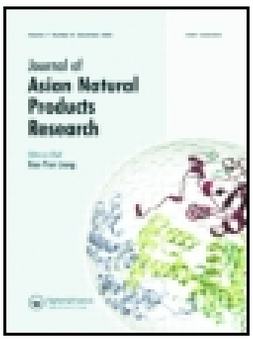

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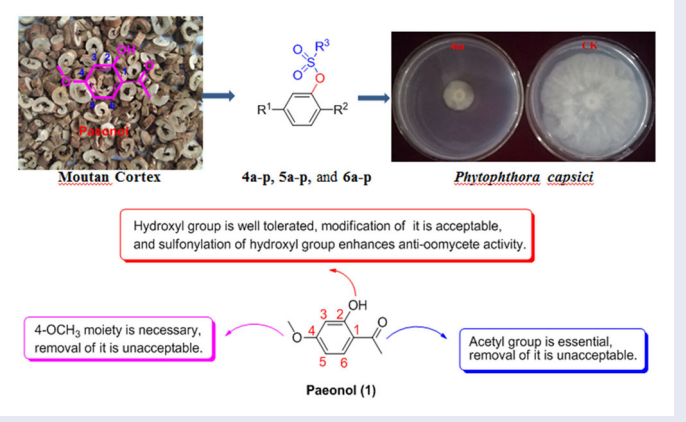
ABSTRACT

Three series of sulfonate derivatives of paeonol were synthesized and screened *in vitro* for their anti-oomycete activity against *P. capsici*, respectively. Among all the compounds, **4m** displayed the best promising and pronounced anti-oomycete activity against *P. capsici* than zoxamide, with the EC_{50} values of 24.51 and 26.87 mg/L, respectively. The results show that acetyl and 4-OCH_3 are two necessary groups. The existence of these two sites is closely related to the anti-oomycete activity. Relatively speaking, hydroxyl group is well tolerated, and the results showed that after modification of hydroxyl group with sulfonyl, the anti-oomycete activity was significantly increased.



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Natural product; paeonol; sulfonylation; anti-oomycete activity; structure–activity relationship

1. Introduction

The impact of oomycetes on humankind is well documented as both a persistent threat to subsistence and commercial farming and as destructive pathogens of native plants [1]. The oomycete vegetable pathogen *Phytophthora capsici*, is a virulent,

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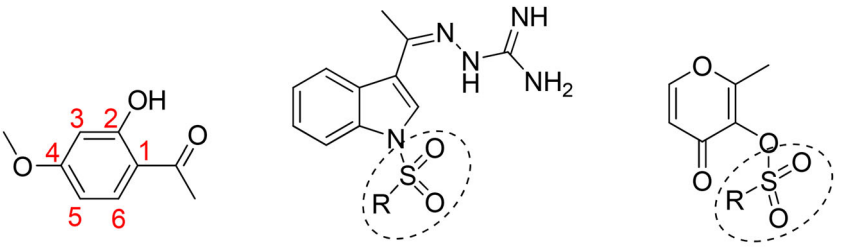


Figure 1. Structures of paeonol (**1**), aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles (**I**) and sulfonate derivatives of maltol (**II**).

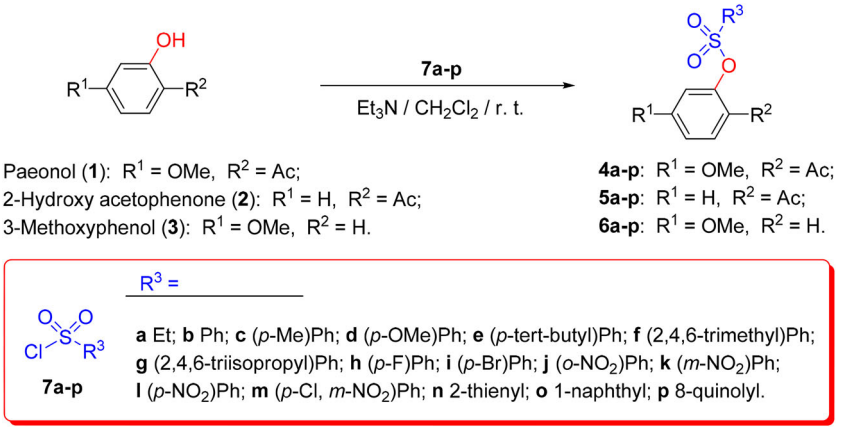
hemibiotrophic pathogen of vegetable crops, inflicting significant losses worldwide [2]. The pathogen *P. capsici* has shown remarkable adaptation to new hosts and fungicides [3]. Due to the lack of the resistant germplasm resources, fungicides controlling is still the main way to reduce the incidence of *P. capsici* on main hosts though resistance is an inevitable result of evolution [4–7]. Therefore, design and synthesis of novel compounds that effectively inhibit those agricultural diseases is still highly desirable.

