transformed into the *N*-(2-hydroxyphenyl)malonamic acids, HPMA and HMPMA, respectively, by endophytes and root-infecting microorganisms of Poaceae (*198, 199, 201, 202*). In addition to the compounds referred to above, several other metabolites have been provisionally characterized which could arise from chemical and microbial transformation of benzoxazolinones in the soil (*203*). Studies of allelopathic properties of rye extracts at various stages of development of the plant suggest that different chemicals and hence different modes of actions may be prevailing at different ages of the crop (*55*).

The fungus *Fusarium verticilloides* is an asymptomatic endophyte of maize plants which produces mycotoxins causing severe diseases in vertebrates. *F. verticilloides* is able to detoxify BOA, a fungitoxic compound derived from DIBOA, by converting it into inocuous HPMA and HPAA via 2-aminophenol (**Figure 5**). The bacterium *Bacillus mojavensis* has been patented primarily to control *F. verticilloides* and reduce the mycotoxins it produces (*204*). In vitro studies showed that *B. mojavensis* interacts with *F. verticilloides* in the presence of BOA preventing its normal transformation into HPMA and HPAA and diverting the intermediate 2-aminophenol into the production of APO (**Figure 5**), a compound toxic to *F. verticilloides* but not to *B. mojavensis*. These results suggest a mechanism for the biocontrol of *F. verticilloides* by *B. mojavensis* (*205*).

Plants are also able to detoxify the products of benzoxazinoid hydroxamic acids decomposition in the soil, particularly BOA and MBOA. Different target species show different detoxification capacities (*206*) and yield different mixtures of detoxification products (*207*) (**Figure 6**). While BOA-6-*O*-Glc as well as methoxy glucoside carbamate were isolated from root extracts of maize seedlings incubated with MBOA (208), BOA-5-*O*-Glc and BOA-6-*O*-Glc were isolated from root extracts from BOA-incubated seedlings of *Portulaca oleracea* (*208*) and glucoside carbamate was isolated from root extracts of BOA-incubated seedlings of *Coriandrum sativum* and *Galinsoga ciliata* and seedling extracts of BOA-incubated maize seedlings (*209*). *Arabidopsis* seedlings detoxified BOA to BOA-6-OH, BOA-6-*O*-Glc and glucoside carbamate. Transcriptional profiling experiments showed that many of the genes responding to BOA exposure are potentially associated with chemical detoxification pathways. It was further shown that some of these genes

are transcriptionally induced by a wide range of xenobiotic chemicals, suggesting they are part of a broad specificity defense network against xenobiotics (*210*).

Compounds arising from the transformation of benzoxazinoid hydroxamic acids in the soil have been tested for allelopathic effects against a wide variety of crop species (*211*) and weeds (*212*−*214*). Hydroxamic acids were the most active compounds, malonamic acids the least, and other compounds show intermediate activities with the exception of APO, which was highly active. Root growth bioassays with *Lolium perenne* and *Myosotis arvensis* have also been carried out with binary and ternary mixtures of benzoxazinoid-derived compounds and allelopathic phenolic compounds (*215*). In the pure state, benzoxazinoid derivatives were more active than phenolic compounds, and the mixtures of allelochemicals showed additive or less than additive effects (*215*). The presence of MBOA and BOA in the rhizosphere of maize plants can have important effects on fungal endophytes and further on the probability of successful infection by pathogenic fungi (*216*).

Exploitation of benzoxazinoid hydroxamic acids and derived products in plant protection should also consider their effect on nontarget organisms. Addition of BOA to the soil had no effect on the structure of the soil microbial community, in evaluations taking place at times which allowed decomposition of BOA as described above (*197*). Ecotoxicological studies have been reported on different sets of benzoxazinoid-derived compounds against various organisms. Lethal and sublethal testing of DIMBOA, MBOA, AMPO and AAMPO against the collembola *Folsomia candida* and the carabid beetle *Poecilus cupreus* showed that the compounds tested could be classified as low risk compounds for aquatic and terrestrial environments, respectively (*217*). Tests with the marine bacterium *Vibrio fischeri*, the freshwater alga *Pseudokirschneriella subcapitata*, the soil alga *Chlorella pyrenoidosa* and the water flea *Daphnia magna* showed that the derived compounds APO, AMPO and AAPO were more inhibitory than the parent compounds DIMBOA, MBOA and BOA (*218*). Toxicological data on the effect of different sets of benzoxazinoid-derived compounds on *F. candida* (*219*) and *D. magna* (*220*) was analyzed through quantitative structure−activity relationships (QSARs). Data on *F. candida* showed the greater importance of steric over polarity effects for activity (*219*). Data on *D. magna* showed that DIMBOA, MBOA and BOA have very similar toxicity modes of action and also similar to those of the synthetic pesticides used to build the mathematical models (*220*).

