

Zanthosimuline and Related Pyranoquinolines as Antifungal Agents for Postharvest Fruit Disease Control

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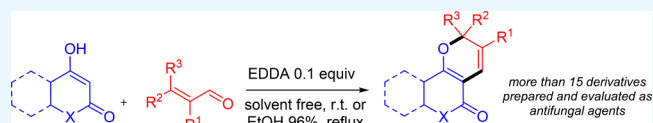


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Supporting Information

ABSTRACT: The natural product zanthosimuline and its 18 analogues were easily prepared from simple starting materials and evaluated in vitro against postharvest fruit fungal pathogens. The panel included *Penicillium digitatum*, *Botrytis cinerea*, *Monilinia fructicola*, and *Rhizopus stolonifer*; all of them causing relevant economic losses worldwide. The minimum inhibitory concentrations and minimum fungicidal concentrations of each compound were determined, and the main structure–activity relationships were established. The biological activity observed was strongly increased by maintaining the prenyl side chain of zanthosimuline in an *N*-demethylated derivative. In addition, the compound that is the most active in the in vitro evaluation was tested in freshly harvested peaches exhibiting a promising brown rot control profile, comparable to the commercial agent carbendazim but demonstrating less toxicity against human liver cell lines.



INTRODUCTION

The high content of water and nutrients and the advent of physical damage during storage and transport make fruits and vegetables vulnerable to pathogen infections after harvesting.¹ Primarily caused by fungi, postharvest diseases are difficult to control and ultimately affect production both quantitatively and qualitatively. Whereas losses due to pests and diseases during storage, transport, and marketing of fruits and vegetables can be estimated to be around 25% in industrialized countries, these can reach up to 50% of the total production in developing countries, which lack suitable advanced technologies.² Indeed, some fungal pathogens that are responsible for postharvest infections also represent a threat to human health. *Penicillium digitatum* (Pers.) Sacc., *Botrytis cinerea* (Pers.: Fr.), *Monilinia fructicola* (G. Wint.) Honey, and *Rhizopus stolonifer* (Ehrenb.: Fr.) Vuill are four of the main phytopathogenic fungi that affect fruit exports and their producers worldwide.

Citrus green mold caused by *P. digitatum* is the most economically important citrus disease, especially in subtropical and tropical production areas such as Argentina.³ Disease management has traditionally been based on chemical fungicide application, but lately, many strains resistant to imazalil (IMZ) or thiabendazole (TBZ), which are two of the main products used to control this infectious agent, have been isolated.^{4–6} *B. cinerea* is a really destructive plant pathogen responsible for the *Botrytis* bunch rot or gray mold, which mainly affects grapes and strawberries, causing great losses to the table grape and wine industry.⁷ This pathogen is currently being controlled with pre- and postharvest fungicides like carbendazim (CBZ) or captan.⁸ On the other hand, *M. fructicola* is the causal agent of brown rot, a serious disease that affects the quality of peaches from the flowering period to the harvesting and storage stages. Its dissemination results in devastating production losses, which have been estimated at

more than 20% for the Chinese market.⁹ Finally, *R. stolonifer* is one of the most common and fastest-growing phytopathogenic species, especially under mild moisture conditions, being considered as one of the most devastating threats.¹⁰ It attacks a wide variety of hosts, and its rapid penetration and colonization capacity result in fast spread from the infected to the healthy fruits at any stage between processing and consumers' houses. In this context and taking into account a global concern on the effect of currently available fungicides and their residues on human health and the environment, the exploration of new alternatives for postharvest disease control is highly stimulated.^{11–15}

Our research group has recently developed an environmentally benign protocol for the synthesis of 2*H*-pyranoquinoline-containing compounds starting from simple substrates in short reaction times and without the use of heat or solvents.¹⁶ Some of the obtained derivatives happen to occur in nature, such as zanthosimuline (**1**) and *N*-methylflindersine (**2**), of which both alkaloids are found in plants belonging to the Rutaceae family such as *Zanthoxylum simulans*, from which Sichuan pepper is produced (Figure 1).^{17–20} These pyranoquinoline compounds belong to an important family of natural products bearing the 2*H*-pyran heterocyclic substructure, which have attracted considerable attention as they have been found to exhibit interesting biological activities such as antimicrobial and antiparasitic.²¹ Although these two alkaloids have been

