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Review

Functional Analogues of Salicylic Acid and Their Use in Crop Protection

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Abstract: Functional analogues of salicylic acid are able to activate plant defense responses and provide attractive alternatives to conventional biocidal agrochemicals. However, there are many problems that growers must consider during their use in crop protection, including incomplete disease reduction and the fitness cost for plants. High-throughput screening methods of chemical libraries allowed the identification of new compounds that do not affect plant growth, and whose mechanisms of action are based on priming of plant defenses, rather than on their direct activation. Some of these new compounds may also contribute to the discovery of unknown components of the plant immune system.

Keywords: salicylic acid; functional analogues; priming; crop protection

1. Introduction

Increasing demand for environmentally-friendly alternatives to traditional pesticides is an impetus for designing new biological strategies for crop protection. Stimulating the natural plant immunity through induced resistance is among those strategies [1]. Upon infection, the plants are able to fight against pathogen attacks by activating their immune mechanisms that are initiated after the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors. This activated immunity is called PAMP-triggered immunity (PTI) [2]. However, some pathogens are able to suppress PTI via effector proteins. In this case, plants are able to defend themselves via effector triggered immunity (ETI) involving resistance genes products (R) and is usually associated with hypersensitive responses (HR) that are characterized by rapid programmed cell death at the penetration site [3]. Both responses involve accumulation of reactive oxygen species (ROS) in infected tissues, followed by the activation of mitogen activated protein kinases (MAPKs) and increase in the expression of defense-related genes, including pathogenesis that are related (*PR*) genes and salicylic acid (SA) accumulation [4,5]. Subsequently an immune response, called systemic acquired resistance (SAR) is induced in distal non-inoculated parts of the plant against broad spectrum of pathogen [6]. Other phytohormones including jasmonic acid (JA), ethylene (ET), and abscisic acid (ABA) are also involved in regulation of induced plant immunity. While SA induces defenses by and against biotrophic pathogens JA mediate defenses by and against necrotrophic pathogens and herbivorous insects. The cross-talk among these different signaling pathways leads to the fine-tune of the plant defense responses against specific aggressors [7,8].

SAR is considered as the most agronomically relevant type of plant immunity [6] and can also be triggered by signal molecules that are involved in plant resistance to pathogens, including SA and a wide range of synthetic compounds. Among these compounds functional analogues of SA are able to activate plant defense responses and provide attractive alternatives to conventional biocidal

agrochemicals. They are able to mimic a subset of known SA functions by directly interfering with its receptors or by triggering transcriptional and physiological responses that are related to those induced by SA without directly interfering with SA targets [9]. Although they generally do not possess antimicrobial activity in vitro and can activate resistance against broad spectra of pathogens by inducing SAR genes that are triggered by biological or SA inducers they are many problems that growers must consider during their use in crop protection, including incomplete disease reduction and the fitness cost for plants [10]. High-throughput screening methods of chemical libraries allowed the identification of new compounds that do not affect plant growth, and whose mechanisms of action are based on priming of plant defenses upon pathogen infection rather on their direct activation [11–13].

After a brief description of the mode of action of SA in plant defense we will review the most important groups of functional analogues of SA with their use as plant protective agents. Particular attention will also be given to the methods used for screening of chemical libraries to obtain new compounds. These new agrochemicals will not only provide resistance against a broader spectrum of plant pathogens, but may also contribute to the identification of novel pathway components of SAR.

2. Mode of Action of SA in Plant Defense

SA is one of several plant hormones acting as an endogenous signal to trigger plant immunity responses and to allow the establishment of disease resistance. The SA pathway is primarily induced by and against biotrophic pathogens and is often hindered by various feedback loops and cross-talk with other phytohormones that modulate the SA signal, including jasmonic acid (JA) and ethylene (ET) [7,8]. Exogenous application of SA can induce ROS production, *PR* genes expression, and disease resistance against a wide range of biotrophic and hemibiotrophic fungal, bacterial, viral, as well as phloem-feeding insects. For instance, exogenous application of SA confers resistance against tobacco mosaic virus (TMV) [7], cauliflower mosaic virus [14] and turnip crinkle virus in *Arabidopsis thaliana* [15]. Treatment of *Nicotiana benthamiana* with SA results in reduced grown gall symptoms caused by *Agrobacterium tumefaciens* [16]. It is also effective in controlling fire blight disease that is caused by the bacterium *Erwinia amylovora* in pear [17]. Regarding phytopathogenic fungi SA induces resistance in *A. thaliana* against the powdery mildew pathogen *Erysiphe orontii* [18] and the downy mildew pathogen *Hyaloperonospora parasitica* [19]. Its efficacy was also probed in tobacco against the powdery mildew pathogen *Oidium* sp. [20], in tomato against leaf blight caused by *Alternaria solani* [21], and in cherry fruits against fruit rot caused by *Monilia fructicola* [22].

SA is synthesized via two distinct and compartmentalized pathways [23]. It is produced through the phenylalanine pathway by decarboxylation of trans-cinnamic acid to benzoic acid, followed by hydroxylation to SA. Alternatively, cinnamic acid may be hydroxylated to o-coumaric acid and then decarboxylated to SA [24]. In the isochorismate pathway, SA synthesis involves isochorismate synthase (ICS), which converts chorismate to isochorismate [25]. The expression of *ICS1* is positively regulated by several transcription factors (TFs), including calmodulin-binding protein 60 g (CBP60g). PAMP recognition generates calcium influx in the cytosol which is transduced to calmodulin-binding protein CBP60g and WRKY28 triggering activation of isochorismate synthase and SA biosynthesis [26]. Recently, a third pathway involving cyanogenic glycosides, such as prunasin and mandelonitrile have been also recognized to be involved in SA synthesis in peach [27].

