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# Induced disease resistance in plants by chemicals

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**Abstract**

Plants can be induced locally and systemically to become more resistant to diseases through various biotic or abiotic stresses. The biological inducers include necrotizing pathogens, non-pathogens or root colonizing bacteria. Through at network of signal pathways they induce resistance spectra and marker proteins that are characteristic for the different plant species and activation systems. The best characterized signal pathway for systemically induced resistance is SAR (systemic acquired resistance) that is activated by localized infections with necrotizing pathogens. It is characterized by protection against a broad range of pathogens, by a set of induced proteins and by its dependence on salicylic acid (SA). Various chemicals have been discovered that seem to act at various points in these defense activating networks and mimic all or parts of the biological activation of resistance. Of these, only few have reached commercialization. The best-studied resistance activator is acibenzolar-S-methyl (BION). At low rates it activates resistance in many crops against a broad spectrum of diseases, including fungi, bacteria and viruses. In monocots, activated resistance by BION typically is very long lasting, while the lasting effect is less pronounced in dicots. BION is translocated systemically in plants and can take the place of SA in the natural SAR signal pathway, inducing the same spectrum of resistance and the same set of molecular markers. Probenazole (ORYZEMATE) is used mainly on rice against rice blast and bacterial leaf blight. Its mode of action is not well understood partly because biological systems of systemically induced resistance are not well defined in rice. Treated plants clearly respond faster and in a resistant manner to infections by the two pathogens. Other compounds like beta-aminobutyric acid as well as extracts from plants and microorganisms have also been described as resistance inducers. For most of these, neither the mode of action nor reliable pre-challenge markers are known and still other pathways for resistance activation are suspected. Resistance inducing chemicals that are able to induce broad disease resistance offer an additional option for the farmer to complement genetic disease resistance and the use of fungicides. If integrated properly in plant health management programs, they can prolong the useful life of both the resistance genes and the fungicides presently used.

## Introduction: induced resistance processes in plants

In nature plants survive in the face of attack by many microbial organisms that threaten their survival and attempt to use them as a food source by employing several layers of defense responses. In addition to specific defense responses based on so-called R-genes, against certain strains of a pathogen, plants have broad-spectrum defense responses which are preformed, such as surface waxes, or that can be induced locally or systemically by biotic or abiotic agents in nature (Kuć,

1982; 1984). A short summary of the current status of the research on induced plant defenses will introduce a discussion of chemical plant activators.

Induced resistance mechanisms change the outcome of subsequent challenge inoculations following initial challenge from normally compatible interactions to incompatible ones, which resemble interactions on genetically resistant cultivars. Phenocopies of a genetically resistant reaction can also be observed following the application of some anti-fungal compounds, such as fosetyl or metalaxyl. These fungicides have a fungistatic action and alter pathogenic fungi in a way such that they are recognized as incompatible by a normally compatible and susceptible host plant (Staub et al., 1992; Sisler and Ragsdale, 1995). This reflects the delicate balance between susceptible plants and compatible pathogens that is required for disease to develop. This balance can be upset from both the plant and the pathogen side to produce incompatible interactions. It is therefore not always trivial to determine whether the primary effect of a compound is on the plant or on the pathogen and it is virtually impossible to do this if only post-challenge evidence is available.

The best understood systemically induced plant defense mechanism is 'systemic acquired resistance' (SAR). It is characterized by broad-spectrum disease resistance that is activated systemically in induced plants following localized inoculations with necrogenic pathogens which can be viruses, bacteria or fungi (Kuć, 1982; Kessmann et al., 1994). The activated disease resistance is effective against both the inducing pathogen and other, unrelated pathogens, which again may be bacteria, viruses or fungi. Classic examples of biological inducers of SAR are tobacco mosaic virus (TMV) on local lesion tobacco lines (Ross, 1961) and tobacco necrosis virus (TNV) or *Colletotrichum lagenarium* on cucumber (Kuć, 1982; 1984). The discovery of chemicals that at very low rates are able to activate SAR type resistance in many plant species, most of which had not been shown previously to contain a SAR response system, has stimulated a great deal of research in this area (Métraux et al., 1991; Kessmann et al., 1994) and produced a wealth of fundamental knowledge about active local and systemic plant defense mechanisms against diseases (Ryals et al., 1996; Sticher et al., 1997).