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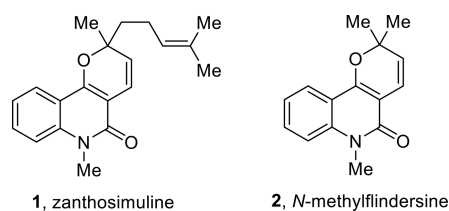


Figure 1. Chemical structures of alkaloids found in the Rutaceae family such as *Z. simulans*.

isolated from plants originally used as therapeutics by different indigenous cultures (e.g., China and India), little is known about their potential as antifungal agents.²² Here, aiming to find new candidates for efficient postharvest fruit pathogen control, we report the synthesis and evaluation of a library of 2*H*-pyrans related to natural products zanthosimuline (1) and *N*-methylflindersine (2).

RESULTS AND DISCUSSION

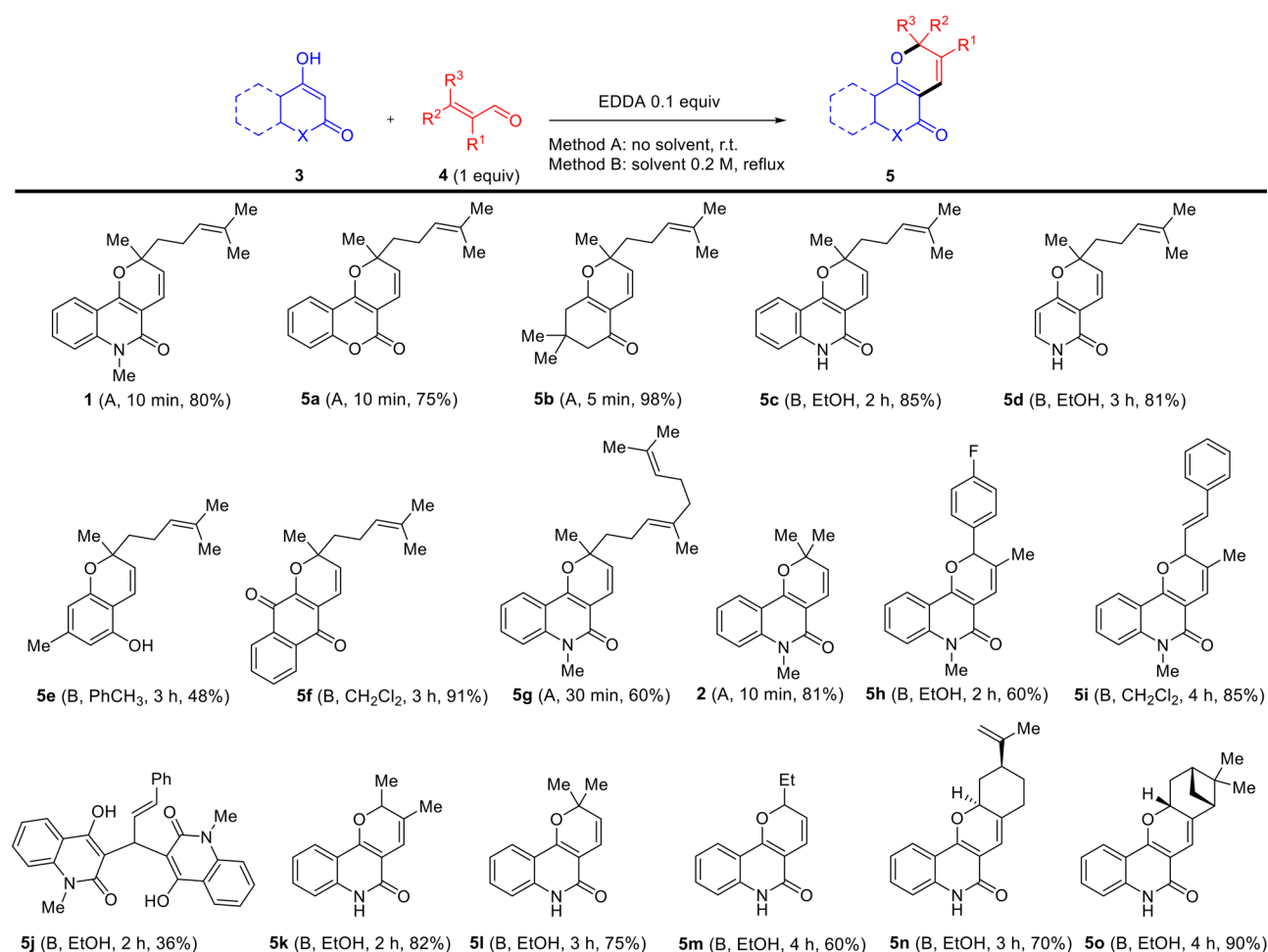
Library Synthesis. The preparation of 2*H*-pyran derivatives 1, 2, and 5 was successfully achieved via domino Knoevenagel condensation/oxa-6*π*-electrocyclization between dicarbonyl substrates 3 and α,β -unsaturated aldehydes 4 catalyzed by ethylenediammonium diacetate (EDDA, Scheme 1).¹⁶ As shown in Scheme 1, natural products 1 and 2 and derivatives 5a, 5b, and 5g could be prepared under the