In *Arabidopsis*, the regulation of SA involves two lipase-like proteins acting upstream of SA: EDS1 (for enhanced disease susceptibility) and PAD4 (for phytoalexin deficient) [28]. EDS1 represents an important node that controls SA production to amplify defense signals. It forms a heterodimer with PAD4 that transduces ROS-derived signals leading to enhanced SA production through the accumulation of benzoic acid (BA) and its conversion to SA by benzoic acid 2-hydroxylase (BA2H) [29,30]. SID2 (for SA induction deficient) encodes for an ICS that is involved in the biosynthesis of SA, because a mutation *sid2* reduces SA synthesis in *A. thaliana* and the expression of the *PR1* gene [25]. EDS5, also named SID1, is involved in the regulation of SA. It belongs to the multidrug and toxin extrusion (MATE) transporter proteins and is located downstream of PAD4. It is involved in the transport of SA

precursors and its expression requires PAD4 [31]. EDS4 is another component that plays a role in SA signaling and in SA-induced SAR [32]. EDS1, PAD4, and EDS4 activate SID2, which produce SA [33].

Upon its synthesis in the chloroplast, SA is transported to the cytosol via EDS5 protein where it will be inactivated via glycosylation or methylation [7,34]. Glycosylation of SA generates SA 2-*O*-β-D-glucoside (SAG), which is transported to the vacuole and will be hydrolyzed to release free SA after pathogen attack [35]. Methylation of SA generates methyl SA (MeSA), which is supposed to be the mobile SAR signal that travels from the infected to the systemic tissues, where it activates resistance following its reconversion to SA. Following pathogen infection, SA levels increase dramatically in the inoculated leaves, however it is converted to biologically inactive MeSA by SA methyl transferase (SAMT). Once SA concentration becomes sufficiently high, it binds in the active site of salicylic acid binding protein 2 (SABP2) and prevents its ability to convert MeSA back into SA [35]. Methylation of SA causes a change in the potential redox of the chloroplast cell wall facilitating its translocation to cytoplasm of the distal, uninfected tissue. Since SA levels in the distal tissue are too low to inhibit SABP2, the transported MeSA is converted to active SA, which then induces systemic defense responses [35]. Other mobile signaling molecules includes a non-proteinaceous amino acid pipecolic acid (Pip) [36] and azelaic acid; a 9-carbon dicarobxylic acid, which has been reported to be limited to vascular sap in *A. thaliana* inoculated with *P. syringae* [37]. The diterpenoid Dehydroabietinal (DA) was also shown to be translocated far from treated tissues in *Arabidopsis*, tobacco, and tomato, where it enhances the accumulation of SA and the expression of *PR1* gene [38]. Other mechanisms that are preventing over-accumulation of SA and generation of the mobile signal of SAR involve its conversion to 2,3-dihydroxybenzoic acid (2,3-DHBA) by SA 3-hydroxylase (S3H; also termed DLOL1) and the formation of SA-amino acid conjugates such as salicyloyl-aspartate (SA-Asp) synthesized by a member of the GH3 acyl adenylase family of early auxin-responsive genes named GH3.5 [39].

Defense signaling downstream of SA is regulated via NPR1 and NPR3/4 homeostasis in a concentration dependent manner. This determines the levels and selective activation of defense responses, which should be switched on during pathogen infection [40]. NPR1 is a considered as master regulator of the SA-mediated defense genes. It binds to SA through two Cysteine residues 521 and 529 [41]. NPR1 is located in the cytoplasm, but pathogen induced SA accumulation activates its expression, and stimulates its translocation into the nucleus where it interacts with TGA transcription factors binding to the so called as-1 (activation sequence-1) like element of the *PR1* promoter [42]. In the absence of infection NPR1 is continuously cleared from the nucleus via proteasome-mediated degradation, a process mediated by NPR3 and NPR4, which are adaptors for Cullin 3 ubiquitin E3 ligase [40]. NPR4 maintains low NPR1 levels, however after infection, at higher concentration SA binds to NPR4 and disrupts the NPR1–NPR4 interaction, allowing for NPR1 to accumulate and defense signaling to occur. In cells containing sufficiently high SA levels, NPR3 binds NPR1; this promotes NPR1 turnover, which optimizes defense activation and resets NPR1 levels [43].

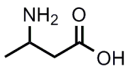
3. Functional Analogues of SA

Although SA is a potent inducer of plant resistance its rapid glycosylation often leads to its reduced efficacy. In addition, its phytotoxicity has prevented its development as plant protection compounds [44]. For this reason, several functional analogues of SA with stable and effective activities have been explored so far. Most of the synthetic compounds targeting SA pathways demonstrated their effectiveness as plant defense activators in the field of crop protection, while others constitute valuable tools for dissecting components of the plant immune system. Apart from β-aminobutyric acid (BABA), we have classified these compounds according to their structures: (I) salicylate and benzoate compounds; (II) nicotinic acid derivatives; (III) pyrazole, thiazole, and thiadiazole heterocycles; (IV) pyrimidin derivatives; and, (V) neonicotinoid compounds.

3.1. β-Aminobutyric Acid

BABA is a non-protein amino acid that is known to induce resistance against many plant pathogens in various systems, by inducing both SA-dependent and SA-independent plant defense mechanisms [45] (Table 1). BABA has been shown to protect *Arabidopsis* against *H. parasitica* and *Botrytis cinerea* [46]. In lettuce, application of BABA prior to inoculation with the fungal pathogen *Bremia lactucae* prevented pathogen development without the involvement of SA [47]. BABA also provided significant control of the late blight pathogen *Phytophthora infestans* on tomato [48]. BABA protected *Brassica napus* against the fungal pathogen *Leptosphaeria maculans* by activating SA synthesis and the expression of *PR1*, but was also found to act as an antifungal agent [49]. Field experiments revealed that BABA was able to reduce severity of *Plasmopara viticola* on grapevine [50]. BABA also provided significant control of potato late blight in the field when used alone or in combination of the standard fungicide [51]. In potato, it was able to induce HR-like lesions surrounded by callose and the production of H_2O_2, as well as the enhancement of phenolic content and activation of PR1 [52]. To elucidate in depth molecular mechanisms of BABA-induced resistance against potato late blight, Bengtsson et al., developed an original approach based on a transcript analysis in combination with quantitative proteomic analysis of the apoplast secretome. They showed that several processes that were related to plant hormones and amino-acid metabolisms were affected, in addition to genes that are involved in sterol biosynthesis that were down regulated and those involved in phytoalexin biosynthesis that were up-regulated [53].