In dicotyledonous plants (dicots) the biological induction of the SAR response by localized infections with necrogenic pathogens is associated with the systemic accumulation of salicylic acid (SA) and certain pathogenesis-related (PR) proteins. In cucumber, tobacco and *Arabidopsis thaliana* (Arabidopsis), SA levels have been shown to increase in the inoculated tissue as well as in uninoculated systemic tissue prior to the establishment of induced disease resistance (Kessmann et al., 1994; Sticher et al., 1997). Removal of SA in transgenic tobacco and Arabidopsis plants that produce the bacterial SA-degrading enzyme salicylate hydroxylase results in plants (NahG) that are a) more susceptible to diseases in general and b) unable to mount an SAR response after biological induction (Gaffney et al., 1993; Ryals et al., 1996). They do not become resistant to subsequent pathogen challenge and they do not accumulate PR-proteins systemically. Earlier grafting experiments had indicated that SA is not the systemic signal but that it is necessary for the activation of the resistant state in the systemic part of biologically induced tobacco plants (Vernooij et al., 1994). More recent studies with plants expressing salicylate hydroxylase with a promotor that is expressed in the phloem suggest that SA in the phloem is important for systemic signaling. The exact role of SA in the systemic signaling pathway is likely to remain a stimulating field of research in the future (Darby et al., 2000).

The discovery of the central role of SA in plant defense and SAR was made several years after it had been found that exogenous application of SA to tobacco plants results in disease resistance which is correlated with PR-gene expression (White, 1979). Both, the spectrum of resistance and the set of PR-proteins that are induced are highly plant specific (Kessmann et al., 1994; Sticher et al., 1997). PR-proteins include glucanases (PR-2), chitinases (PR-3) and a thaumatin-like protein (PR-5); for others, such as PR-1, no known biochemical function has been defined. Some anti-fungal or anti-bacterial activity has been demonstrated *in vitro* for PR-proteins and in some cases transgenic plants over-expressing PR-proteins became more resistant. However, the spectrum of the activities described for individual PR-proteins was much narrower than that observed on SAR activated plants (Kessmann et al., 1994; Ryals et al., 1996). Thus, the broad spectrum of resistance characteristic for SAR may require the coordinated expression of the full complement of PR-genes.

In monocotyledonous plants (monocots) less information is available on pathogen-induced SAR. Only a few reports exist in the literature describing local and systemic acquired resistance in monocots resulting

from predisposing pathogen inoculations (Kessmann et al., 1994; Sticher et al., 1997). Also, the role of PR-proteins and SA has not been established for these systems (Vallelian-Bindschedler et al., 1998). It is more difficult therefore to correlate the activity of putative chemical inducers of SAR to the biological systems in monocots. However, SAR can be chemically activated in monocots by the same chemicals as in dicots (see below) which suggests that the key parts of the target area in the SAR signaling pathway are also conserved in monocots.

A biological system of induced systemic resistance (ISR) distinct from SAR has been described for rhizosphere bacteria in several dicots (van Loon et al., 1998). It is not dependent on SA accumulation in the plants but requires functioning jasmonic acid (JA) and ethylene (ET) responses for activation. No clear biochemical markers have been established for this biological system for the induced state, but resistance responses are more effective in induced plants against a broad spectrum of diseases. Application of higher levels of JA or ET induces the production of antimicrobial peptides (defensins), which however, do not seem to be required for rhizobacteria-induced resistance (Pieterse et al., 1998). JA, ET and defensins also seem to be involved in the systemic activation of resistance in Arabidopsis by Alternaria. For defensins to be expressed in this system, JA and ET responses seem to have to work in parallel (Penninckx et al., 1998).