Some of the mechanisms which may be involved in the allelopathic effects of benzoxazinoid hydroxamic acids have been studied. Normal plants of *Arabidopsis thaliana* fed with aglucones of benzoxazinoid hydroxamic acids died while transgenic plants with incorporated benzoxazinoid hydroxamic acid glucosyltransferase survived (*23*), showing that exogenous aglucones of benzoxazinoid hydroxamic acids applied to roots are taken up by the plant and exert toxic effects. The growth inhibition of coleoptiles of *Avena sativa* by DIMBOA was ascribed to increased rate of NADH oxidation of cell wall peroxidases with concomitant production of H_2O_2, an agent involved in the coupling of phenols at the cell wall producing cell wall rigidity (*173*). Exposure of one side of a maize coleoptile to blue light up-regulated the activity of β-glucosidase (*221*) and caused the hydrolysis of DIMBOA-Glc with the corresponding increase in DIMBOA concentration (*222*). The phototropism shown by the illuminated coleoptile (bending toward the light source) was attributed to an increase of H_2O_2 concentration caused by the DIMBOA released, followed by lignin accumulation, cell-wall stiffness and eventually growth suppression (*223*). Other mechanisms have also been explored: alterations in root growth and development of *Cucumis sativus* by DIBOA and BOA were attributed to disruption of lipid metabolism, protein synthesis and transport or secretory capabilities (*224*); and decreased radicle elongation in *Avena sativa* caused by DIBOA and BOA was correlated with decreased H^+-ATPase activity (*225*).

Synthesis of numerous benzoxazinoids has been achieved with the aim to define the structural features, mainly lipophilicity and charge distribution, which determine and maximize their phytotoxic activity and also their specificity (*211*−*213*, *226*, *227*). Absence of substituents at C-2 (*211*, *212*), medium size acyl derivative at N-4, particularly propanoyl and valeroyl (*226*), halogens at C-6 and fluorine at C-7 (*226*) led to the most active and selective compounds.

Defense against the European Corn Borer. The European corn borer *Ostrinia nubilalis* (Hbn) (Lepidoptera: Pyralidae) is a major pest of maize in North America, where it shows mainly a bivoltine life cycle, the first generation feeding on leaves of maize seedlings and the second generation feeding on the leaf sheath and collar whorl of mature maize plants. Early work showed that leaf feeding resistance of maize was correlated with concentration of benzoxazinoid hydroxamic acids in the leaves (*228*, *229*). Resistance decreased as the plant matured, consistent with a decrease in the concentration of benzoxazinoid hydroxamic acids with plant age (*230*). A series of crosses between hybrids varying in resistance levels showed that leaf feeding resistance of the progeny was positively correlated with concentrations of benzoxazinoid hydroxamic acids (*230*). Furthermore, in a series of maize lines of various origins, seedling concentrations of benzoxazinoid hydroxamic acids were significantly correlated with laboratory and field leaf damage ratings by the European corn borer (*231*). The mechanism of resistance seems to be related to an antifeeding effect of benzoxazinoid hydroxamic acids (*232*), and also to the inhibition of digestive proteases (*233*, *234*). Leaf feeding resistance to European corn borer based on benzoxazinoid hydroxamic acids has been incorporated into commercial maize hybrids (*235*).

Although benzoxazinoid hydroxamic acids have been shown to be a major resistance factor to leaf feeding European corn borer, other physical and chemical factors have been shown to be involved in resistance to whorl feeding larvae (*236*). A detailed study of feeding sites in the maize whorl showed that third instar European corn borer larvae preferred immature tissues (*237*), characterized by the relative absence of physical defense mechanisms and a higher nutritional value (*237*), in spite of their higher concentrations of benzoxazinoid hydroxamic acids. As the larvae matured and became capable of coping with tougher tissue, they preferred older tissue with relatively lower concentrations of benzoxazinoid hydroxamic acids (*238*). Thus, the feeding site of European corn borer larvae seems to be determined by a combination of physical and chemical properties of the plant in relation with mechanical and detoxifying capacities of the larva as it matures. Recently, it was shown that, in maize genetically modified with the wheat oxalate oxidase gene, the concentration of benzoxazinoid hydroxamic acids was lower, phenolic acid concentration higher and European corn borer resistance higher than in the corresponding null line. This suggested that phenolic acids, in particular ferulic acid, are involved as a defense mechanism against the European corn borer in this transgenic line (*238*).

The activity of several detoxification enzymes in the midgut of fifth instar larvae of the European corn borer (cytochrome

b_5, NADPH-cytochrome *c* reductase, NADPH oxidase and *O*-demethylase) increased when larvae fed on leaves of maize varieties differing in resistance to leaf damage and in concentration of benzoxazinoid hydroxamic acids at the seedling stage relative to a meridic diet lacking benzoxazinoid hydroxamic acids (*239*). The activity increases were correlated with leaf resistance levels and concentration of benzoxazinoid hydroxamic acids in the varieties at the seedling stage. Studies with benzoxazinoid hydroxamic acids added to artificial diets and in vitro studies with pure benzoxazinoid hydroxamic acids added to the enzyme assay medium confirmed their effect on the enzymes (*239*).