Table 1. β-Aminobutyric acid and used pathosystems.

Chemical Name	Chemical Structure	Plant/Pathogen Interaction Laboratory/Field Experiments)	Reference
β-Aminobutyric acid		*Arabidopsis*/*hyaloperonospora parasitica, Botrytis cinerea* (Laboratory)	[46]
		Brassica napus/*Leptosphaeria maculans* (Laboratory)	[49]
		Lettuce/*Bremia lactucae* (Laboratory)	[47]
		Tomato/*Phytophthora infestans* (Laboratory)	[48]
		Potato/*Phytophthora infestans* (Laboratory/Field)	[51,52]
		Grapevine/*Plasmopara viticola*	[50]

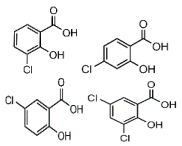
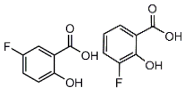
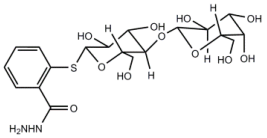
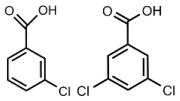
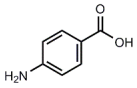
3.2. Salicylate and Benzoate Derivatives

Several derivatives of SA were tested as SAR activators in the greenhouse [54] (Table 2). 3,5-dichlorosalicylic acid, 4-chlorosalicylic acid, and 5-chlorosalicylic acid, induced *PR1* gene expression and enhanced disease resistance to TMV infection in tobacco [55]. Screening experiments revealed that the monosubstituted salicylates; 3-chlorosalicylic acid, 3-fluorosalicylic acid and 5-fluorosalicylic acid caused increased PR1 induction than SA and that substitution on position 3- or 5 enhanced further PR1 activity [56]. Recently, Cui et al. [57] synthetized a series of salicylic glycoconjugate containing hydrazine and hydrazone moieties and found that the salicylate hydrazine derivative was able to enhance cucumber resistance against several phytopathogenic fungi including *Colletotrichum orbiculare*, *Fusarium oxysporum*, *Ralstonia solani* and *Phytophthora capsici*. Although it is structurally related to SA it did not mimic the mode of action of SA as it activated the JA rather than SA pathway [57].

Aminobenzoic derivatives were also reported to induce SAR (Table 2). For instance, Para-aminobenzoic acid (PABA), which is a cyclic amino acid that belongs to the vitamin B group, was able to induce SAR in pepper against cucumber mosaic virus (CMV) and *Xanthomonas axonopodis* pv. *vesicatoria* through SA pathway [58]. The substituted benzoates, 3-chlorobenzoic acid and 3,5-dichlorobenzoic acid induced basal defense against *H. parasitica* in *A. thaliana* [54]. The compound 3,5-dichlorobenzoic acid, known as 3,5-dichloroanthranilic acid (DCA), was reported to efficiently trigger resistance of *A. thaliana* against *H. parasitica* and *P. syringae*. It up-regulates transcript levels of various known SA-responsive defense-related genes, such as *PR1*, *WRKY70*, and *CaBP22*. DCA does not require accumulation of SA and triggered immune responses that are largely independent

from *NPR1*. However, it partially targets a *WRKY70*-dependent branch of the defense signaling pathway [54]. Microarray analyses revealed that DCA triggers the expression of 202 genes that are commonly regulated by other functional analogues such as INA, and BTH, but also the expression of unique genes [59].

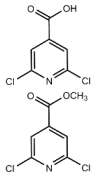
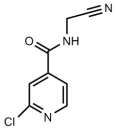
Table 2. Salicylate and benzoate derivatives and used pathosystems.

Chemical/Trade Name	Chemical Structure	Plant/Pathogen Interaction Laboratory/Field Experiments)	Reference
3-chlorosalicylic acid, 4-chlorosalicylic acid, 5-chlorosalicylic acid, 3,5-dichlorsalicylic acid		Tobacco/TMV (Laboratory)	[55]
3-fluorosalicylic acid, 5-fluorosalicylic acid		Tobacco/TMV (Laboratory)	[56]
2-(3,4-dihydroxy-6-(hydroxymethyl)-5-(3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl) thio)benzohydrazide: SA glucoconjugate hydrazine		Cucumber/*Colletotrichum orbiculare*, *Fusarium oxysporum*, *Ralstonia solani*, *Phytophthora capsici* (Laboratory)	[57]
3-chlorobenzoic acid, 3,5-dichlorobenzoic acid		*Arabidopsis*/*Hyaloperonospora parasitica*, *Pseudomonas syringae* (Laboratory)	[54]
Para amino benzoic acid		Pepper/CMV, *Xanthomonas axonopodis* pv. *Vesicatoria* (Laboratory)	[58]

3.3. Nicotinic Acid Derivatives: 2,6-dichloro-isonicotinic Acid (INA) and N-cyanomethyl-2-chloro isonicotinic Acid (NCI)

INA is very effective in protecting various crops against a wide range of pathogens (Table 3). This includes tobacco against TMV and cucumber against *Colletotrichum lagenariunm* [60] *Cercospora nicotianae*, *Peronospora tabacina*, *Phytophthora parasitica* var *nicotianae*, and against *P. syringae* pv. *tabaci* [61]. Although, INA has not been commercialized because of its high phytotoxicity it is considered as useful tools to study mechanisms of induced resistance. INA is considered as a functional SA analogue that acts downstream of SA because it does not trigger any changes of SA content and it induces SAR in salicylate hydroxylase (*NahG)* transgenic plants [62,63]. Like SA, INA is able to inhibit catalase and ascorbate peroxidase (APX) activity and to induce ROS accumulation [64]. INA mediates its defense-related effects upon interaction with NPR1-related proteins, which control several TGA transcription factors. INA seems to be a true SA agonist. It is able to promote NPR1–NPR3 interactions, and to reduce the binding affinity of SA to NPR3 and NPR4 by competing with SA [40].