There is increasing evidence to show that interactions exist between the different defense signaling pathways for resistance activation against microbial pathogens and insects (Bostock, 1999). Induced insect resistance is a well characterized wound response in tomatoes that involves the systemic signal peptide systemin and JA for the induction of proteinase inhibitors in protected leaves. This response can be inhibited by SA that is required for the SAR pathway. Another interaction between pathways is described in Arabidopsis for pathogen-induced SAR and rhizobacteria-induced ISR which both require the wild-type NIM1 gene product for activation (van Loon et al., 1998). This wild-type gene is required for both biological and chemical activation of SAR (Lawton et al., 1996). The increasing knowledge about the network of defense signaling pathways that are activated in plants as a response to biological and physical stimuli makes it possible to investigate more rapidly the mode of action of novel chemicals that are proposed to activate plant resistance mechanisms.

## Chemicals with resistance inducing activity

In this chapter we review defined synthetic chemicals that are shown or proposed to be activators of disease resistance in plants with some pre-challenge evidence for resistance activation and their possible impact for crop protection. Natural signaling molecules like SA, JA, systemin and elicitors are components of the biological induction and will not be reviewed in detail in this chapter. Many reports exist in the literature about undefined chemicals and about extracts from plants and microbes with suggested resistance inducing activity that for the most part have not been commercialized (Sisler and Ragsdale 1995; Sticher et al., 1997; Lyon and Newton 1999). For some of these agents, the evidence for inducing activity via the plant is not conclusive and more research is needed to demonstrate it.

### *Isonicotinic acids and benzothidiazoles (BTH) as substitutes for SA acid in SAR*

Using the biologically well defined model for SAR on cucumber (Kuć, 1982), two classes of chemicals were discovered that mimic the biological activation of SAR by necrogenic pathogen (Figure 1): 2,6-dichloro isonicotinic acid (INA) and its derivatives (Métraux et al., 1991) and the benzo[1,2,3]thiadiazole derivatives (Kunz et al., 1997) with S-methyl benzo[1,2,3]thiadiazole-7-carbothiate (acibenzolar-S-methyl (ASM) in Figure 1) as the first commercial product marketed under the trade names BION®, ACTIGARD™ and BOOST®. These chemicals do not show any antimicrobial activity *in vitro* and activate resistance against the same spectra of pathogens as the biological inducers of SAR on the plant species where this information is available. At the molecular level, these chemicals induce the same characteristic set of SAR genes as does biological or SA induction (Friedrich et al., 1996). From these findings and results with NahG plants and SAR-deficient *nim1* mutants of Arabidopsis, it was concluded that both chemicals act as functional analogs of SA in the SAR signaling pathway (Lawton et al., 1996; Kessmann et al., 1996; Ryals et al., 1996). It is interesting to note that the discovery of these two chemical classes of SAR inducers was made through serendipity before the important endogenous role of SA in the biological induction of SAR in cucumber, tobacco and Arabidopsis was found (Kunz et al., 1997).

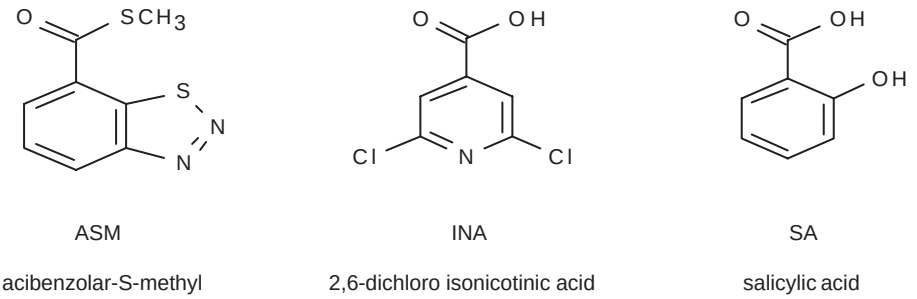



*Figure 1.* Chemical activators of SAR: acibenzolar-S-methyl (ASM), a benzothiadiazole (BTH) derivative; 2,6-dichloro isonicotinic acid (INA) and the natural SAR signal molecule salicylic acid (SA).