Defense against Aphids. Numerous correlations have been reported between aphid performance and concentration of benzoxazinoid hydroxamic acids in their feeding substrates. Thus, intrinsic rate of increase of the grain aphid *Sitobion avenae* (*116, 136*) and the bird cherry-oat aphid *Rhopalosiphum padi* (*116*) and mean relative growth rates of the greenbug *Schizaphis graminum* and *S. avenae* (*240*) were negatively correlated with benzoxazinoid hydroxamic acids concentration in wheat seedlings, and survival and reproduction of *R. padi* were negatively correlated with benzoxazinoid hydroxamic acids concentration in wild *Hordeum* species (*74*). Benzoxazinoid hydroxamic acids determined the preference of alate morphs of *S. avenae* in a test offering seedlings of ten wheat cultivars differing in benzoxazinoid hydroxamic acids concentration (*80*). Performance of *S. avenae* was higher in ears at the beginning of anthesis of five wheat cultivars than in the flag leaf at flag leaf emergence of the same cultivars, consistent with benzoxazinoid hydroxamic acids concentration being higher in the flag leaves than in the ears (*241*). An inverse relationship was reported between concentration of benzoxazinoid hydroxamic acids in 26 Hungarian winter wheat genotypes and infestation rating in the field by *R. padi* at two stages of plant development (*242*). In the latter work, no significant relationship was found between grain yield and benzoxazinoid hydroxamic acids concentration, suggesting that accumulation of the compounds does not impose a cost to the plant in terms of grain yield and supporting the potential of benzoxazinoid hydroxamic acids as breeding targets for aphid resistance (*242*). The correlations between benzoxazinoid hydroxamic acids concentration and aphid performance have been complemented by reports in which benzoxazinoid hydroxamic acids concentrations increased through induction by several agents and aphid performance concomitantly decreased. Thus, when maize leaves were crushed, survival and growth of *R. padi* on them decreased as compared to undamaged leaves (*243*), and treatment of wheat plants with *cis*-jasmone increased DIMBOA levels in extracts of aerial parts and roots (*153*) and also induced resistance against *S. avenae* (*244*). Furthermore, benzoxazinoid hydroxamic acids in both the glucosidic and the agluconic forms added to artificial diets decreased various performance parameters of several cereal aphid species (*245*−*247*).

On the other hand, correlations were not significant between concentration of benzoxazinoid hydroxamic acids in a series of maize inbreds and infestation by the corn leaf aphid *Rhopalosiphum maidis* (*248*), in tetraploid and hexaploid wheats and infestation by *R. padi* (*249*), and in tetraploid and hexaploid wheats and infestation by *S. avenae (241)*. The absence of correlations in these cases may be related to the genotype-dependency found for the effect of benzoxazinoid hydroxamic acids on aphids (*250, 251*).

Electrical penetration graphs have been extensively used to study aphid feeding behavior (*252, 253*). Time for the aphid's stylets to reach the phloem in seedlings of wheat cultivars differing in concentration of benzoxazinoid hydroxamic acids was positively correlated with benzoxazinoid hydroxamic acids concentration in the seedlings, time of continuous ingestion from the phloem was independent of the concentration of benzoxazinoid hydroxamic acids in the plants, and time ingesting from diets with different concentrations of added DIMBOA or DIMBOA-Glc was negatively correlated with benzoxazinoid hydroxamic acids in the diet for five cereal aphid species: *S. avenae, S. graminum, R. padi, R. maidis* and *M. dirhodum* (*240, 246*). A similar study showed that, in the Russian wheat aphid *Diuraphis noxia*, performance was lower, aphids required more time to reach the phloem and a lower proportion of them reached the phloem within the duration of the experiment in a wheat cultivar with high than in one with low concentration of benzoxazinoid hydroxamic acids; again, the time of continuous ingestion from the phloem was not affected by benzoxazinoid hydroxamic acids concentration in the plants (*254*). Another study with *D. noxia* on wheat, rye, triticale and barley cultivars also showed less probing activity before reaching the phloem phase and a lower percentage of aphids achieving a sustained phloem feeding in taxa with higher concentration of benzoxazinoid hydroxamic acids, and also a total time of phloem feeding independent of benzoxazinoid hydroxamic acids concentration (*255*). Ingestion times of *R. padi* were shorter when feeding on leaves of barley, a cereal lacking benzoxazinoid hydroxamic acids, which had been immersed in solutions with higher DIBOA concentrations (*89*). Feeding behavior of the blackberry-grain aphid *Sitobion fragariae* differed in several parameters related to cell punctures and salivation in the sieve elements between wheat cultivars with high and low concentrations of benzoxazinoid hydroxamic acids, the results suggesting a feeding deterrent effect of benzoxazinoid hydroxamic acids at the epidermis and mesophyll (*256, 257*) and the alteration of the salivation process at the sieve elements (*256*). In another study with *S. fragariae*, the total time to produce a first salivation in the sieve elements was longer in the cultivar with high than in the one with low concentration of benzoxazinoid hydroxamic acids; however, the time to the next salivation process (after the first one had been interrupted) was significantly reduced in the cultivar with high concentration of benzoxazinoid hydroxamic acids, reaching the limits observed for the plants with low benzoxazinoid hydroxamic acids concentration. If the experimental plant was replaced by an unattacked plant after the first salivation process, the behavior described was maintained, thus excluding the possibility of aphid-induced plant susceptibility. These results suggest an ability of aphids to avoid benzoxazinoid hydroxamic acids on their way to the phloem once they have experienced their deterrent effects (*258*).

On the other hand, a study of the genetic origin of resistance to *D. noxia* in a series of wheat lines identified resistance genes which were not related to the accumulation of benzoxazinoid hydroxamic acids (*83*), and aphid interference with the phloem sealing system of seedlings of *Triticum monococcum* lines was suggested as responsible for their host or nonhost character toward the aphid *S. avenae* (*123*).

Aphids are able to transmit viruses to cereal plants, particularly barley yellow dwarf virus (BYDV). Concentration of benzoxazinoid hydroxamic acids at the seedling stage was correlated with resistance rating against BYDV infection by *R. padi*, and infection of wheat seedlings with BYDV was highest in wheat cultivars in which aphids took less time to arrive at the phloem and in which more aphids reached the phloem within a given time period (*259*).