Table 3. Nicotinic acid derivatives and used pathosystems.

Chemical/Common or Trade Name	Chemical Structure	Plant/Pathogen Interaction (Laboratory/Field Experiments)	Reference
2,6-dichloro-isonicotinic acid (INA)(CGA41396), CGA41397		Tobacco/TMV, *Cercospora nicotiana*, *Peronospora tabacina* (Laboratory) Cucumber/*Colletotrichum lagenarium* *Sphaerotheca fuliginea* (Laboratory) Bean/*Uromyces appendiculatus* (Laboratory)	[60,61]
N-cyanomethyl-2-chloro isonicotinic acid (NCI)		Tobacco/Tobacco mosaic virus, *Oidium lycopersici*, *Pseudomans syringae* pv. *tabaci* (Laboratory) Rice/*Xanthomonas oryzae* pv. *oryzae*, *Magnatoporthe grisea* (Field)	[65]

A second isonicotinic acid derivative, named *N*-cyanomethyl-2-chloro isonicotinic acid (NCI), was identified by Nihon Nohyaku Co., Ltd. (Tokyo, Japan) as a potent defense inducer against rice blight under field conditions [65] (Table 3). It does not show any antifungal activity in vitro against *Magnatoporthe oryzae*, and its activity is long-lasting. In tobacco, NCI induces resistance against several pathogens including TMV, *Oidium lycopersici* and *P. syringae* pv. *tabaci*, and enhances the expression of several *PR* genes. NCI-induced resistance does not require SA accumulation, but NPR1 is involved. Therefore, NCI seems to interfere with defense signaling steps operating between SA and NPR1 [66].

3.4. Pyrazole, Thiazole and Thiadiazole Derivatives

The heterocycles pyrazole, thiazole, and thiadiazole nucleus are prevalent five-membered ring system harboring heteroatom nitrogen, or sulfur. They are considered as the most important components of a wide variety of natural products and medicinal agents. Their derivatives are known for their pharmacological activities, such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, and antitubercular [67–69]. Some of them are extensively used as plant defense inducers [70,71].

The pyrazole carboxylic acid derivative, 3-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid (CMPA), is a very potent inducer of rice defense against bacterial blast that is caused by *X. oryzae* pv. *oryzae* and rice blight without exhibiting any antimicrobial activity in vitro [72,73] (Table 4). The carboxyl group at 5-position plays an important role in the observed activity, but the halogen atom at 3-position enhanced further this activity. In rice, CMPA acts downstream of SA and upstream of NPR1 [66]. In tobacco, it enhances resistance against *P. syringae* pv. *tabaci* and *Oidium sp* [74]. CMPA also induces the expression of several *PR* encoding genes. However, SA accumulation is not required and may interfere with defense signaling downstream from SA. In *A. thaliana* CMPA induced resistance through NPR1 [66,74].

Table 4. Pyrazole, thiazole, and thiadiazole derivatives and used pathosystems.

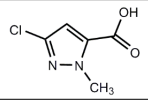
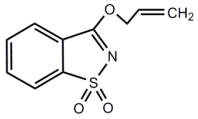
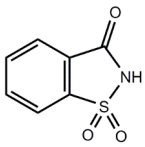
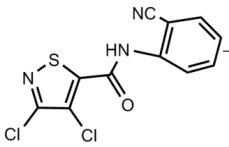
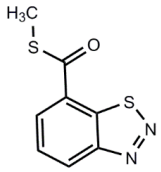
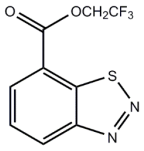
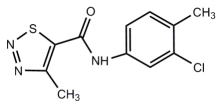
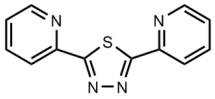
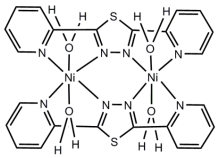
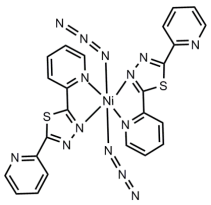
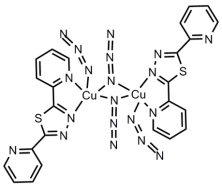
Chemical/Trade Name	Chemical Structure	Plant/Pathogen Interaction (Laboratory/Field Experiments)	Reference
3-chloro-1-methyl-1*H*-pyrazole-5-carboxylic acid (CMPA)		Tobacco/*Pseudomonas syringae* pv. *tabaci*, *Oidium* sp. (Laboratory)	[72,74]
		Rice/*Xanthomonas oryzae* pv. *Oryzae* (Field)	[73]
3-allyloxy-1,2-benzithiazole1-1-dioxide (Probenazole, PBZ/Oryzemate®)		Rice/*Magnaporthe oryzae* (Field)	[70]
1,2-benzisothiazolin-3-one-1,1-dioxide (BIT, Saccharin)		Tobacco/TMV (Laboratory) Rice/*Magnaporthe grisea*, *Xanthomonas oryzae* pv. *Oryzae* (Field) Barley/*Blumeria graminis* f. sp. *Hordei* (Laboratory) Cucumber/*Colletotrichum lagenarium* Bean/*Uromyces faba* (Laboratory) Soybean/*Phakospora pachirhizi* (Laboratory)	[75–78]
3,4-dichloro-2′-cyano-1,2-thiazole-5-carl Isothianil (Isotianil/Stout®)		Rice/*Xanthomonas oryzae* pv. *oryzae*, *Magnaporthe grisea* (Field) Wheat/*Blumeria graminis* f. sp. *Tritici* (Laboratory) Cucumber/*Colletotrichum orbiculare*, *Xanthomonas campestris* pv. *Cucurbitae* (Laboratory)	[71]
		Chinese cabbage/*Alternaria brassicae* (Laboratory) Pumpkin/*Sphaerotheca fuliginea* (Laboratory) Strawberry/*Colletotrichum acutatum* (Laboratory) Peach/*Xanthomonas campestris* pv. *Pruni* (Laboratory)	[79–81]
Benzo-1,2,3-thiadiazole-7-carbothionic acibenzolar-*S*-methyl ester (BTH/Bion®/Actigrad®)		Apple/*Erwinia amylovora* (Field)	[82]
		Citrus/*Xanthomonas citri*, *Xanthomonas axonopodis* pv. *Citrucula* (Field)	[83]
		Rape/*Pseudomonas syrngae* pv. *maculicola*, *leptosphaera maculans* (Laboratory)	[84]
		Japanese pear/*Venturia nashicola* (Laboratory)	[85]
		Cowpea/*Colletotrichum destructivum* (Laboratory)	[86]
		Tobacco/TMV, CMV, Tomato spotted wilt virus (Laboratory)	[87,88]
		Cucumber/*Colletotrichum orbiculare*, CMV (Laboratory)	[85,89]
		Tomato/*Clavibacter michighanensis* subs. *michiganensis*, *Verticillium dahliae* (Laboratory/Field)	[90,91]
		Oil seed rape/*Leptosphaeria maculans* (Laboratory/Field)	[92]
2,2-2trifluoroethylbenzo(*d*) (1,2,3) thiadiazole-7-carboxylatic acid		Cucumber/*Erysiphae cichoracearum*, *Colletotrichum lagenarium* (Field)	[93]