While none of the INA derivatives (Figure 1) were commercialized (mainly due to insufficient crop tolerance), they served as important research tools to investigate the biology and the mode of action of SAR induced by chemicals. This led to the first demonstration that xenobiotic compounds can induce the same resistance spectrum and the same biochemical changes as previously described for the biological SAR induction on cucumbers and tobacco (Metraux et al., 1991; Kessmann et al., 1994). INA is fully systemic and does not require SA production for the activation of the SAR response (Metraux et al., 1991).

Like INA, the spectrum of resistance activation and the induced biochemical changes by ASM matches that of the biological induction on those crops where such information is available (Lawton et al., 1996; Friedrich et al., 1996). In wild-type plants, this activation by ASM takes place without the accumulation of SA. On NahG tobacco and Arabidopsis plants, which lack SA and do not respond to biological induction, ASM is still fully active. In addition, *nim1* mutants of Arabidopsis selected for ASM insensitivity lost at the same time their responsiveness to SA and INA as well as to biological inducers of SAR (Ryals et al., 1996). This is therefore strong evidence that ASM and INA are acting in the signal pathway of biological SAR induction at or downstream of the SA site of action (Figure 2) (Kessmann et al., 1996; Ryals et al., 1996). These compounds are systemic themselves and therefore may not induce the still elusive systemic signal of the biological SAR process, nor do they induce the production of SA in the treated plants (Figure 2).

In wheat, the same set of genes (WCI genes) was induced by the synthetic chemical SAR activators, INA and ASM, as well as by SA (Goerlach et al., 1996). Induction of WCI genes by the three chemicals correlated with the protection of treated wheat against powdery mildew. PR1 type genes, common markers for SAR in several dicots, are induced by pathogens in wheat but not by the SAR activators (Molina et al., 1999a). In corn, on the other hand, a PR1 type protein is induced by both pathogens and chemical SAR activators (Morris et al., 1998). In the absence of good biological inducers of SAR in monocots, these results suggest a strong similarity between critical parts of the SAR type signal pathway in dicots and monocots and that the sets of induced proteins during activation of SAR are also crop specific in monocots.

ASM activates a very wide spectrum of resistance under practical field conditions that includes fungal, bacterial and viral pathogens. This is illustrated for tobacco in Figure 3 with data from Novartis. Of particular relevance is the protection against the destructive blue mold as well as against bacterial and virus diseases. Against some of the latter, no effective chemical control methods are available today and the blue mold pathogen has developed resistance against the most effective fungicides. On tobacco, one interesting difference between the chemical and the biological induction is the duration of protection. Chemical treatments need to be applied at intervals of 1–2 weeks, while the biological induction lasts much longer (Kuć, 1984).

Other dicots where ASM has shown activation of broad-spectrum disease resistance under field conditions are tomatoes, and some vegetable and fruit crops (Tally et al., 1999). The spectrum of protection is specific for each crop and in some cases includes some insects and nematodes (Inbar et al., 1998; Owen et al., 1998). There is a need for careful adherence to the use recommendations for each crop to optimize resistance activation and yield benefits as well as to avoid negative side-effects on plant growth. Often, best result are obtained when ASM is combined with low rates