originally reported conditions that do not involve the use of solvents or heat (method A).¹⁶ For the other derivatives to be prepared efficiently, reactions were performed in a solvent at reflux. For these cases, many reactions could be fortunately run in pharmaceutical ethanol at reflux (method B). Remarkably, the use of cinnamaldehyde as the electrophilic component did not lead to a pyran product. Instead, a product arising from initial Knoevenagel condensation followed by Michael addition from a second equivalent of dicarbonyl substrate was isolated (5j).²³

In order to achieve more diversity in the prepared library, zanthosimuline (1) was also subjected to hydrogenation and hydration to afford derivatives 6 and 7, respectively (Scheme 2). It should be noted that, apart from 1 and 2, prepared 2*H*-pyran 5l also occurs in nature. Alkaloid flindersine (5l) was isolated for the first time from *Flindersia* species in 1914, but then it was found in several other species of the Rutaceae family such as *Geijera parviflora*, *Fagara zanthoxyloide*, and *Haplophyllum tuberculatum*. The slight antifungal activity of 5l against *Colletotrichum fragariae*, *C. gloeosporioides*, *C. acutatum*, *B. cinerea*, *Fusarium oxysporum*, and *Phomopsis obscurans* was previously demonstrated by Cantrell and co-workers.²²

In Vitro Antifungal Evaluation and Main Structure–Activity Relationships. The library of 2*H*-pyran derivatives was then evaluated for their antifungal activity. As shown in Table 1, minimum inhibitory concentrations (MICs) and minimum fungicidal concentrations (MFCs) were determined

Scheme 1. Domino Synthesis of 2*H*-Pyrans 1, 2, and 5a–o (Yields in Parentheses)



Scheme 2. Structural Modifications on Natural Product 1 (Yields in Parentheses)

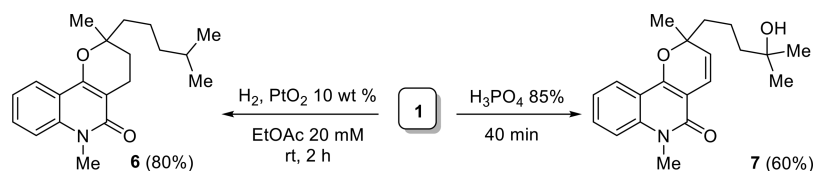


Table 1. Minimum Inhibitory Concentrations (MICs) and Minimum Fungicidal Concentrations (MFCs) ($\mu\text{g}/\text{mL}$) of Synthesized 2*H*-Pyrans against Selected Postharvest Fruit Pathogens^a

