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FULL PAPER

CHEMISTRY & BIODIVERSITY

Synthesis and Anti-Oomycete Activity of 1-Sulfonyloxy/Acyloxydihydroeugenol Derivatives

Genqiang Chen[+],[a] Lina Zhu[+],[a] Jiaxuan He[+],[a] Song Zhang,[a] Yuanhao Li,[a] Xiaolong Guo,[a] Di Sun,[a] Yuee Tian,*[a] Shengming Liu,[a] Xiaobo Huang,[a] and Zhiping Che*[a]

[a] Laboratory of Pesticidal Design and Synthesis, Department of Plant Protection, College of Horticulture and Plant Protection, Henan University of Science and Technology, Luoyang 471023, P. R. China,
e-mail: zhipingche@163.com; tianyuee1985@163.com

Endeavor to discover biorational natural products-based fungicides, two series (26) of novel 1-sulfonyloxy/acyloxydihydroeugenol derivatives (**3a**–**p** and **5a**–**j**) were prepared and assessed for their fungicidal activity against *P. capsici* Leonian, *in vitro*. Results of fungicidal activity revealed that, among all compounds, especially compounds **3a**, **5c**, and **5e** displayed the most potent anti-oomycete activity against *P. capsici* with EC_{50} values of 69.33, 68.81, and 67.77 mg/L, respectively. Overall, the anti-oomycete activities of 1-acyloxydihydroeugenol derivatives (**5a**–**j**) were higher than that of 1-sulfonyloxydihydroeugenol derivatives (**3a**–**p**). It is proved that the introduction of the acyl group at hydroxy position of dihydroeugenol is more beneficial to improve its anti-oomycete activity than that of the sulfonyl group. These preliminary results will pave the way for further modification of dihydroeugenol in the development of potential new fungicides.

Keywords: natural bioresource, dihydroeugenol, 1-sulfonyloxy/acyloxy, fungicidal activity, botanical fungicides.

Introduction

The filamentous oomycete pathogen *Phytophthora capsici*, is a virulent and hemibiotrophic pathogen, causes root, crown, foliage and fruit rot on a number of important vegetables, such as pepper and cucurbits.[1] *P. capsici* is one of the most destructive pathogens of vegetables, which causes serious significant losses worldwide every year.[2–4] The reason is that the *P. capsici* has strong adaptability to fungicides and new hosts plants.[1–6] Fungicide is still an effective way to control *P. capsici* because the research on resistant germplasm resources lags behind the evolution of pathogens.[5–9] Like other members of this destructive genus, *P. capsici* has strong infectivity, a wide host and high resistance frequency.[1–6] Therefore, it is still a feasible way to control *P. capsici* effectively to research and develop high-efficiency and low-risk small-molecule green-fungicide.

Essential oils (Eos) do not have any obvious physiological significance for the growth of the plant itself but function mainly as defense mechanisms against a variety of pathogenic infections, including oomycetes, fungi, bacteria, and virus.[10] Eos play a very important role in the discovery of new fungicides.[11–13] Thus, it is in line with the development trend of pesticide science to develop botanical fungicides with plant secondary metabolites with antifungal activity as leading compounds.[14]

Dihydroeugenol (**1**; *Figure 1*), 2-methoxy-4-propylphenol is the reducing product of eugenol (4-allyl-2-methoxyphenol). Eugenol was mainly isolated from the unopened and dried flower buds of *Syzygium aromaticum* of the Myrtaceae family. Studies have shown that eugenol, dihydroeugenol and its derivatives have many biological activities, such as antibacterial activity,[15–18] antidiabetic and anticholinergic activity,[18] antioxidant activity,[19] insecticidal activity,[20,21] antifungal activity,[22] etc. More recently, sulfonate esterification of hydroxy of maltol, paeonol,

[+] These authors contributed equally to this work.