Table 4. *Cont.*

Chemical/Trade Name	Chemical Structure	Plant/Pathogen Interaction (Laboratory/Field Experiments)	Reference
N-(3-Chloro-4-Methylphenyl)-4-Methyl-1,2,3-thiadiazole-5-Carboxamide Tiadinil (TDL, V-GET®)		Rice/*Magnoporthe grisea* (Field)	[80]
		Tobacco/Tobacco mosaic virus, *Pseudomonas syringae* pv. *tabaci*, *Erysiphae cichoracearum* (Laboratory)	[66,94]
		Tea/*Colletotrichum theaasinensis*, *Pestalotiopsis longista* (Field)	[95]
2,5-bis (pyridi-2-yl)-1,3,4-thiadiazol		Tomato/*Verticillium dahliae* (Laboratory)	[96]
Bis(μ-2,5-bis(pyridin-2-yl)-1,3,4-thiadiazoleκ4*N*2,*N*3:*N*4,*N*5)bis (dihydrato-κ*O*)nickel(II)) (NiL_2)		Tomato/*Verticillium dahliae* (Laboratory)	[96]
bis(azido-κ*N*)bis(2,5-bis(pyridin-2-yl)-1,3,4-thiadiazole-κ2*N*2,*N*3)nickel(II) ($NiL_2(N_3)_2$)		Tomato/*Verticillium dahliae* (Laboratory)	[97]
Bis((2,5-bis(pyridine-2-yl)-1,3,4-thiadiaz copper(II)) ($CuLN_3)_2$		Tomato/*Verticillium dahliae, Agrobacterium tumefaciens* (Laboratory)	[98]

The thiazolic compound probenazole (PBZ) (3-allyloxy-1,2-benzisothiazole-1,1-dioxide) is an inducer of plant defense that was developed by Meiji Seika Ltd. (Tokyo, Japan) to control the fungal rice blast disease for more than four decades (Table 4). It was the first commercialized inducer of resistance under the trade name of Oryze mate®. PBZ inhibits hyphal penetration into the host tissue, lesion expansion and sporulation [70]. It provides an excellent blast control lasting for more than two months. Despite of its direct antifungal activity, it is able to dramatically enhance the activity of several enzymes that are involved in plants defenses, such as peroxidase (POX), polyphenol oxidase (PPO), phenyl alanine ammonia lyase (PAL), tyrosine ammonia lyase (TAL), and catechol-*O*-methyltransferase, as well as transcript accumulation of *OsPR1a* and *PBZ1*, a gene belonging to *PR10* family that is used as a marker for responses to the synthetic elicitor.

1,2-benzisothiazoline-3-one-1,1-dioxide (BIT) is the derivative metabolite of PBZ. It is well known as saccharin and it also induces resistance against a broad spectrum of pathogens in cereals and leguminous plants. In rice, PBZ-induced defense is independent from the accumulation of SA. PBZ enhances transcripts of SA glucosyltransferase b(*OsSGT1*), which is involved in the conversion of free SA to SAG [99]. However, in *A. thaliana* and tobacco, PBZ mimics the effects of SA since it stimulates the expression of *PR* genes and induces SA accumulation. Since PBZ failed to induce plant defense responses in *npr1* mutants or *nahG* transgenic plants, it seems to interfere only with defense signaling steps upstream from SA accumulation [70,100].

The isotianil compound 3,4-dichloro-2′-cyano-1,2-thiazole-5-carboxanilide is an isothiazole derivative that was developed by Bayer Crop Science (Monheim am Rhei, Germany) and the Japanese company Sumitomo Chemical Co., Ltd (Tokyo, Japan) (Table 4). It is registered under the trade name

of Stout®(Sumitomo Chemical Co., Ltd, Tokyo, Japan) to fight against rice blast. Isotianil does not show any direct antimicrobial activity [79,80], but it is able to activate defense responses against a wide range of pathogens in various plants even at very low concentrations. These include rice blight and powdery mildew in wheat, anthracnose, and bacterial leaf spot in cucumber, alternaria leaf spot in chinese cabbage, powdery mildew in Pumpkin, anthracnose in strawberry, and bacterial shot hole in peach [79,81]. In rice, it was reported to enhance the accumulation of defense-related enzymes such as PAL and lipoxygenase (LOX) in rice [79,80]. However, several, isotianil-responsive genes that are involved in SA pathway were identified. These include, *NPR1, NPR3*, the transcription factors *OsWRYK45*, *OsWRYK62*, *OsWRYK70*, *OsWRYK76*, as well as genes that are involved in SA catabolism such as *OsSGT1* and *OsBMST1* leading to the mobile signal MeSA [81].