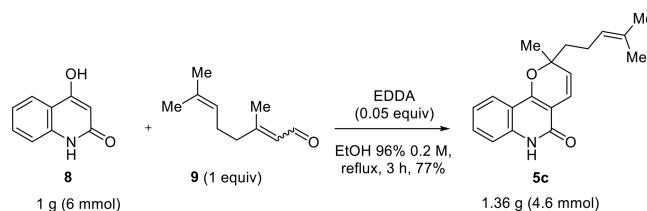
compound	MICs/MFCs ($\mu\text{g}/\text{mL}$)			
	<i>Pd</i>	<i>Bc</i>	<i>Mf</i>	<i>Rs</i>
1	I	I	15.6/I	31.25/I
2	31.25/125	31.25/250	31.25/62.5	31.25/I
5a	I	I	125/250	250/I
5b	I	I	I	I
5c	I	7.8/15.6	7.8/7.8	31.25/I
5d	250/I	125/I	62.5/125	62.5/I
5e	250/I	62.5/62.5	I	31.25/31.25
5f	I	I	I	I
5g	I	I	I	I
5h	I	250/I	62.5/I	I
5i	I	250/I	250/I	250/I
5j	I	I	I	I
5k	I	I	I	I
5l	I	I	I	I
5m	I	125/125	250/250	I
5n	I	I	I	I
5o	I	I	I	I
6	125/I	250/I	125/I	62.5/250
7	I	I	125/I	I
IMZ	7.8/7.8	1.95/1.95	0.12/0.12	15.62/15.62
CBZ	15.62/15.62	62.5/62.5	0.97/0.97	125/250
captan	7.8/7.8	1.95/1.95	1.95/1.95	7.8/7.8

^a*Pd*: *P. digitatum* CCC-102; *Bc*: *B. cinerea* CCC-100; *Mf*: *M. fructicola* INTA-SP345; *Rs*: *R. stolonifer* LMFIQ-317. Commercial antifungals imazalil (IMZ), carbendazim (CBZ), and captan were used as positive controls. I: inactive (MIC or MFC > 250 $\mu\text{g}/\text{mL}$).

against four postharvest phytopathogenic fungi that particularly affect oranges, strawberries, and peaches. The natural product zanthosimuline (1) displayed an important fungistatic activity against *M. fructicola* and *R. stolonifer* (MICs 15.6 and 31.25 $\mu\text{g}/\text{mL}$, respectively) but no fungicidal activity. Maintaining the prenyl side chain, the structural alteration of the quinolone nucleus led to significant changes on the activity; which decreased or was completely lost by replacement of the quinolone system in 1 by a coumarin system (5a), a saturated cycle (5b), a pyridone ring (5d), or a quinone derivative (5f). Cannabichromene-C1 (5e), on the other hand, displayed both fungistatic and fungicidal activities against *B. cinerea* and *R. stolonifer* (MICs = MFCs, 62.5 and 31.25 $\mu\text{g}/\text{mL}$, respectively) but inactive against *M. fructicola* and *P. digitatum*. Interestingly, an *N*-demethylated derivative of zanthosimuline (5c) turned out to be the most active derivative, displaying fungistatic and fungicidal activities against *B. cinerea* and *M. fructicola* with MICs/MFCs = 7.8/15.6 and 7.8/7.8 $\mu\text{g}/\text{mL}$, respectively, and fungistatic against *R. stolonifer* at 31.25 $\mu\text{g}/\text{mL}$. The modification of the prenyl side chain had a higher impact on the biological activities of the polycyclic pyrans evaluated:

replacement by a geranyl chain (5g), hydrogenation (6), hydration (7), and other structural modifications on the substituents attached to the pyran ring at C-2 led to partial or complete loss of activity. The only exception was the natural product *N*-methylflindersine (2), which showed an interesting activity against the four pathogens evaluated with MICs = 31.25 $\mu\text{g}/\text{mL}$ and MFCs between 62.5 and 250 $\mu\text{g}/\text{mL}$.