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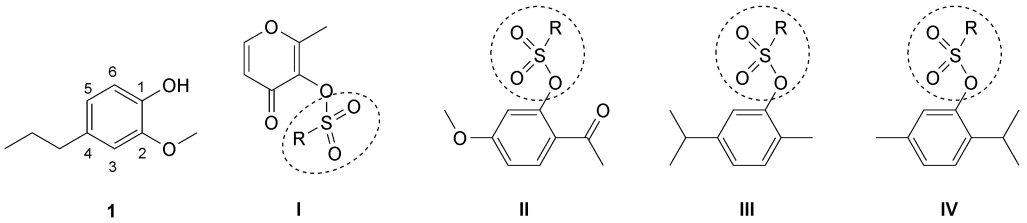


Figure 1. Chemical structures of dihydroeugenol and sulfonate derivatives of maltol (**I**), paeonol (**II**), carvacrol (**III**), and thymol (**IV**).

carvacrol and thymol had been investigated in our research group, and some sulfonate derivatives of maltol (**I**), paeonol (**II**), carvacrol (**III**) and thymol (**IV**, *Figure 1*) exhibited more pronounced anti-oomycete activity against *P. capsici*.[23–25] Overall, to the best of our knowledge, study on the synthesis of novel 1-sulfonyloxy/acyloxydihydroeugenol derivatives (**3a**–**p** and **5a**–**j**, *Schemes 1* and *2*) as fungicidal agents against *P. capsici* has not yet been reported. In the meantime, our long-term goal is to find more active natural product-based antifungal hits.[23–25] Given that, we designed and synthesized of novel dihydroeugenol derivatives (*Schemes 1* and *2*) by introducing of the sulfonyloxy or acyloxy fragments on the dihydroeugenol skeleton. The antifungal activities of two series of dihydroeugenol derivatives against *P. capsici in vitro* were reported for the first time.

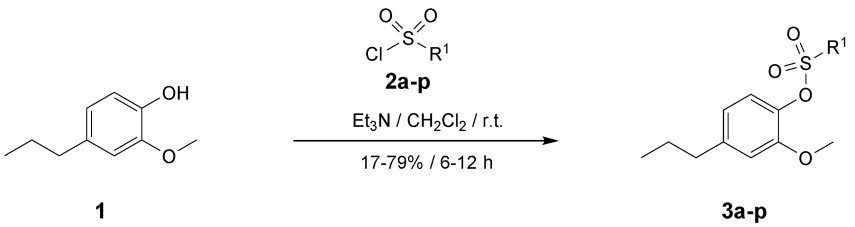
Results and Discussion

Chemistry

As depicted in *Scheme 1*, **1** reacted with R^1SO_2Cl (**2a**–**p**) to afford a series of 1-sulfonyloxydihydroeugenol derivatives (**3a**–**p**) in suitable yields.[23–25] Meanwhile, as described in *Scheme 2*, R^2COOH (**4a**–**j**) first reacted with Br_3CSO_2Ph to obtain the corresponding acyl bromine. Then introduction of the different acyloxy groups at the C-1 position of **1** gave 1-acyloxydihydroeugenol derivatives (**5a**–**j**) in suitable yields.[26] The structures of all title compounds were well characterized by ^{1}H-NMR, HRMS, and m.p., and the data of **3a**–**p** and **5a**–**j** can be found in the Supporting Information.