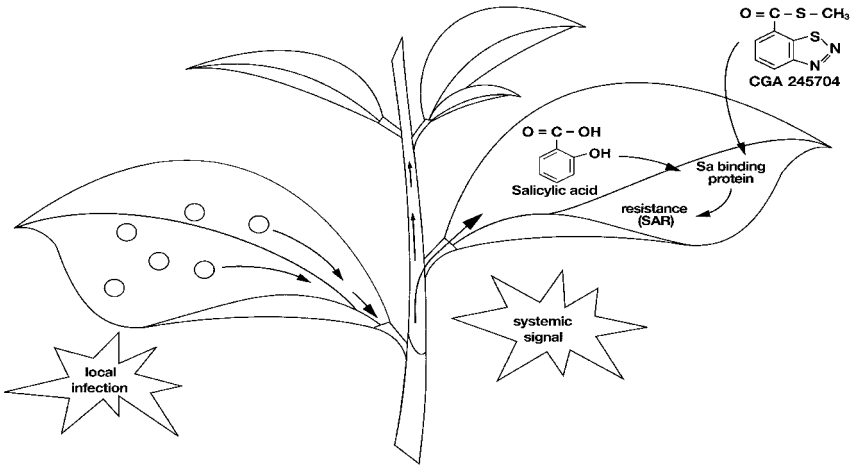



*Figure 2*. Site of action of ASM (CGA 245704) in the SAR signal transduction pathway (from Kessmann et al., 1996).

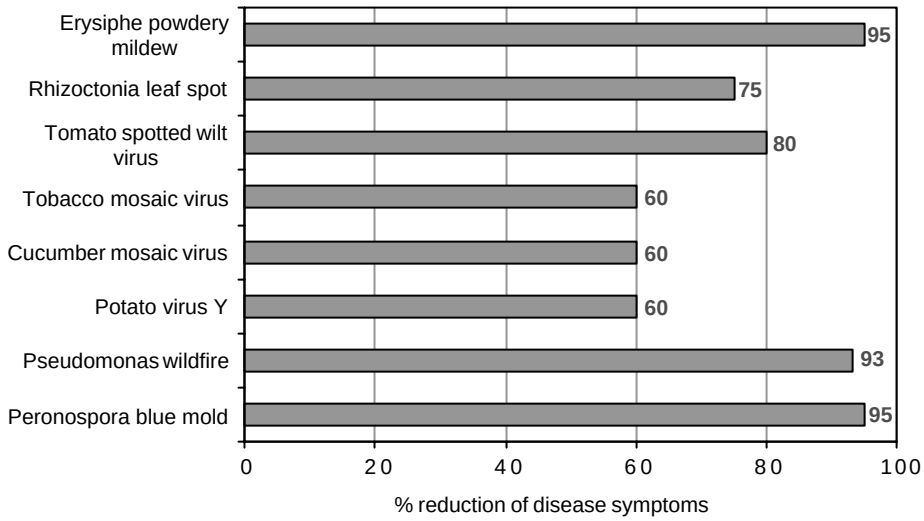



*Figure 3*. Broad-spectrum SAR activation by ASM against diseases of tobacco: summary of field trial results with BION®/ACTIGARD™ used at 12–37 g ASM per ha (Novartis data).

of fungicides or bactericides (Ruess et al., 1996; Tally et al., 1999).

The resistance spectrum activated by ASM on wheat covers mainly powdery mildew, with side-effects against Septoria and leaf rust (Ruess et al., 1996). Resistance activation of wheat by a low rate of 30 g ai/ha of ASM in the field confers a protection of up to 10 weeks against powdery mildew. It has to be applied preventatively because established infections cannot be stopped by ASM activation of SAR (Ruess et al., 1996). Field results with ASM (Figure 4) illustrate some key features of the resistance activation by ASM on wheat compared to the activity of fungicides. The initial reduction of powdery mildew symptoms was stronger for the fungicide mixture propiconazole (PPZ) plus fenpropidin (FPD) than for ASM. However, resistance activation by ASM showed a superior long-term protection. The combination of the two principles – ASM activating host resistance and the direct action of fungicides – gave best results. Similar results from practical trials on wheat were reported by others (Ruess et al., 1996; Rossignol et al., 1997).