Gram-Scale Synthesis of 2*H*-Pyran 5c. The finding of compound 5c as a promising antifungal candidate prompted us to further evaluate its potential as a postharvest treatment in peaches inoculated with *M. fructicola*. To this aim, a gram-scale synthesis was first pursued. To our delight, using 6 mmol of the corresponding commercial substrates 2,4-quinolinediol (8) and citral (9) and only 5 mol % catalyst EDDA in ethanol at reflux, 1.36 g of 5c was obtained (77% yield, Scheme 3).

Scheme 3. Gram-Scale Synthesis of 2*H*-Pyran 5c

Ex Vivo Antifungal Activity. The effect of compound 5c, the most active pyranoquinoline derivative in vitro, was then examined ex vivo in fresh peaches infected with the pathogen *M. fructicola*, comparing the results with the commercial product CBZ (Figure 2). A control set without antifungal agents was also prepared. After 10 days, it was observed that the fruits present in the control set were completely rotten by the fungal infection. Consequently, both sets of treated fruits indicated that 5c and CBZ had protected the fruits, inhibiting

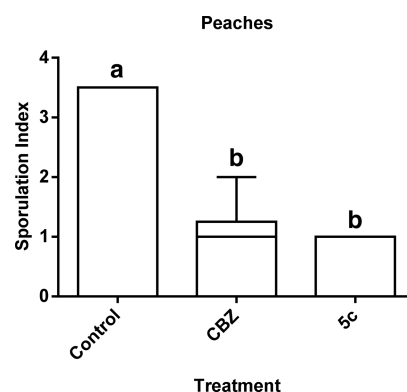


Figure 2. Evaluation of *M. fructicola* sporulation index on wound inoculated peaches treated with compound 5c and commercial antifungal CBZ. Different letters means statistically significant differences according to Tukey's multiple-comparison tests ($P < 0.05$).

the fungal growth. Furthermore, while examination of the set of peaches treated with the commercial agent revealed that some fruits had clear signs of fungal infection, less specimens of those exposed to **5c** seemed to be infected. While no significant difference was observed between the fruits treated with CBZ and those with **5c**, the results suggest that the latter could be even more powerful than the commercial agent. So, the efficacy of compound **5c** to control *M. fructicola* applied to wound-inoculated peaches by immersion at a 7.8 $\mu\text{g/mL}$ solution reduced significantly the brown rot sporulation index with respect to control peaches and showed no significant differences between commercial antifungal CBZ responses (Figure 2).

Cytotoxicity Evaluation. As shown in Figure 3, the viabilities of Huh7 cells were 52.86 ± 1.37 and $45.00 \pm 3.08\%$

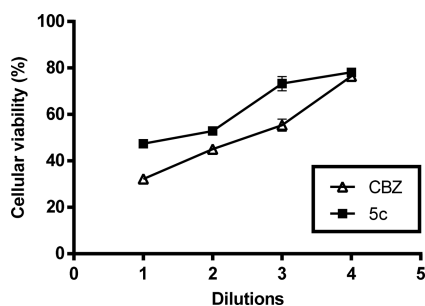


Figure 3. Cellular viability of Huh7 cells in the presence of compound **5c** and commercial antifungal CBZ at different concentrations: Dilutions 1, 2, 3, and 4 correspond to 2 \times , 1 \times , $\frac{1}{2}\times$, and $\frac{1}{4}\times$ MIC, respectively. Values are expressed as mean \pm SD, determined in triplicate.

in the presence of **5c** and CBZ, respectively, at their MIC values (dilution 2). This means that compound **5c** seems to be less cytotoxic than commercial antifungal CBZ at these concentrations. Notice that the dilution axis shows the serial dilutions from the most concentrated **5c** and CBZ solutions (dilution 1), which are twice as concentrated as their MIC values (dilution 2), and so on. Therefore, dilution 4 is the most diluted solution of each compound, and it presents the highest viability.