The path followed by stylets on their way to the phloem was studied in *R. maidis* on maize plants. Exclusively intercellular pathways occurred twice as often as mixed inter/intracellular pathways in seedlings and at about the same rate in whorl stage plants, and damage to cell walls and extrusion of stylet sheath material into cells was observed in intercellular penetration tracks (*260*). The honeydew of aphids feeding on wheat cultivars with different concentrations of benzoxazinoid hydroxamic acids contained DIMBOA-Glc but not DIMBOA or MBOA (*261*), consistent with the finding of DIMBOA-Glc in the phloem of wheat seedlings (*122*). Both honeydew production and concentration of DIMBOA-Glc in the honeydew followed a biphasic pattern with respect to concentration of benzoxazinoid hydroxamic acids in plants of the cultivars studied, i.e. as the concentration of benzoxazinoid hydroxamic acids in the seedling increased, the dependent variables first increased and then decreased (*261*). This suggested passive uptake of phloem at low concentration of benzoxazinoid hydroxamic acids in the seedling and increasingly limited ingestion at higher benzoxazinoid hydroxamic acids concentrations. This evidence suggests the following model for the chemical nature of the aphid−plant interface in cereals: when aphids penetrate the plant, their stylets disrupt cellular compartmentation causing the hydrolysis of benzoxazinoid hydroxamic acids glucosides, ingest the benzoxazinoid hydroxamic acids aglucones and suffer their feeding deterrent effect; this increases the time the aphid takes to reach the phloem and decreases the rate of virus transmission; once aphids are feeding on the phloem, they ingest benzoxazinoid hydroxamic acids glucosides in concentrations insufficient to cause a feeding deterrent effect, although continuous feeding and ingestion eventually cause toxic effects (*262*). In support of this suggestion, aphid infested tissues contain more MBOA than uninfested ones (*136*), reflecting the hydrolysis of the glucoside and subsequent decomposition of the aglucone to the benzoxazolinone (**Figure 4**).

A wide range of enzymes involved in xenobiotic detoxification in aphids are affected by their feeding on substrates containing benzoxazinoid hydroxamic acids. Some enzyme activities decrease with increasing concentration of benzoxazinoid hydroxamic acids in the feeding substrate, e.g. UDP-glucose tranferases of *S. avenae* (*263*), and acetylcholinesterase (*169*), esterases and glutathione *S*-transferases of *R. padi* (*264*), whereas others show positive correlations with concentration of benzoxazinoid hydroxamic acids in the feeding substrate, e.g. glutathione *S*-transferases (*265*), catalase and cytochrome *c* oxidase of *S. avenae* (*266*). The activity of five detoxification enzymes of *S. avenae* was followed for ten generations in wheat cultivars with high and low concentration of benzoxazinoid hydroxamic acids. The slope of lines of specific activity per individual aphid vs generations was higher in aphids feeding on the cultivar with low than on the one with high concentration of benzoxazinoid hydroxamic acids for NADPH cytochrome *c* reductase, glutathione *S*-transferases, catalase and esterases; the slopes did not differ in the case of cytochrome P-450 monooxygenases. The sustained differential induction of detoxification enzymes by wheat cultivars differing in benzoxazinoid hydroxamic acids concentration suggests a mechanism for the acquisition of insect resistance to benzoxazinoid hydroxamic acids in plants (*267*).

A clonal line of *S. avenae*, characterized by its random amplified polymorphic DNA-polymerase chain reaction (RAPD-PCR) phenotypic pattern, was grown on plants of two wheat cultivars differing in benzoxazinoid hydroxamic acids concentration and of an oat cultivar lacking benzoxazinoid hydroxamic acids. After exposure to the plants for four to five generations, two new RAPD-PCR variants appeared on the cultivar with high concentration of benzoxazinoid hydroxamic acids, one on the cultivar with low concentration and none on oat. The number of RAPD-PCR phenotypes in two field-grown wheat cultivars varied along the season, decreasing on the cultivar with low concentration of benzoxazinoid hydroxamic acids and increasing on the cultivar with high concentration. The preferential appearance of new RAPD-PCR phenotypes of *S. avenae* on the cultivar with high benzoxazinoid hydroxamic acids was attributed to mutagenesis induced by benzoxazinoid hydroxamic acids and by the products of their transformation within the aphid (*178*).

Structure−activity relationships were established by testing a series of benzoxazinoids against *S. avenae* in diet bioassays. Antifeedant and mortality indexes increased with the presence of a hemiacetal instead of an acetal at C-2, the presence of a hydroxyl group at C-4 (hydroxamic acid) instead of a hydrogen atom (lactam), the presence of electron-donating groups at C-7 of the aromatic moiety, and also the replacement of the oxygen atom by sulfur in the heterocyclic ring (*268*). Repellency of diets containing benzoxazinoids against *R. padi* showed the importance of the electrophilic character of the hydroxamic acid function, the presence of a hemiacetal at C-2 and the lipophilic character of the molecule (*269*).

Application of the pesticide deltamethrin to two wheat cultivars infested by *S. avenae* showed that aphids on the more resistant cultivar (with higher benzoxazinoid hydroxamic acids concentration) were more susceptible to the pesticide than aphids in the more susceptible cultivar, thus demonstrating the synergistic action of plant resistance and pesticide effects (*270*).