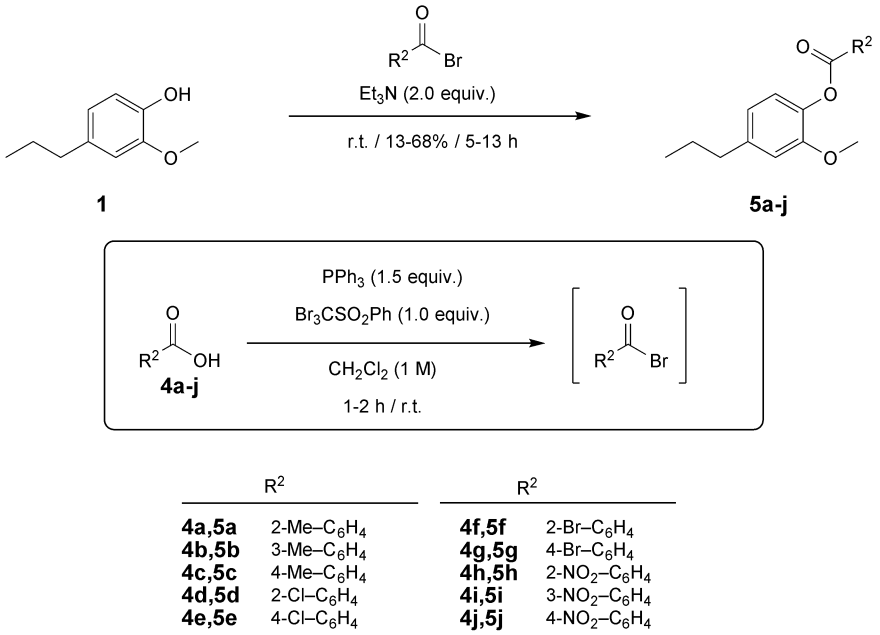
Anti-Oomycete Activity

The anti-oomycete activity of dihydroeugenol (**1**), eugenol, novel 1-sulfonyloxydihydroeugenol derivatives (**3a**–**p**) and 1-acyloxydihydroeugenol derivatives (**5a**–**j**) against *P. capsici* is outlined in *Table 1*.



	R^1		R^1
2a,3a	Et	**2i,3i**	4-Br–C_6H_4
2b,3b	Ph	**2j,3j**	2-NO_2–C_6H_4
2c,3c	4-Me–C_6H_4	**2k,3k**	3-NO_2–C_6H_4
2d,3d	4-MeO–C_6H_4	**2l,3l**	4-NO_2–C_6H_4
2e,3e	4-^{t}Bu–C_6H_4	**2m,3m**	3-NO_2-4-Cl–C_6H_3
2f,3f	2,4,6-Me_3–C_6H_2	**2n,3n**	2-thienyl
2g,3g	2,4,6-^{i}Pr$_3$–C_6H_2	**2o,3o**	1-naphthyl
2h,3h	4-F–C_6H_4	**2p,3p**	8-quinolyl

Scheme 1. Synthetic route for the preparation of **3a**–**p**.



	R^2		R^2
4a,5a	2-Me–C_6H_4	**4f,5f**	2-Br–C_6H_4
4b,5b	3-Me–C_6H_4	**4g,5g**	4-Br–C_6H_4
4c,5c	4-Me–C_6H_4	**4h,5h**	2-NO_2–C_6H_4
4d,5d	2-Cl–C_6H_4	**4i,5i**	3-NO_2–C_6H_4
4e,5e	4-Cl–C_6H_4	**4j,5j**	4-NO_2–C_6H_4

Scheme 2. Synthetic route for the preparation of **5a**–**j**.

Results of fungicidal activity showed that, out of twenty-six evaluated compounds, three (**3a**, **5c**, and **5e**) exhibited significant anti-oomycete activity (EC_{50} values of 69.33, 68.81, and 67.77 mg/L, respectively), ten (**3c**, **3m**, **3n**, **5a**, **5b**, **5d**, **5f**–**h**, and **5j**) showed moderate anti-oomycete activity (EC_{50} values of 93.94, 86.71, 90.18, 74.50, 81.96, 83.50, 84.27, 77.72, 83.96, and 80.50 mg/L, respectively), while the remaining compounds displayed weak anti-oomycete activity (EC_{50} values of 101.35 to 177.17).