In summary, natural products zanthosimuline, *N*-methyl-flindersine, flindersine, and a series of synthetic derivatives were prepared in good to excellent yields, fully characterized, and evaluated in vitro as antifungal agents against a panel of four relevant strains of postharvest fruits phytopathogenic fungi: *P. digitatum*, *B. cinerea*, *M. fructicola*, and *R. stolonifer*. The structure–activity relationship analysis of the in vitro results revealed that the observed biological activity was strongly increased by maintaining the prenyl side chain of zanthosimuline in an *N*-demethylated derivative. The activity of the most active compound (**5c**) was tested ex vivo on freshly collected peaches, demonstrating that, under the experimental conditions, the results of applying the pyranoquinoline derivative are not statistically different from those obtained from exposing the fruits to the commercial product carbendazim. The overall results are promising and suggest that this compound may have great potential to be further developed as a usable protective-contact fungicide especially because it is less cytotoxic than commercial CBZ. Furthermore, the synthesis of **5c** is simple and straightforward, requiring

inexpensive and easily available precursors and uncomplicated synthetic methodology.

EXPERIMENTAL SECTION

Chemicals and Instruments. All reagents and solvents were commercially available and used directly without further purification. All chemical reactions were monitored by thin-layer chromatography performed on silica gel 60F₂₅₄ precoated aluminum sheets, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 4-anisaldehyde. Column flash chromatography was performed using silica gel 60 (230–400 mesh). Melting points (m.p.) were taken on an electrothermal melting point apparatus and are uncorrected. ¹H and ¹³C nuclear magnetic resonance spectra were acquired at 300 MHz for ¹H and 75 MHz for ¹³C using CDCl₃ as solvent and tetramethylsilane as the internal standard (TMS). IR spectra were obtained using an FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded with a Q-TOF mass spectrometer equipped with an ESI source (detection of the ions was performed in electrospray ionization, positive-ion mode).

Synthesis. The synthetic routes to the target compounds **1**, **2**, **5a–o**, **6**, and **7** are outlined in Schemes 1 and 2. Compounds **1**, **2**, and **5a–o** were prepared via EDDA (ethylenediammonium diacetate)-catalyzed domino Knoevenagel condensation/oxa-6 π electrocyclization reaction between dicarbonyl substrates **3** and unsaturated aldehydes **4**. These reactions were performed at room temperature under solvent-free conditions as previously reported by our group for compounds **1**, **2**, **5a**, and **5b**¹⁶ or in a solvent with heating at reflux. Compounds **6** and **7**, on the other hand, were prepared starting from compound **1** via hydrogenation and hydration, respectively. Compounds **5g**, **5h**, **5j**, **6**, and **7** are new substances. Compounds **5c**, **5d**, and **5k–o** were previously prepared using EDDA as the catalyst and dichloromethane as solvent at room temperature.^{21b} Compound **5e** was prepared in toluene as reported by Lee and co-workers using EDDA as the catalyst.^{21g} Compound **5f** was previously prepared using EDDA in benzene at reflux.^{21f} Compound **5i** was previously prepared by us using EDDA in dichloromethane at reflux.²⁴

General Synthetic Procedure for Compounds **1, **2**, **5a**, **5b**, and **5g** (Method A).** A mixture of dicarbonyl equivalent (**3**, 1 mmol), α,β -unsaturated aldehyde (**4**, 1 mmol, 1 equiv.), and ethylenediammonium diacetate (EDDA, 18.0 mg, 0.1 mmol, 0.1 equiv.) was ground in a mortar at room temperature for 5–30 min. The residue was then purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford the corresponding product.