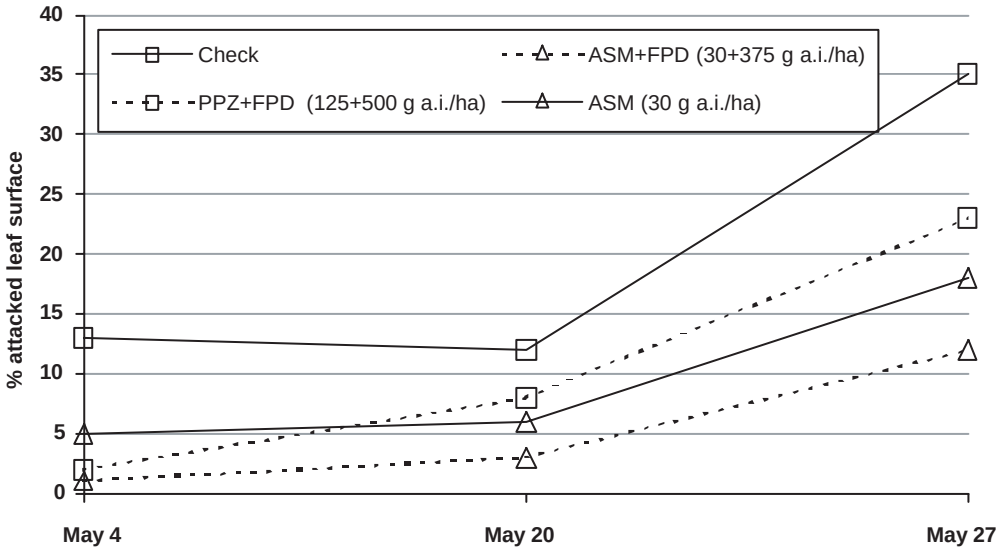



*Figure 4.* Resistance activation by ASM on wheat against powdery mildew under field conditions: BION® (ASM) applied alone and in combination with fenpropidin (FPD) in comparison to the fungicide mixture fenpropidin/propiconazole (PPZ). Foliar applications April 15 at GS 31.

On activated plants, the powdery mildew infections are stopped by hypersensitive reactions and by the faster formation of papillae at the sites of attempted penetration (Goerlach et al., 1996). Histological studies showed that the development of powdery mildew on activated wheat leaves was inhibited at several stages from initial penetration to the formation of the secondary haustoria. This observation suggests that, as is in dicots, multiple mechanisms operate in activated wheat to stop powdery mildew infections. This is likely to limit the pathogen's possibilities to develop resistance against activation of SAR (Kessmann et al., 1996).

Several other monocots such as rice and bananas respond well to SAR activators under practical conditions (Tally et al., 1999). On transplanted rice, application of low rates of ASM to seedling boxes induces long-lasting resistance to rice blast up to panicle formation (Staub et al., 1997). Generally, on monocots the resistance induced by ASM appears to be much longer lasting than that induced on dicots. The basis for this interesting difference is not known.

The spectra of resistance activation by ASM against major pathogen groups is summarized in Table 1 for some important crops and crop groups (Tally et al., 1999). It is evident from this Table that the spectra of resistance activated by ASM are very crop specific. For example, on tomatoes, resistance is activated against late blight (*Phytophthora infestans*) while on potato no reliable activation against the same pathogen is observed following ASM applications (Tally et al., 1999). Thus, assumptions cannot be made for resistance activation based on the relatedness of pathogens; the spectrum is determined for each crop.

*Table 1.* Summary of resistance activation spectra observed for ASM on different crops and crop groups. Adapted from Tally et al. (1999)

| Crop | Bacteria | Viruses | Fungi | Insects | Nematodes |
|---|---|---|---|---|---|
| Cereals | | | ✓ | | |
| Rice | ✓ | | ✓ | | |
| Tobacco | ✓ | ✓ | ✓ | | |
| Potato | | ✓ | | ✓ | |
| Tomato | ✓ | ✓ | ✓ | ✓ | |
| Vegetables | ✓ | ✓ | ✓ | ✓ | |
| Pome fruit | ✓ | | ✓ | | |
| Stone fruit | ✓ | | | | |
| Mango | ✓ | | ✓ | | |
| Citrus | ✓ | ✓ | ✓ | | |
| Grapes | | | ✓ | | ✓ |
| Banana | | | ✓ | | ✓ |

✓ = activation of resistance reported in field trials.