Defense against Other Insects. The role of benzoxazinoid hydroxamic acids in cereal resistance against feeding by lepidopterous larvae has been examined in several species other than the European corn borer. In most instances, positive relationships between concentration of benzoxazinoid hydroxamic acids and resistance have been shown. The effect of benzoxazinoid hydroxamic acids on the stalk corn borer *Sesamia nonagrioides* was studied by feeding larvae with plant tissues from maize lines with different concentrations of benzoxazinoid hydroxamic acids (*271*) and also with artificial diets with added DIMBOA (*272*). In the first study, mortality was higher, development slower and fecundity lower when larvae fed on tissues from maize lines with higher concentrations of benzoxazinoid hydroxamic acids (*271*). In the second study, DIMBOA reduced the efficiency of conversion of ingested food but did not affect consumption, thus confirming a toxic effect. Toxicity by DIMBOA was explained by its effects on several digestive proteases and detoxification enzymes (*272*).

In vitro assays with the Asian cornborer *Ostrinia furnicalis* showed that DIMBOA was a feeding deterrent at concentrations comparable to those of benzoxazinoid hydroxamic acids occurring in plants (*273*), and affected the activity of enzymes of the larval nervous system and also detoxification enzymes (*274*).

In the case of the Southern armyworm *Spodoptera erinania* high concentrations of benzoxazinoid hydroxamic acids could not be associated with leaf feeding resistance, presumably due to its generalist nature and hence its capacity to detoxify the compound and to compensate its deleterious effects through higher consumption rates (*275*, *276*). The effect of DIMBOA on two other *Spodoptera* species has been tested. Dual-choice bioassays showed an antifeedant effect of DIMBOA on *Spodoptera exigua* and a feeding stimulant effect on *Spodoptera frugiperda*. DIMBOA in diets decreased relative growth rate

and survival and increased development time relative to control diets for *S. exigua* but not for *S. frugiperda*. Although both larvae are generalists, the latter prefers members of the Poaceae, and hence may be better adapted to deal with toxic compounds present in them (*277*).

Resistance of maize to the Southwestern cornborer *Diatraea grandiosella* was associated with the presence of HDMBOA in whorl surface waxes where the larvae feed since the compound was found in higher concentrations in resistant lines and exhibited toxic effects to larvae in diets (*278*).

Studies with the coleopteran pest, the Western corn rootworm *Diabrotica virgifera virgifera*, have positively correlated resistance to concentration of benzoxazinoid hydroxamic acids in roots. Thus, a high DIMBOA maize line showed higher larval resistance and less damage by larval feeding than a low DIMBOA line (*117*), corn rootworm-resistant inbreds had a higher benzoxazinoid hydroxamic acids concentration than susceptible lines (*79*), larval development parameters, including survival, weight, and head capsule width, were significantly and negatively correlated with benzoxazinoid hydroxamic acids concentrations in the roots of seven maize lines (*79*), root damage was negatively correlated with the concentration of benzoxazinoids in root tissues early but not late in the growth season (*279*), and recovery of infested plants after the time of maximal root damage was more pronounced in an inbred with high than in one with low concentration of benzoxazinoid hydroxamic acids (*280*). Yield reduction in infested plants was lower in maize inbreds with high than in ones with low benzoxazinoid hydroxamic acids concentration in the roots. In vitro studies showed that DIMBOA added to fresh maize roots caused mortality in larvae, possibly due to feeding deterrent and toxic effects (*117*), and also altered feeding behavior, reduced burrowing, and increased avoidance of roots (*281*). The lack of correlation between benzoxazinoid hydroxamic acids concentration and larval resistance in four particular maize lines was rationalized in terms of benzoxazinoid hydroxamic acids concentrations being below the threshold necessary for resistance (*282*). On the other hand, several maize cultivars differing in benzoxazinoid hydroxamic acids concentration in the whorl did not show differences in root damage rating by larvae (*283*), presumably because concentration of benzoxazinoid hydroxamic acids in aerial and underground plant parts are not necessarily correlated (*89*).

Defense against Diseases. Several reports have implicated benzoxazinoid hydroxamic acids in fungal resistance of cereals. A negative correlation was found between infection rating of maize inbreds to Northern corn leaf blight by *Helminthosporium turcicum* and benzoxazinoid hydroxamic acids concentration in leaves at midstalk (*284*, *285*); the correlation was supported by in vitro assays where fungal development was inhibited by DIMBOA (*286*). Resistance rating of maize cultivars to stalk rot by *Cephalosporium maydis* was negatively correlated with concentration of benzoxazinoid hydroxamic acids in the third internode of maize plants; resistance declined upon aging of the plant, concomitant with a decrease in benzoxazinoid hydroxamic acids concentration (*287*). Resistance rating of wheat cultivars to stem rust caused by *Puccinia graminis* was negatively correlated with benzoxazinoid hydroxamic acids concentration at the seedling stage (*186*, *288*), and a negative correlation was found between the number of races of *P. graminis* that infect wheat varieties and their benzoxazinoid hydroxamic acids concentration at the seedling stage (*289*). The concentrations of benzoxazinoids in wheat ears were correlated with susceptibility to head blight produced by a mixture of *Fusarium* and *Microdochium* species (*290*).