The effective ways for pesticide innovation are to develop new fungicides with independent intellectual property rights from plant secondary metabolites as lead compounds [8]. 2-Hydroxyl-4-methoxyacetophenone (**1**, Figure 1) is what people commonly call "Paeonol," which is one of the main phenolic components in moutan cortex [9–11]. Paeonol is a traditional Chinese medicine, the derivatives of which exhibit numerous biological activities, such as antitumor activity [12], anti-inflammatory activity [13], anti-HBV activity [14], mushroom tyrosinase inhibitor [15], insecticidal activity [16], acaricidal activity [17], and antifungal activity [18]. Recently, we investigated the antifungal activity of paeonol containing hydroxyl against *Botrytis cinerea* and *Fusarium oxysporum* [19]. We found that aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles (**I**, Figure 1) exhibited the promising and pronounced antifungal activity [20]; and sulfonate derivatives of maltol (**II**, Figure 1) showed significant anti-oomycete activity [21]. Inspired by the above-mentioned interesting results, and according to the principle of superposition of bioactivity, we have designed and prepared three series of sulfonate derivatives of paeonol in this study [22–25], and first report the results of the anti-oomycete activity of forty-eight sulfonate derivatives of paeonol against *P. capsici in vitro*. Additionally, their structure-activity relationship (SAR) studies were also described.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 1, paeonol/2-hydroxy acetophenone/3-methoxyphenol (**1**/**2**/**3**) reacted with 1.2 equiv. of ethanesulfonyl chloride/arylsulfonyl chloride (**7a–p**) in the presence of 1.5 equiv. of triethylamine to obtain three series of sulfonate derivatives of paeonol (**4a–p, 5a–p,** and **6a–p**) in relatively good yields. The structures of all target compounds were well characterized by ^{1}H NMR, ESI-MS, and m.p.



Scheme 1. The synthetic route of sulfonate derivatives of paeonol (**4a–p**, **5a–p**, and **6a–p**).

2.2. Anti-oomycete activity

Forty-eight sulfonate derivatives of paeonol (**4a–p, 5a–p,** and **6a–p**) were screened *in vitro* for their anti-oomycete activity against *P. capsici*. Zoxamide, a commercially available agricultural fungicide, was used as a positive control. And the inhibitory effects showed an obviously dose-dependent manner that with the concentration of compound increased, the colony diameter decreased.

As depicted in Table 1, among these tested sulfonate derivatives of paeonol, compounds **4h**, **4k**, **4m**, **4n–p**, and **6m** exhibited obvious anti-oomycete activity for *P. capsici* with EC_{50} values of 45.23, 46.92, 24.51, 46.18, 47.66, 47.16, and 42.72 mg/L, respectively. Among the compounds, **4m** displayed the most promising and pronounced anti-oomycete activity against *P. capsici* than zoxamide (EC_{50}=26.87 mg/L). Meanwhile, a brief structure activity relationship (SAR) was determined. (1) Generally, the introduction of different substitutions at the hydroxyl position of paeonol/2-hydroxy acetophenone/3-methoxyphenol (**1**/**2**/**3**) has remarkable effect on anti-oomycete activity. (2) The presence of two sites acetyl and 4-OCH_3 groups is closely related to its resistance activity; For example, the EC_{50} values of **1**, **2** and **3** against *P. capsici* were 75.47, 93.02 and 85.10 mg/L, respectively. Hydroxyl group is well tolerated, and sulfonylation of hydroxyl group enhances its anti-oomycete activity; For example, the EC_{50} values of **4m, 5m** and **6m** for *P. capsici* were 24.51, 52.82 and 42.72 mg/L, respectively. (3) Moreover, through a comparative study on the relationship between the chemical structures and anti-oomycete activity of **4a–p, 5a–p,** and **6a–p**, some interesting results were found as follows: (a) It is noteworthy that the introduction of 4-chloro-3-nitrophenylsulfonyl as a two-electron-withdrawing substituent (such as NO_2 and Cl) could result in more potent compounds **4m, 5m** and **6m** relative to those containing phenylsulfonyl as a one-electron-withdrawing substituent (e.g., **4h–l, 5h–l** and **6h–l**). For example, the EC_{50} values of **4h–l, 5h–l** and **6h–l** for *P. capsici* were 45.23/75.23/65.10/46.92/51.91, 77.56/97.76/90.56/69.54/75.23 and 69.54/92.56/77.56/114.34/101.63 mg/L, respectively. (b) The introduction of 4-fluorophenylsulfonyl at the hydroxyl position of paeonol could lead to more potent

Table 1. Anti-oomycete activities of compounds **4a–p**, **5a–p**, and **6a–p** against *P. capsici in vitro*.