Several benzothiadiazoles have been found to behave as functional analogues of SA. The Benzo-1,2,3-thiadiazole-7-carbothionic acid-S-methyl ester (BTH) or ASM (for acibenzolar-*S*-methyl) was the first commercialized thiadiazole derivative. It was registered under the tradename of BION®(Syngenta, Bâle, Switzerland) in Europe in 1989 and Actigard®(Syngenta, Bâle, Switzerland) in the US in 1990 [70]. BTH is effective against a broad spectrum of pathogens, it does not show antimicrobial activity at the concentration used for in planta protection (Table 4). BTH seems to activate SA-dependent signaling pathways by interfering as SA agonists with targets that are located downstream from SA accumulation, and can activate the same *PR* genes that are induced by SA. However, BTH treatment induces SAR in *nah*G transgenic plants, which fail to accumulate SA, suggesting that accumulation of SA is not required for BTH-induced SAR [101]. In *Arabidopsis*, BTH triggers *NPR1*-dependent SAR [102]. It inhibits catalase and APX, which lead to enhanced H_2O_2 content and to activation of plant defenses [103]. It was suggested that BTH is converted into acibenzolar by SABP2, which, in turn, activates a disease resistance signaling pathway that is similar to that activated by SA [104]. In addition, a BTH-binding protein kinase (BBPK) isolated from tobacco leaves was reported to regulate NPR1 activity through phosphorylation.

Until now, BTH has been tested in more than 120 pathosystems. These include resistance against *E. amylovora*, the causal agent of fire blight in apple and pear [82] and against bacterial canker that is caused by *Clavibacter michiganensis* subsp. *michiganensis* in tomato [90]. When applied as foliar spray or soil drench, in the field, BTH was able to reduce the lesions produced in grapefruit by *Xanthomonas citri* and *X. axonopodis* pv. Citrumelo [83]. BTH enhanced resistance against the bacterial pathogen *Pseudomonas syringae* pv. *maculicola* and the fungal pathogen *Leptosphaeria maculans* in *Brassica napus* in SA dependent manner [84]. In Japanese pear, BTH reduced scab disease caused by *Venturia nashicola* and was correlated with enhancement of several lines of plant defenses, including antioxidant defenses, polygalacturonase-inhibiting proteins (PGIP), MAPK, and leucin-rich repeat Receptor like kinase [85,105,106]. BTH enhanced resistance against the anthracnose pathogens *Colletotrichum destructivum* in cowpea seedlings [86] and *Colletotrichum orbiculare* in cucumber [107]. BTH also induced resistance in oil seedrape against phoma stem canker caused by *Leptosphaera maculans* [92]. In tomato, BTH significantly reduced disease incidence and severity against *Verticillium dahliae* [91] and *Botrytis cinerea* [108]. It is also relatively effective in controlling various viral diseases in tobacco, such as TMV, tobacco necrosis virus (TNV), and tomato spotted wilt virus (TSWV) [87,88]. Its efficacy was also reported in tomato against cucumber mosaic virus (CMV), and TSWV [89,109]. Because disease reduction conferred by BTH in the field is generally incomplete Du et al. performed several modifications in the 7-ester group of BTH to enhance its efficacy. They found that adding fluorine resulted in compounds with enhanced protective ability against cucumber *Erysiphe cichoracearum* and *Colletotrichum lagenarium* [93].

N-(3-Chloro-4-Methylphenyl)-4-Methyl-1,2,3-thiadiazole-5-Carboxamide known as tiadinil (TDL), is the second commercialized thiadiazole derivative. It was registered under the trade name of V-GET®in 2003 by Nihon Nohyaku Co., Ltd. (Tokyo, Japan) (Table 4). It confers rice blight resistance without exhibiting any antimicrobial activity [80,110]. Its metabolite, 4-methyl-1,2,3-thiadiazole-5-carboxylic acid (SV-03), seems to be responsible for SAR activation [94]. TDL also protects tea

plants in the field against the fungal diseases that are caused by *Colletotrichum theaesinensis* and *Pestalotiopsis longiseta* [95]. In tobacco, TDL and SV-03 induce resistance against TMV, the wildfire bacterial pathogen, and the powdery mildew. TDL acts in similar way to BTH by activating signals downstream of SA [66,94]. They failed to induce accumulation of SA in tobacco or to activate defense genes in *Arabidopsis npr1* mutants. However, they enhanced resistance against TMV and *P. syringae* pv. *tabaci*, as well as *PR* gene expression in *NahG* transgenic tobacco plants.

Recently, several derivatives of the isomer 1,3,4-thiadiazole were synthetized and tested as SAR inducers against Verticillium wilt and crown gall diseases (Table 4). The derivative 2,5-bis(pyridin-2-yl)-1,3,4-thiadiazole was reported to enhance tomato disease resistance and to activate plant defense mediated by ROS [96]. Furthermore, several metallic complexes harboring Ni or Cu as transient metal were synthetized and proved to activate SAR against *Verticillium* wilt. Their protection ability was associated with modulation of ROS accumulation and priming the activity of several plant defense-related enzymes, including peroxidase and polyphenol oxidase [96–98]. However, further experiments are needed to determine whether they act in similar way to BTH or not.

3.5. Pyrimidine Derivatives

A new plant defense activator, 5-(cyclopropylmethyl)-6-methyl-2-(2-pyridyl)pyrimidin-4-ol, named PPA (pyrimidin-type plant activator), belonging to the pyridyl-pyrimidine derivative family was reported to enhance the expression of genes related to ROS, defenses, and SA in *A. thaliana*. PPA was able to reduce disease symptoms that were caused by *P. syringae* pv. *maculicola* and to enhance plant defenses against pathogen invasion through the plant redox system [111]. Recently, Narusaka and Narusaka identified several thienopyrimidine-type compounds that enhance disease resistance against *Colletotrichum higginsianum* and *P. syringae* pv. *maculicola* in *A. thaliana.* However, they induce the expression of both *PR1* and *PDF1.2* [112].