*Chemicals inducing SAR via local lesions*

Localized application of various salts, such as phosphates, silicates and oxalates, to plants are reported to systemically induce resistance to a range of pathogens (Mucharromah and Kuć, 1991; Sticher et al., 1997). Activation was usually highest when there was lesion-like tissue damage at the points of application, suggesting that these chemicals mimic the biological SAR induction by inducing local lesions. Local lesion formation may also be the initial step for SAR type resistance induction by unsaturated fatty acids in potato (Cohen et al., 1991) and that described for harpin proteins from phytopathogenic bacteria or elicitin peptides from Phytophthora species (Sticher et al., 1997). In addition, sublethal concentrations of PPO type herbicides have been shown to induce SAR via lesion formation (Molina et al., 1999b). In contrast to the SA independent SAR activation by ASM and INA, such chemicals would be expected to induce systemic signals and the production of SA. This type of chemical activation of resistance has not been developed for practical use yet. It may be difficult to develop for safe use in practice since lesion-like damage is inherent in the mode of action.

*Probenazole*

Probenazole is mainly used on rice against rice blast (*Pyricularia oryzae*) and bacterial blight (*Xanthomonas oryzae*) either as seedling box treatment or a granular treatment of paddy rice (Watanabe, 1977). In addition, it is registered in several other crops mainly against bacterial pathogens. Probenazole is taken up by rice plants after spray or paddy application and distributed throughout the plants as the parent compound or as one of its metabolites (Figure 5). The main metabolites of probenazole in rice are 2-sulfamoylbenzoate, saccharin and N-$\beta$-D-glucopyranosylsaccharin (Uchiyama et al., 1973).

The weak activity observed *in vitro* against these rice pathogens and the strong protective effect on treated rice plants suggested that the main activity is via activation of host defense mechanisms. Watanabe et al. (1979) reported an increase of antifungal lipid fractions in treated non-inoculated rice plants. A RPR1 gene (rice probenazole responsive) is induced in rice treated with probenazole, ASM and SA (Sakamoto et al., 1999). The induction of this gene correlated with protection against *P. oryzae*. The RPR1 protein contains a nuclear binding site and leucine rich repeats, thus resembling several known R gene products. When tested on cultured parsley cells, saccharin, but not probenazole, showed sensitizing activity for enhanced response to fungal cell wall elicitors (Siegrist et al., 1998). It is not known, however, whether transformation of probenazole to saccharin in rice is required for its activity. When tested on cellophane membranes *in vitro*, probenazole at 3 ppm had considerable negative effects on appressoria formation by Pyricularia, almost completely blocking penetration of the membrane (Watanabe, 1977). This suggests that part of the protective effect against this pathogen might be due to direct effects on the fungus.

*$\beta$-Amino butyric acid (BABA)*

D,L-$\beta$-aminobutyric acid (BABA) or its 3-(S)-enantiomer have been reported to activate disease resistance, especially against downy mildews in various crops, when used at relatively high rates. Interestingly, a curative effect of BABA application has also been reported (Cohen, 1995; Tosi et al., 1998). The mode of action of proposed resistance induction by

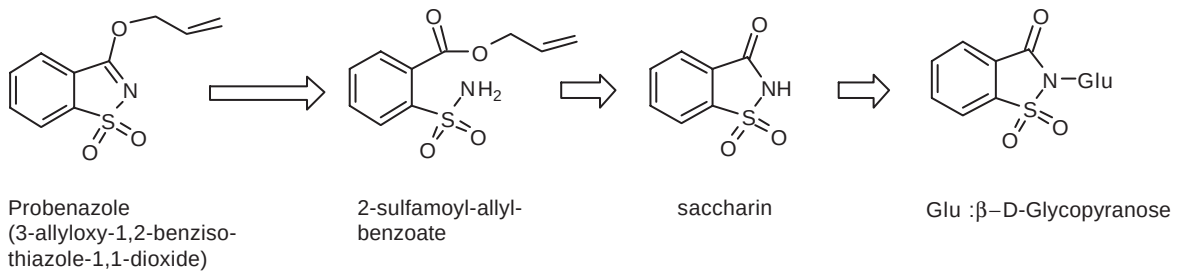
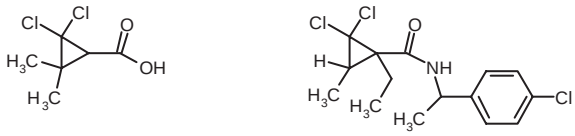



*Figure 5.* Probenazole and its metabolites in rice plants.