On the other hand, several reports have shown that benzoxazinoid hydroxamic acids are not the most prevalent resistance mechanisms in cereals against fungal diseases. Severity of anthracnose caused by *Colletotrichum graminicola* in different leaves and leaf parts of maize was not correlated with concentration of benzoxazinoid hydroxamic acids; neither was disease rating of 11 maize cultivars with benzoxazinoid hydroxamic acids concentration in the third leaf (*291*). Ratings of stalk rot by *Gibberella zeae* and of corn smut by *Ustilago zeae* were not correlated with benzoxazinoid hydroxamic acids concentrations in maize seedlings (*231*), and benzoxazinoid hydroxamic acids were shown not to constitute an effective resistance mechanism against *Fusarium verticilloides* (*292*). Resistance in the *rhm1* (locus for resistance to *Helminthosporium turcicum*) mutant maize line to Southern corn leaf blight caused by *Bipolaris maydis* was shown not to be related to the presence of benzoxazinoid hydroxamic acids (*293*). An asymmetric mutualistic interaction between the root fungus *Trichoderma harzianum* and two wheat cultivars differing in benzoxazinoid hydroxamic acids concentration at the seedling stage was described which depended on water availability but not on cultivar (*294*); however, the concentration of benzoxazinoid hydroxamic acids in roots or root exudates was not determined, and concentration in these compartments is not necessarily correlated with concentrations in the seedling as a whole (*89*).

Several reasons can account for the ambiguous relationship between benzoxazinoid hydroxamic acids concentrations in cereals and fungal resistance. Studies have been carried out on different sets of cereal germplasm where the relative importance of benzoxazinoid hydroxamic acids as a mechanism of resistance may differ (*293*) or where the concentrations of benzoxazinoid hydroxamic acids may be not high enough to affect fungal development (*290*). On the other hand, the type of damage caused by the fungus during infection may affect the nature of benzoxazinoids present in the plant and hence the resulting antifungal activity (*295*−*298*). Thus, the nature of the plant−fungus interface may determine the type of chemical the fungus will encounter and its concentration. This concentration may or may not be correlated with that determined in the seedling as a whole. Moreover, transformation products of benzoxazinoid hydroxamic acids may be detoxified to different extents by different fungi (*198*, *199*, *299*).

Benzoxazinoid Hydroxamic Acids as Induced Defenses. The interaction of a cereal plant with other organisms can also affect the concentration of benzoxazinoid hydroxamic acids in the plant, the effect being a function of the cereal species and cultivar, and the nature of the interacting organism. Thus, infestation of wheat seedlings by the aphids *M. dirhodum* (*300*) and *S. avenae* (*136*) either increased the concentration of benzoxazinoid hydroxamic acids or had no effect on it, depending on the cultivar. The ability of wheat seedlings to exhibit benzoxazinoid hydroxamic acids induction upon feeding by the aphid *R. padi* (*301*) was shown to depend on temperature, but the effect was mediated by plant growth rate (*148*). Studies on the infestation of *Triticum uniaristatum* by the aphid *R. padi* showed that induction occurred only when the primary leaf was infested (*76*); furthermore, the increase in benzoxazinoid hydroxamic acids concentration in the primary leaf was due to translocation from the roots and stems (*131*). These results supported the extension of the optimal defense theory to induced defenses. Thus, as commonly applied to constitutive defenses, the theory predicts higher allocation of defenses to plant tissues

with higher probability of being attacked; applied to induced defenses, the theory should predict higher allocation of induced defenses to tissues where an actual attack has occurred. As expected from translocation not involving a metabolic cost, infestation of the primary leaf did not lead to differences in growth, size and survival of the plant (*131*).

An increase was found in the concentrations of DIMBOA in extracts of maize plants infested by the stalk corn borer *S. nonagrioides* (*302*). Besides changes in concentration, larval feeding can also produce transformations among benzoxazinoids, as is the case of the transformation of DIMBOA-Glc into HDMBOA-Glc in maize leaves as a consequence of feeding by the rice armyworm *Leucania separata* (*297*). Contrastingly, feeding by larvae of the Asian cornborer *O. furnicalis* did not alter the concentration of benzoxazinoid hydroxamic acids in maize plants (*303*).

The effect of herbivory has been mimicked by wounding or pruning the plant. Artificial damage of maize plants led to increased accumulation of benzoxazinoid hydroxamic acids (*118*), rye tissue developing after successive defoliations showed lower benzoxazinoid hydroxamic acids concentrations in the shoots and higher benzoxazinoid hydroxamic acids concentrations in root exudates than prior to defoliation (*304*, *305*), and maize developing after defoliation contained lower benzoxazinoid hydroxamic acids concentrations than prior to defoliation, albeit only in shoot tissue (*306*). Interestingly, transcripts encoding monooxygenases involved in the benzoxazinoid hydroxamic acids biosynthetic pathway were induced by wounding (*307*).