In order to elucidate the anti-oomycete activity of compounds **3a**–**p** and **5a**–**j** at a molecular basis and to reveal structural features critical for their anti-oomycete activity, a brief investigation of structure-activity relationship (SAR) was determined, which revealed how the substituents on **3a**–**p** and **5a**–**j** were related to the anti-oomycete. This mainly includes six aspects. (1) On the whole, the anti-oomycete activity of dihydroeugenol with the acyloxy group was higher than that with the sulfonyloxy group, and the EC_{50} values of **3a**–**p** and **5a**–**j** were 69.33–177.17 mg/L and 67.77–101.35 mg/L, respectively. In addition, it is noteworthy that introduction of the acyl group at the hydroxy position of **1** could lead to produce more potent compound compared to their precursor dihydroeugenol (e.g., **5a**–**j** *vs.* **1**). (2) Interrestingly, we found that the introduction of the nitrophenylsulfonyl/nitrobenzoyl/methylbenzoyl at the hydroxy position of **1**, the nitro/methyl groups at different positions of the benzene ring could lead to derivatives with different anti-oomycete activities (*para* > *ortho* > *meta* position, e.g., **3l** > **3j** > **3k**, **5j** > **5h** > **5i** and **5c** > **5a** > **5b**). For example, the EC_{50} values of **3l**, **3j**, **3k**, **5j**, **5h**, **5i**, **5c**, **5a** and **5b** against *P. capsici* were 108.69, 145.64, 177.17, 80.50, 83.96, 101.35, 68.81, 74.50 and 81.96 mg/L, respectively. Similarly, the introduction of the *p*-chlorobenzoyl/*p*-bromobenzoyl at the hydroxy position of **1** could lead to produce more potent compound than introducing of the *o*-chlorobenzoyl/*o*-bromobenzoyl groups (e.g., 67.77 and 77.72 mg/L for **5e** and **5g** versus 83.50 and 84.27 mg/L for **5d** and **5f**). (3) In 1-sulfonyloxydihydroeugenol derivatives, as compared with fused ring (1-naphthalensulyonyl and 8-quinolinesulfonyl) derivatives, 2-thiophenesulfonyl derivative displayed the best anti-oomycete activity (**3n** > **3p** > **3o**, e.g., EC_{50} = 90.18 mg/L for **3n** versus EC_{50} = 115.68 mg/L for **3p** and EC_{50} = 125.37 mg/L for **3o**). (4) The introduction of the tosyl at the hydroxy position of **1** could lead to more potent compound than possessing of the phenylsulfonyl group, *p*-tert-butylphenylsulfonyl group, and *p*-methoxyphenylsulfonyl group (**3c** > **3b** > **3e** > **3d**). For example, the EC_{50} values of **3c**, **3b**, **3e** and **3d** against *P. capsici* were 93.94, 127.12, 132.76 and 143.34 mg/L, respectively. Similarly, comparing the EC_{50} value of R^1 = 2,4,6-trimethylphenyl derivative (EC_{50} = 104.90 mg/L for **3f**), it exhibited more potent anti-oomycete activity than R^1 = 2,4,6-triisopropyl-

Table 1. Anti-oomycete activities of compounds **3a**–**p** and **5a**–**j** against *P. capsici in vitro*.

Compound	*P. capsici*
	EC_{50} (mg/L)
1	108.17
Eugenol	243.19
3a	69.33
3b	127.12
3c	93.94
3d	143.34
3e	132.76
3f	104.90
3g	138.88
3h	134.73
3i	170.47
3j	145.64
3k	177.17
3l	108.69
3m	86.71
3n	90.18
3o	125.37
3p	115.68
5a	74.50
5b	81.96
5c	68.81
5d	83.50
5e	67.77
5f	84.27
5g	77.72
5h	83.96
5i	101.35
5j	80.50
Zoxamide	26.87

phenyl derivative (EC_{50} = 138.88 mg/L for **3g**). (5) It is noteworthy that the introduction of the *p*-chloro-*m*-nitrophenylsulfonyl as a two-electron-withdrawing substituent (such as NO_2 and Cl) could result in more potent compound **3m** relative to those containing phenylsulfonyl as a one-electron-withdrawing substituent (e.g., **3h**–**l**). For example, the EC_{50} values of **3h**–**m** against *P. capsici* were 134.73, 170.47, 145.64, 177.17, 108.69 and 86.71 mg/L, respectively. Moreover, the introduction of 4-fluorophenylsulfonyl to the hydroxy position of dihydroeugenol could lead to more potent compound than possessing 4-bromophenylsulfonyl group (e.g., 134.73 mg/L for **3h** versus 170.47 mg/L for **3i**). (6) The anti-oomycete activity of eugenol was significantly improved after allyl reduction (e.g., EC_{50} = 243.19 mg/L for eugenol versus EC_{50} = 108.17 mg/L for **1**). In addition, the substituent ^1R is aliphatic, which is essential for anti-oomycete activity (EC_{50} = 69.33 mg/L for **3a**). In the future, we can consider the synthesis of derivatives with the proper chain length of R^1.