General Synthetic Procedure for Compounds **5c–f and **5h–o** (Method B).** A mixture of dicarbonyl equivalent (**3**, 1 mmol), α,β -unsaturated aldehyde (**4**, 1 mmol, 1 equiv.), and ethylenediammonium diacetate (EDDA, 18.0 mg, 0.1 mmol, 0.1 equiv.) in the appropriate solvent (5.0 mL, 0.2 M) was heated at reflux for 2–3 h. The solvent was then evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford the corresponding product.

Synthetic Procedure for Compound **6.** To a solution of alkaloid **1** (101 mg, 0.33 mmol) in ethyl acetate (16.0 mL, 0.02 M) was added PtO₂ (10 mg, 10 wt %), and the resulting suspension was degassed three times (three vacuum/hydrogen cycles to remove air). The suspension was vigorously stirred under a hydrogen atmosphere (balloon, ca.1 atm) at room

temperature for 2 h, filtered through celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexanes/ethyl acetate as the eluent to obtain **6** as a colorless liquid (82 mg, 0.26 mmol, 80% yield).

Synthetic Procedure for Compound 7. Compound **1** (129 mg, 0.42 mmol) was stirred in H_3PO_4 (85 wt %, 1 mL) for 40 min at room temperature. Brine (20 mL) and diethyl ether (20 mL) were then added. The organic phase was washed twice with saturated NaHCO_3 solution (30 mL) and then dried over Na_2SO_4 . The solvent was then evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford the corresponding product **7** as a colorless solid (82 mg, 0.25 mmol, 60% yield).

Gram-Scale Synthesis of 2H-Pyran 5c. A mixture of dicarbonyl equivalent (**8**, 1 g, 6.02 mmol), α,β -unsaturated aldehyde (**9**, 1.09 mL, 6 mmol, 1 equiv.), and ethylenediammonium diacetate (EDDA, 54.0 mg, 0.05 mmol, 0.05 equiv.) in 96% ethanol (30.0 mL, 0.2 M) was heated at reflux for 3 h. The solvent was then evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 85:15) to afford the corresponding product **5c** in 77% yield (1.36 g, 4.6 mmol).

Microorganisms and Media. Monospore strains of each fungus were obtained from fruits that exhibited the correspondent disease symptoms and were morphologically characterized by the Mycology Reference Center (CCC, Rosario, Argentina), the National Institute of Agricultural Technology (INTA, San Pedro, Argentina), and the Microbiology Department of the Chemical Engineering Faculty (LMFIQ, Santa Fe, Argentina). Strains of *P. digitatum* CCC-102, *B. cinerea* CCC-100, *M. fructicola* INTA-SP345, and *R. stolonifer* LMFIQ-317 were grown on the potato-dextrose-agar (PDA) medium using Petri dishes for 48 h to 6 days at 15–25 °C (as needed for the growth of each one) and subcultured every 15 days to prevent pleomorphic transformations. The inoculums of spore suspensions were obtained according to the Clinical & Laboratory Standards Institute (CLSI) reported procedures and adjusted to 1×10^4 cfu/mL.²⁵

In Vitro Antifungal Assays. The minimum inhibitory concentration (MIC) values were determined by using broth microdilution techniques according to the CLSI guidelines for filamentous fungi (document M38-A2, CLSI 2008).²⁵ MIC values were determined in the RPMI-1640 medium (Sigma, St. Louis, MO, USA) buffered to pH 7.0 with MOPS (Remel, Lenexa, KS, USA). Microtiter trays were incubated at 15–25 °C in a moist and dark chamber, and MIC values were visually recorded at 48 h for *R. stolonifer* and at a time according to the control growth, for the remaining fungi. For the assay, solutions of 12.5 mg/mL concentration of each compound were prepared in dimethyl sulfoxide (DMSO). 40 μL of these was diluted in 960 μL of Roswell Park Memorial Institute (RPMI) media to obtain stock solutions of 500 $\mu\text{g}/\text{mL}$ that were serially diluted from 500 to 7.9 $\mu\text{g}/\text{mL}$ (final volume = 100 μL) in the corresponding wells of a microtiter plate. A volume of fungal suspension (100 μL) was added to each well, except for the sterility control, where sterile water was added instead. The commercial antifungal agents carbendazim (InsuAgro) and imazalil (Fungaflor) at their commercial presentations (50% w/v solutions) were used to carry out the positive controls during the antifungal assays. The MIC