3.6. Neonicotinoid Compounds

The neonicotinoid imidacloprid (IMI) and clothianidin (CLO) basically used to control crop pests have also been reported to induce plant defenses that are associated with SA and to inhibit the growth of powdery mildew in *A. thaliana* [113]. However, their effect was mainly due to their respective metabolites; 6-chloropyridinyl-3-carboxylic acid and 2-chlorothiazolyl-5-carboxylic acid. While CLO enhanced SA accumulation through the upregulation of *ICS* transcripts, and activated the expression of *PR1* gene, IMI does not induce endogenous synthesis of SA, but it is further transformed to 6-chloro-2-hydroxypyridinyl-3-carboxylic acid, a potent inducer of *PR1* and inhibitor of SA-sensitive enzymes [113]. In addition, IMI activates *PR2* gene expression and induces high and long-lasting levels of resistance against the bacterial canker of Citrus *X. citri* [114].

4. Limitations of the Use of Functional Analogues of SA: Towards a New Generation of Compounds

4.1. Allocation Fitness Cost

Limitations of the use of SA analogues in the field include their transient effect and their limited disease spectrum and target crops. However, the major drawback is related to their phytotoxicity when applied at higher doses. These effects are likely to be caused by the strong induction of defense responses, which is associated with growth inhibition [115]. Resources used in the primary metabolism are deviated and used for synthesis of defensive compounds, resulting in plant growth inhibition, a phenomenon known as 'allocation fitness cost' or 'trade-off' [116–119]. This notion comes from the use of *Arabidopsis* mutants and the observation that higher doses of SA or its functional analogues are often associated with direct inhibition of plant growth and seed production [10,120,121]. While mutants of *Arabidopsis* expressing constitutively *PR* genes were dwarfed and severely affected in seed production [11,122], those that are affected in SA accumulation, such as *NahG* or *ICS1*, showed

enhanced growth and seed production [121,123]. High concentrations of BTH in sunflower resulted in light chlorosis and reductions in fresh weight [124]. Repetitive application of BTH also provoked yield reduction in pepper [124]. The beneficial effects of SA-regulated defenses were particularly apparent under low-nutrient conditions [125], which supports the theory of allocation costs as a driver of the evolution of inducible defenses. BTH-treated wheat exhibited reduced growth and decreased seed production, mainly under deficiency of nitrogen [120]. Since reduced vigor observed after treatment with BTH was alleviated in *npr1* mutants, it was suggested that NPR1 plays a pivotal role in inhibiting plant growth when SA-dependent resistance mechanisms are activated [10]. In addition to SA pathway, several interconnecting signals interacting synergistically or antagonistically, such as JA, ethylene, ABA, auxins, cytokinins, and ROS regulate development and disease resistance. For instance, BTH inhibits the growth by the suppression of auxin and the down regulation of several genes involved in auxin perception, transport and signaling [126,127]. In addition, BTH affects auxin homeostasis through the activation of the expression of gene encoding GH3.5. This family of adenylating enzymes conjugates acyl substrates, such as IAA to the Asp amino-acid [128].

4.2. Priming Effect

Several researchers attempted to identify compounds that induce SAR without affecting plant growth in the field [129]. Another form of plant defense is priming, a phenomenon, which is defined as the enhancement of the basal level of resistance in plants, resulting in a faster and stronger resistance response following subsequent pathogen attack [130]. Defense priming can be regarded as an efficient mechanism to manipulate the "trade-off" machinery, resulting in minimizing the allocation fitness cost [129].

The discovery of immune-priming compounds started accidently with the use of probenazole to protect paddy field rice from the blast fungus and the bacterial leaf blight, and prompted the development of similar compounds, such as tiadinil and isotianil [70,79,80]. However, most of the classical activators of plant defenses can induce priming when used at lower doses that are insufficient to trigger detectable levels of defense responses. For instance, BABA primes host plants to activate SA-dependent signaling system [45,46] or other signaling systems, depending on the nature of challenging pathogen [131]. BTH and INA were able to prime a wide range of cellular responses, including alterations in ion transport across the plasma membrane, enhanced synthesis of phytoalexins, cell wall phenolics and lignin-like polymers, and activation of various defense genes [106,132].

Although still poorly understood, the molecular basis of priming started to be unraveled. NPR1 plays important role in inducing high levels of chromatin modification on promoters of the transcription factor genes. Priming involves a cyclic non-protein amino acid pipecolic acid as mobile signal and MAPK. Beckers et al. [133] showed that pre-stress deposition of MAPK3 and MAPK6 plays an important role during BTH-induced priming in *A. thaliana*. Exposure to the challenges of stressors results in the phosphorylation and activation of these two kinases in primed plants relative to non-primed plants, which is linked to enhanced defense gene expression. Priming is controlled epigenetically and relies on the ability of plant to reprogram the pattern of expression of thousands of genes. The process is initiated through the *Arabidopsis* subtilase SBT3.3, a proteolytic extracellular enzyme, which is involved in activation of chromatin remodeling, covalent histone modifications and defense genes become poised for enhanced activation following pathogen attack [3,134]. During priming, BTH increased acetylation of histone H3 at Lys-9 (H3K9ac) and trimethylation of histone H3 at Lys-4 (H3K4me3) in the promoter regions of the transcription factors WRKY6, WRKY29, and WRKY52 [135]. In addition, DNA methylation and histone modifications are regulated by RNA Polymerase V [136] and are involved in the transmission of a priming state or stress memory, suggesting that plants may inherit priming sensitization [137]. Transgenerational epigenetic effect of priming was reported to be triggered by BABA in *Arabidopsis* [138], and more recently in the potato relative *Solanum physalifolium* [139]. This effect could be considered as robust and a broadly distributed

mechanism of phenotypic plasticity to plant diseases. Therefore, screening for new immune-priming compounds is highly needed.