Conclusion

In summary, 26 novel 1-sulfonyloxy/acyloxydihydroeugenol derivatives (**3a**–**p** and **5a**–**j**) were prepared and their structures were well characterized by ^{1}H-NMR, HRMS, and m.p. Their fungicidal activity was evaluated against *P. capsici in vitro*. Among all of the tested compounds, half of the compounds **3a**, **3c**, **3m**, **3n**, **5a-h**, and **5j** showed more potent anti-oomycete activity than their precursor dihydroeugenol, and the EC_{50} values of 69.33, 93.94, 86.71, 90.18, 74.50, 81.96, 68.81, 83.50, 67.77, 84.27, 77.72, 83.96, and 80.50 mg/L, respectively. Especially compounds **3a**, **5c**, and **5e**, displayed the most potent anti-oomycete activity against *P. capsici* with EC_{50} values of less than 70 mg/L. Overall, the anti-oomycete activities of 1-acyloxydihydroeugenol derivatives (**5a**–**j**) was higher than that of 1-sulfonyloxydihydroeugenol derivatives (**3a**–**p**). It is proved that the introduction of the acyl group at hydroxy position of dihydroeugenol is more beneficial to improve its anti-oomycete activity than that of the sulfonyl group. This will pave the way for further design, structural modification, and to develop dihydroeugenol derivatives as fungicidal agents.

Experimental Section

Chemistry

Dihydroeugenol (2-methoxy-4-propylphenol, **1**), Eugenol (4-allyl-2-methoxyphenol), ethanesulfonyl chloride ($C_2H_5SO_2Cl$), arylsulfonyl chloride (R^1SO_2Cl), aryl acid (R^2COOH), and triethylamine (Et_3N) were ordered from Aladdin Chemistry Co., Ltd. (Shanghai, China). Triphenylphosphine (PPh_3), and phenyl tribromomethyl sulfone (Br_3CSO_2Ph) were ordered from Shanghai Macklin Biochemical Co., Ltd. (Shanghai, China).

General Procedure for Preparation of 1-Sulfonyloxydihydroeugenol Derivatives (**3a**–**p**)

To a mixture of 2-methoxy-4-propylphenol (**1**, 1.0 mmol) and R^1SO_2Cl (**2a**–**p**, 1.2 mmol) in dry CH_2Cl_2 (10 mL) at room temperature, a solution of Et_3N (1.5 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise for 5 min. The reaction was detected by TLC, H_2O (15 mL) was added to the reaction, and extracted with CH_2Cl_2 (30 mL × 3). Subsequently, the organic phase

was combined, washed by saturated aq. brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by CC to obtain 1-sulfonyloxydihydroeugenol derivatives in 17–79% yields.[23–25]. The data of **3a**–**p** can be found in the *Supporting Information*.

General Procedure for Preparation of 1-Acyloxydihydroeugenol Derivatives (**5a**–**j**)

To a mixture of R^2COOH (**4a**–**j**, 1.0 mmol), PPh_3 (1.5 mmol) and Br_3CSO_2Ph (1.0 mmol) in dry CH_2Cl_2 (1 M), the mixture was stirred at room temperature for 1–2 h, and the reaction process was checked by TLC analysis. Then, 2-methoxy-4-propylphenol (**1**, 1.0 mmol) and Et_3N (2.0 mmol) were added to the reaction. After the addition, the solution was continually stirred at room temperature for 5–13 h. The reaction was detected by TLC, H_2O (15 mL) was added to the reaction, and extracted with CH_2Cl_2 (30 mL×3). Subsequently, the organic phase was combined, washed by saturated aq. brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by CC to obtain 1-acyloxydihydroeugenol derivatives in 13–68% yields.[26–28] The data of **5a**–**j** can be found in the Supporting Information.

Bioassay Method

The fungicidal activity of dihydroeugenol (**1**), eugenol, **3a**–**p**, **5a**–**j**, and zoxamide (positive control) against *P. capsici* was evaluated by using the mycelial growth rate method.[23–25] The specific method can refer to the *Supporting Information*.

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Author Contribution Statement

Designed the experiments, synthesized the compounds, and analyzed the data: Lina Zhu, Jiaxuan He, Song Zhang, Yuanhao Li, Xiaolong Guo, Di Sun, Yuee Tian, Shengming Liu, Xiaobo Huang Genqiang Chen and Zhiping Che; Wrote the article: Genqiang Chen and Zhiping Che; All authors approved the final manuscript.

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