end points are defined as the lowest concentration of compound visually resulting in total inhibition of fungal growth compared to the growth in the control wells containing no antifungal agent. The minimum fungicidal concentration (MFC) is defined as the lowest concentration of compound that fully killed the fungi. The MFC values were determined after assessing the MIC ones by transferring sample aliquots (5 μL) from each clear well of the microtiter tray onto a 150 mm RPMI-1640 agar plate buffered with 3-(*N*-morpholino)propanesulfonic acid (MOPS). The inoculated plates were incubated at 15–25 °C; the MFC values were recorded after 48 h for *R. stolonifer* and at later times, according to the corresponding control growth, for the rest of the fungi.

Ex Vivo Antifungal Assay in Wounded Fruits. Peaches (*Prunus persica*, Red Globe variety) were harvested from the Experimental Field of Intensive and Forestry Crops (Facultad de Ciencias Agrarias, Universidad Nacional de Litoral) at the mature stage (when the firmness of the fruits was about 6.5 ± 0.5 kg/cm² as the ripening index) and sorted based on size and absence of physical injuries or disease infection. Fruits were collected before any commercial postharvest treatment was applied and were surfaced-disinfected with 2% (w/v) sodium hypochlorite for 3 min, rinsed with tap water, and then air-dried. Fruits were randomly distributed into three groups with 10 units each: one group was submitted to treatment with compound **5c** at 7.8 $\mu\text{g}/\text{mL}$ according to the in vitro antifungal assay result, while the other groups were used as a negative control (sterile water treatment) and a positive one employing commercial CBZ at 0.97 $\mu\text{g}/\text{mL}$, also according to the in vitro assay result. Each peach was wounded with a sterile tip in the upper zone, and 10 μL of a conidial suspension (10^5 cfu/mL) of *M. fructicola* was placed into each wound. After 2 h, the treatments were carried out by immersion for 3 s of each inoculated fruit into a beaker with the corresponding solutions (compound **5c**, sterile water, or CBZ). The treated fruits were put into 300 mm \times 500 mm \times 100 mm plastic boxes covered in the bottom with filter papers embedded with 25 mL of sterile water in order to maintain high relative humidity (90–95%). The boxes were stored at 20 °C for 10 days, and after storage, the degree of *M. fructicola* sporulation on the surface of decayed fruits was evaluated on a zero to 4 scale (sporulation index), in which zero indicates negligible sporulation and 4 refers to a dense fungal sporulation over the entire fruit. The index value for each fruit was treated as a replication, and the treatment mean values were subjected to statistical analysis.²⁶

Cell Viability Assay. Human hepatoma (Huh7) cells were treated for 24 h with different concentrations of compound **5c** and CBZ ($2\times$, $1\times$, $\frac{1}{2}\times$, and $\frac{1}{4}\times$ MIC), and the cell viability was estimated by the MTT assay.²⁷ Experiments were done in triplicate, and means followed by standard deviation were calculated. As a positive control (100% death), we used 10% DMSO as the starting dilution, and the reading for all the dilutions was considered 0% viability. As a negative control (0% death), we used 0.1% DMSO, and the reading for all the dilutions was considered 100% viability.

Statistical Analysis. Experimental data were analyzed statistically by one-way ANOVA followed by Tukey's multiple-comparison test ($\alpha = 0.05$) using the software GraphPad Prism 7.0. (GraphPad Prism Software Inc., San Diego, CA, USA).

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.0c00225>.

General experimental procedures, characterization data, ^1H , ^{13}C , 2D NMR spectra of new substances, and pictures of fruits under antifungal treatments (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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