4.3. Screening for New Compounds

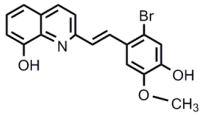
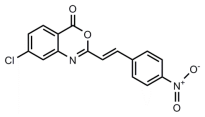
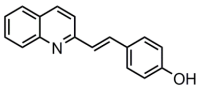
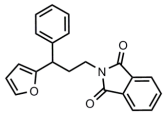
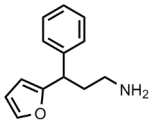
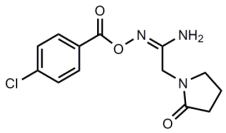
Evaluation of new compounds requires a large quantity of chemicals and is time and space consuming, thus restricting the range of chemicals that can be tested. Large-scale screening of a broad range of compounds led to the identification of several functional SA analogues that could be used as plant activators in the field of crop protection [11,138].

The first high-throughput screening method involves young seedlings that are grown in liquid, facilitating the uniform application of chemicals from small-molecule libraries in standard 96-well plates [54]. This system is based on the use of β-glucuronidase (GUS) histochemical staining assay and the promoter of *CaBP22* of *A. thaliana* gene, which encode a putative calmodulin-like binding protein. Screening of collection of 42,000 various molecules allowed the identification of the plant defense inducers DCA and 2-(5-bromo-2-hydroxy-phenyl)-thiazolidine-4-carboxylic acid (BHTC), which act, respectively in NPR1 independent and in NPR1 dependent manners [54,140]. By using the same system Bektas et al. identified a new compound named 2,4-dichloro-6-{(E)-((3-methoxyphenyl)imino)methyl}phenol (DPMP), which acts as a partial agonist of SA [141].

A combination of this system with GUS fused to the promoters of *A. thaliana* defense-related genes that are involved in SA and JA/ET signaling allowed the identification of PPA [142,143] and thienopyrimidine-type compounds [112]. To avoid unfavorable side effects, such as phytotoxicity, and to distinguish between compounds that directly activate plant defenses responses from those doing so exclusively in the presence of the pathogen, Noutoshi et al., established a new high throughput screening technique based on the use of the pathosystem *Arabidopsis* suspension-cultured cells/*P. syringae* with 96 well plates [11]. This system allowed for the elimination of compounds that induce cell death, evaluated after Evans blue staining and identification of compounds that promote pathogen resistance in *Arabidopsis* by invoking the hypersensitive cell death pathway in response to pathogen attack. Five new immune-priming compounds were selected from a chemical library of 10,000 molecules were called imprimatins A1, A2, A3, B1, and B2 (Table 5). Two of them acted by inhibiting SAGT, allowing then, SA accumulation. To access the effect of these new immune-priming compounds on the growth, *Arabidopsis* seeds were germinated and grown in liquid MS media containing imprimatins. In contrast to tiadinil, which prominently inhibited seedling growth, imprimatin A2, B1, and B2 exhibited only moderate growth inhibitory effects, in a concentration-dependent manner. However, imprimatin A1 and A3 did not affect at all the growth at the concentration range effective for immune priming [12].

Using this screening strategy, Noutoshi et al. isolated imprimatins C that behave as functional analogues of SA [12]. They effectively induce the expression of *PR1* gene and enhance disease resistance in *A. thaliana*, however, they lack antagonistic activity against JA [12]. Furthermore, structure-activity relationship analyses implicated that the potential downstream metabolites of imprimatin C compounds, including 4-chlorobenzoic acid, 3,4-dichlorobenzoic acid, and their derivative 3,5-DCBA also act as partial agonists of SA with various potencies [13]. Therefore, imprimatin C compounds can potentially assist to better understand the molecular events that are involved in SA defense signaling and their putative functional metabolites can serve as valuable tools to address the complexity intrinsic on the activities of SA receptors, providing insights into the mechanisms governing early SA perception and NPR1 regulation and its role in plant immune signaling.

Table 5. Imprimatins as new immune priming compounds.

Chemical/Trade Name	Chemical Structure	Plant/Pathogen Interaction	Reference
2-((E)-2-(2-bromo-4-hydroxy-5-methoxyphenyl)ethenyl) quinolin-8-ol: Imprimatin A1		*Arabidopsis thaliana/Pseudomonas syringae* pv. *tomato* DC3000 *avrRp m1*	[11]
7-chloro-2-((E)-2-(4-nitrophenyl)ethenyl)-4*H*-3,1-benzoxazin-4-one: Imprimatin A2		*Arabidopsis thaliana/Pseudomonas syringae* pv. *tomato* DC3000 *avrRp m1*	
4-((E)-2-(quinolin-2-yl)ethenyl)phenol: Imprimatin A3		*Arabidopsis thaliana/Pseudomonas syringae* pv. *tomato* DC3000 *avrRp m1*	
2-(3-(2-furyl)-3-phenylpropyl) benzo(c)azoline-1,3-dione: Imprimatin B1		*Arabidopsis thaliana/Pseudomonas syringae* pv. *tomato* DC3000 *avrRp m1*	
3-(2-furyl)-3-phenylpropylamine: Imprimatin B2		*Arabidopsis thaliana/Pseudomonas syringae* pv. *tomato* DC3000 *avrRp m1*	
((E)-(1-amino-2-(2-oxopyrrolidin-1-yl) ethylidene)amino) 4-chlorobenzoate: Imprimatin C1		*Arabidopsis thaliana/Pseudomonas syringae* pv. *tomato* DC3000 *avrRp m1*	[144]

5. Conclusions

The activation of induced resistance using functional analogues of SA requires large energy input, and thus compromises other metabolic processes. Therefore, their success may depend on managing the tradeoff between defense and growth. There are many evidences that signaling crosstalks are involved in the tradeoff. Identification of signaling components that directly affect these crosstalk and designing new compounds that will affect these components will be the most important challenge for crop protection. The discovery of NPR1 as receptor of SA will be very helpful for future chemical screening of immune-priming compounds that destabilize NPR1 by binding to SA [145]. Understanding of the molecular mechanisms underlying priming may also help to design new chemicals that stimulate the plant's inherent disease resistance mechanisms.

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