WL 28325 Carpropamide

*Figure 6.* Chemical structure of WL 28325 and carpropamide.

BABA has not been elucidated. PR1 induction has been reported after applications of high concentration of the compound in tomato (Cohen et al., 1994) and activation has been reported to depend on SA accumulation and lesion formation (Siegrist et al., 2000). However, the activation of resistance in Arabidopsis by BABA does not seem to function via SA, JA or ET dependent signal pathways (Mauch-Mani, 1999).

*Cyclopropane carboxylic acid derivatives: WL 28325 and carpropamide*

2,2-Dichloro-3,3-dimethylcyclopropane carboxylic acid (WL 28325) (Figure 6) has been known for more than 20 years as a specific and systemic research compound against rice leaf blast. It shows low direct fungitoxicity against pathogen *P. oryzae* and treated plants respond more quickly and in a resistant manner to infection (Langcake et al., 1983). Clear pre-challenge markers for the putative induced state are lacking. However, a faster reaction of treated plants to picolinic acid, a pathotoxin from *P. oryzae*, is good evidence that this chemical activates resistance responses in the treated rice plants (Langcake et al., 1983).

In carpropamide ((1RS, 3SR)-2,2-dichloro-N-1-(4-chlorophenyl)ethyl-1-ethyl-3-methyl-cyclopropane-carboxamide), a similar carboxylic acid moiety is incorporated. While the main protective effect against *P. oryzae* is based on the inhibition of fungal melanin biosynthesis, it has been proposed, that the long-lasting activity after single treatments originates from the cyclopropane part of the molecule which may act as a plant activator (Thieron et al., 1998). The indirect evidence for inducing activity by carpropamide is that the reversal of melanin inhibition by feeding of blocked precursors does not result in loss of protection on treated rice plants. Tricyclazole, which interferes at a different step in melanin biosynthesis and lacks the cyclopropane moiety, lost its protective activity upon feeding of the appropriate melanin precursor (Thieron et al., 1998).

**Outlook for chemical activators of disease resistance in crop protection**

Research on chemically induced disease resistance with the commercially available activators, and a large number of studies with various biological systems and experimental agents has led to a dramatic increase in our knowledge about the various defense signaling pathways in plants. Of these pathways, the SA dependent SAR pathway seems to be the most robust to be exploited for practical crop protection. With this knowledge and with the pathway mutant sets available in Arabidopsis, it will be much easier in the future to determine quickly whether novel disease control chemicals with suspected inducing activity do in fact have primary targets in the plant. This will also help the optimal utilization of the complex interactions between the various signaling pathways for practical crop protection. Unfortunately, no such model system is available in monocots, where much less is known about the signaling pathways involved in biological or chemical stimulation of disease resistance. However, the experience with the chemical plant activators available, so far, suggests that some basic inducible broad-spectrum defense responses are preserved across the plant kingdom.

Chemical activation of disease resistance in plants represents an additional option for growers to protect their crops from losses due to plant diseases. Against some pathogens, like bacteria and viruses, it may be the best option for chemical control where genetic resistance is not available or not sufficient. Against dynamic fungal pathogens with a history of adaptation to fungicides or to resistant cultivars the integration of this new technology of activating broad-spectrum plant defenses with genetic resistance and fungicides is likely to offer a more sustainable plant health management system. There are indications from other pathosystems that such adaptation of pathogens to genetically resistant cultivars can indeed be slowed down by plant activators such as ASM (Romero et al., 1998).

A synthetic resistance activator must fit the same stringent set of criteria concerning environmental and toxicological safety and reliability under practical conditions and it must be commercially interesting for agrochemical producer, farmer and supplier. Integration into existing crop management schemes or development of new crop management programs may be possible with this novel tool of induced plant defense.

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