Plant pathogens may also alter the nature and concentration of benzoxazinoids in cereals, depending on the way they interact with the plant. Thus, the nature and concentration of benzoxazinoids found in pathogen-infested cereals was found to depend on the degree of pathogenicity of the infecting organism as well as the type of damage provoked in the plant. In a study of wheats of various levels of resistance to infection by the fungus *Puccinia graminis*, concentration of DIMBOA-Glc and HMBOA-Glc decreased with time in infected and uninfected seedlings; in the most resistant cultivar, infection by *P. graminis* brought an increase of the concentration of HDMBOA-Glc (*295*). Similarly, transformation of DIMBOA-Glc into HDMBOA-Glc in maize leaves occurred as a consequence of infection by the pathogenic fungus *Bipolaris maydis*; infection by the weakly pathogenic fungus *Curvularia lunata* and by the nonpathogenic fungus *Alternaria alternata* also increased HDMBOA-Glc in maize leaves, but the effect showed a delay with respect to that of the pathogenic fungus (*297*). Infection of maize by the fungus *Ustilago maydis* led to an increase in DIMBOA concentrations in tumors relative to mock-infected controls (*298*). During fungal infection of wheat, the ratio of DIMBOA-Glc to DIMBOA changed as a function of the mode of infection of the fungus (*296*). Thus, infection by the pathogenic necrotroph *Septoria tritici* resulted in significant hydrolysis of DIMBOA-Glc, infection by *Drechslera teres*, a necrotroph incompatible with wheat, caused only a small reduction of DIMBOA-Glc concentration, and no change in DIMBOA-Glc concentration was evident following infection by the obligate parasite *Puccinia recondita* (*296*).

EFFECTS OF BENZOXAZINOID HYDROXAMIC ACIDS AT THE THIRD TROPHIC LEVEL

The coccinellid aphid predator *Eriopis connexa* fed with aphids reared on three wheat cultivars differing in benzoxazinoid hydroxamic acids concentration showed the longest development times when the aphid prey came from a cultivar with intermediate benzoxazinoid hydroxamic acids concentration (*308*). DIMBOA in diets was deleterious to the coccinellid (*308*). It was suggested that aphids from the cultivar with intermediate concentration of benzoxazinoid hydroxamic acids were most deleterious to the predator because, at lower concentrations in the plant, the aphids had passively ingested less benzoxazinoid hydroxamic acids and hence were less toxic (*49*), and at higher concentrations aphids had also ingested less benzoxazinoid hydroxamic acids on account of their feeding deterrent effect and hence were also less toxic (*261*). The fact that the development time of the predator was lowest when it fed on aphids from the wheat cultivar with highest concentration of benzoxazinoid hydroxamic acids suggests that an increase of benzoxazinoid hydroxamic acids in the plant, useful for aphid resistance, would result in the additional benefit of minimizing the effect of the toxin on the predator (*308*).

The microhymenopteran parasitoid *Aphidius rhopalosiphi* found and attacked the aphid *S. avenae* grown on a wheat cultivar with high concentration of benzoxazinoid hydroxamic acids at frequencies similar to aphids grown on a cultivar with low concentration, while aphids from both cultivars showed similar frequencies of kicking and production of cornicle secretion. The stabbing success of parasitoids was higher on aphids fed on the cultivar with low benzoxazinoid hydroxamic acids concentration, presumably because kicking by bigger aphids from this cultivar was more effective in avoiding parasitoid stabbing (*309*). An increase in egg-larval development time was observed in the cultivar with high concentration of benzoxazinoid hydroxamic acids relative to the low concentration cultivar and also in diets with high concentration of benzoxazinoid hydroxamic acids compared to low concentration diets (*309*). A study on the joint action of the aphid parasitoid *A. rhopalosiphi* and the entomopathogenic fungus *Erynia neoaphidis* on the aphid *S. avenae* growing on seedlings of two wheat cultivars differing in benzoxazinoid hydroxamic acids concentration showed that significant reductions of population growth rate of aphids could be obtained with the joint action of wheat resistance and natural enemies (*310*).

Similarly, increased parasitization by the microhymenopteran parasitoid *Diadegma terebrans* of European corn borer larvae resulted when the larvae were fed with artificial diets containing benzoxazinoid hydroxamic acids with respect to control diets lacking them, presumably on account of sluggishness of intoxicated larvae to avoid the parasitoid (*311*).

Taken together, the evidence presented advocates for use of plant resistance and biological control based on benzoxazinoid hydroxamic acids on account of their negative effects on the pest and positive or neutral effects at the third trophic level.

OTHER ECOLOGICAL ROLES OF BENZOXAZINOID HYDROXAMIC ACIDS

The incorporation of rye as cover crop before planting cotton reduced damage by the root-knot nematode *Meloidogyne incognita* (*312*), the effectiveness of the treatment decreasing with time (*313*). Since rye herbage contains benzoxazinoid hydroxamic acids and their concentration decreases with time, these results suggested their involvement in nematode control. In vitro bioassays were performed on the effects of DIBOA, DIMBOA and their decomposition products, MBOA and BOA, respectively on second-stage juveniles of *M. incognita* (*314*). All compounds negatively affected survival of second-stage juveniles; in general, DIBOA was more deleterious than DIMBOA and BOA, and DIBOA proved to be mainly nema-

tistatic rather than nematicidal. On the other hand, concentration of benzoxazinoid hydroxamic acids in seedlings was not related to *M. incognita* host status of six commonly used rye cultivars (*315*), and no relationship was found between reproduction of the stubby-root nematode *Paratrichodorus minor* and total concentration of benzoxazinoids in the roots of 12 maize inbreds (*316*). It would be interesting to study the in vitro effects on nematodes of other products derived from the transformation of benzoxazinoid hydroxamic acids in the soil as well as to analyze benzoxazinoid hydroxamic acids concentrations in root exudates of the cereals examined in relation to nematode resistance.

Triazine derivatives are frequently used herbicides, particularly in maize due to the tolerance exhibited by this crop. Detoxification of these herbicides occurs by hydroxylation mediated by benzoxazinoid hydroxamic acids, conjugation to glutathione catalyzed by glutathione *S*-transferases (*317*), and N-dealkylation probably catalyzed by cytochrome P450 (*318*). The relative importance of these three mechanisms varied as the maize plant aged: high hydroxylating activity was found in leaves of young seedlings, medium hydroxylation activity which did not vary with age was observed in the roots, glutathione conjugation was highest in older plants, and dealkylation represented only a small proportion of detoxification pathways (*319*). Pure benzoxazinoid hydroxamic acids and also maize root exudates were able to in vitro detoxify triazines and also their dealkylation products by converting them to hydroxyatrazines (*320*). On the other hand, the tolerance of vetiver (*Chrysopogon zizanioides*, Poaceae) to atrazine in the growth medium was shown not to depend on the presence of benzoxazinoid hydroxamic acids and hydroxylation of the triazines (*321*). The chemical role of benzoxazinoid hydroxamic acids as a catalyst or as a reagent in the hydroxylation reaction is not yet clear (*322*).

Benzoxazinoid hydroxamic acids are strong chelating agents (*323, 324*). When DIMBOA-iron and DIBOA-iron chelates were supplied in the hydroponic growth medium of maize, rice and oat seedlings presenting iron-deficiency chlorotic symptoms, the chelates were taken up by plant tissues and the chlorotic symptoms eventually disappeared (*132*). These experiments suggest that benzoxazinoid hydroxamic acids present in root exudates (*125*) can act as phytosiderophores. Furthermore, benzoxazinoid hydroxamic acids present in roots of maize have been proposed to detoxify aluminum incorporated into the plant from the root environment by chelation, thus providing evidence for a role of benzoxazinoid hydroxamic acids in plant defense against aluminum toxicity (*325*).

USE OF BENZOXAZINOID HYDROXAMIC ACIDS IN PEST AND WEED CONTROL

The information accumulated on benzoxazinoid hydroxamic acids from cereals has clearly demonstrated the important role these compounds play in the defense of the plant against a wide variety of organisms. During the last decades, some success has been achieved in the production through conventional breeding of cereal cultivars with resistance to certain organisms based on benzoxazinoid hydroxamic acids. Further efforts should take into acount that the increase of benzoxazinoid hydroxamic acids concentration in a plant is not devoid of risks in terms of yield costs and the potential to induce resistance in the target organisms. Although limited studies have shown these two factors not to be of paramount concern (on one hand, grain yield in a set of 26 Hungarian wheat genotypes was not correlated with benzoxazinoid hydroxamic acids concentrations, suggesting that accumulation of benzoxazinoid hydroxamic acids does not impose a cost (*242*), and on the other, biochemical studies have shown that the mode of action of benzoxazinoid hydroxamic acids on target organisms tends to be multifactorial, thus decreasing the chances of resistance emergence), these potential problems can be minimized by directing breeding programs to specific combinations of plant germplasm and target organisms in such a way that benzoxazinoid hydroxamic acids increases are obtained only when needed, where needed, and to the levels needed. Such programs could be based on screening germplasm of cereals and their ancestors for resistance toward relevant pests or for allelopathic properties, detailed knowledge of the life cycle of the pest or weed in relation to that of the crop, detailed knowledge of the interface between the plant and the pest, weed or microorganism, and in vitro effects of targeted allelochemicals on the target organisms.

The use of *Agrobacterium tumefaciens* for transformations aiming at increased benzoxazinoid hydroxamic acids concentrations can also be considered in view of current information available. Thus, although DIMBOA in maize seedling extracts was shown to inhibit the growth of *A. tumefaciens* and was a potent inhibitor of the acetosyringone-induced expression of the *vir* gene necessary for DNA transfer to the bacterium host (*326*), and also that HDMBOA present in the maize root exudates was a strong inhibitor of growth of *A. tumefaciens* and also *vir* gene expression (*187*), variants of the bacterium resistant to HDMBOA-mediated inhibition of *vir* gene expression could be selected, thus expanding the biotechnological potential for transformation of maize plants using *Agrobacterium* (*187*), and DIMBOA-resistant strains of *A. tumefaciens* have been found and used to transfer genes in maize meristems and immature embryos (*327*). These results open the way toward the transformation of cereals with nil or low concentrations of benzoxazinoid hydroxamic acids by incorporation or augmentation of the number of copies of *Bx* genes, respectively.

Interesting challenges remain ahead if the full potential of benzoxazinoid hydroxamic acids as defensive or allelopathic compounds of cereals is to be achieved. Although the concentration of benzoxazinoid hydroxamic acids in the young plant seems sufficient to confer resistance toward a variety of organisms, the decrease of benzoxazinoid hydroxamic acids concentration with plant age renders them ineffective toward pests of mature plants or weeds at the mature crop stage. Efforts could be directed toward increasing benzoxazinoid hydroxamic acids concentrations in the plant as a whole at all its development stages or, preferably, they could be aimed at increasing benzoxazinoid hydroxamic acids at the tissues where they are required for a particular plant−pest or plant−weed interaction and to the minimal level which will efficiently control such pest or weed. Efforts to increase benzoxazinoid hydroxamic acids concentration at a particular stage of the plant when they are mostly needed for pest or weed control will rely on the identification of factors controlling the expression of genes involved in benzoxazinoid hydroxamic acids biosynthesis. It should be borne in mind however that alteration of a biosynthetic pathway may create shortages in the intermediates needed for the biosynthesis of other important metabolites or even produce the accumulation of toxic intermediates eventually leading to autotoxicity.

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