Compounds	*P. capsici* EC_{50} (mg/L)
1/2/3	75.47/93.02/85.10
4a/5a/6a	93.88/120.41/131.20
4b/5b/6b	80.91/102.66/94.6
4c/5c/6c	50.00/95.26/114.34
4d/5d/6d	79.58/95.26/131.24
4e/5e/6e	53.33/75.23/76.37
4f/5f/6f	92.56/98.10/101.11
4g/5g/6g	65.10/135.43/73.02
4h/5h/6h	45.23/77.56/69.54
4i/5i/6i	75.23/97.76/92.56
4j/5j/6j	65.10/90.56/77.56
4k/5k/6k	46.92/69.54/114.34
4l/5l/6l	51.91/75.23/101.63
4m/5m/6m	24.51/52.82/42.72
4n/5n/6n	46.18/93.43/65.10
4o/5o/6o	47.66/79.14/112.42
4p/5p/6p	47.16/78.34/50.91
Zoxamide	26.87

compound than introducing 4-bromophenylsulfonyl group (e.g., 45.23 mg/L for **4h** versus 75.23 mg/L for **4i**). In addition, we found that the introduction of nitrophenylsulfonyl at the hydroxyl position of paeonol, and the nitro group at different position of the benzene ring, could lead to derivatives with different anti-oomycete activity [meta-position for **4k** (EC_{50}=46.92 mg/L) versus para-position for **4l** (EC_{50}=51.91 mg/L), ortho-position for **4j** (EC_{50}=65.10 mg/L)]. (c) Some compounds containing fused heterocycles (2-thiophenesulfonyl, 8-quinolinesulfonyl and 1-naphthalensulyonyl) exhibited more potent anti-oomycete activity (**4n–p**). For example, the EC_{50} values of **4n–p** for *P. capsici* were 46.18, 47.66 and 47.16 mg/L, respectively.

3. Experimental

3.1. General experimental procedures

Melting points were taken on an X-6 microscopic melting point apparatus (Beijing Tech instrument Co., Ltd., Beijing, China) and are uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance DMX 400 MHz instrument (Bruker Daltonik, Bremen, Germany) in $CDCl_3$ (^1H at 400 MHz) using TMS (tetramethylsilane) as the internal standard. Electrospray ion trap mass spectrometry (ESI-TRAP-MS) was carried out with a Bruker ESI-TRAP Esquire 6000 plus mass spectrometry instrument (Bruker, Germany). Paeonol, triethylamine, ethanesulfonyl chloride and arylsulfonyl chloride were purchased from Aladdin Chemistry Co., Ltd. (Shanghai, China). Ethyl acetate, dichloromethane and petroleum ether were purchased from Beichen Fangzheng Reagent Factory (Tianjin, China). Analytical thin-layer chromatography (TLC) was performed with silica gel plate using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd., Shandong, China). Silica gel column chromatography was performed with silica gel 200-300 mesh (Qingdao Haiyang Chemical Co., Ltd., Shandong, China).

3.2. General procedure for the synthesis of sulfonate derivatives of paeonol (4a–p, 5a–p, and 6a–p)

To a solution of paeonol/2-hydroxy acetophenone/3-methoxyphenol (**1**/**2**/**3**, 1.0 mmol) and ethanesulfonyl chloride/arylsulfonyl chloride (**7**, 1.2 mmol) in dry dichloromethane (CH_2Cl_2, 10 ml) at room temperature, a solution of triethylamine (Et_3N) (1.5 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise for 10 min. When the reaction was completed by TLC analysis, the reaction mixture was diluted with water (15 ml), and extracted with CH_2Cl_2 (30 ml × 3). Subsequently, the combined organic phase was washed by saturated aq. brine (30 ml), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography to obtain title compounds. The data for **4a–p**, **5a–p**, and **6a–p** are shown as follows.

3.2.1. Data for 4a

Yield = 38%, Reddish brown oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, J= 8.8 Hz, 1H), 6.94 (d, J= 2.4 Hz, 1H), 6.89 (dd, J= 8.8, 2.4 Hz, 1H), 3.87 (s, 3H), 3.47 (q, J= 7.6 Hz, 2H), 2.59 (s, 3H), 1.58 (t, J= 7.6 Hz, 3H). ESI-MS: m/z (%) 259 $[M+H]^+$ (100).

3.2.2. Data for 4b

Yield = 48%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, J= 8.8 Hz, 2H), 7.67–7.73 (m, 2H), 7.57 (t, J= 8.0 Hz, 2H), 6.85 (dd, J= 8.8, 2.4 Hz, 1H), 6.60 (d, J= 2.4 Hz, 1H), 3.77 (s, 3H), 2.46 (s, 3H). ESI-MS: m/z (%) 307 $[M+H]^+$ (100).

3.2.3. Data for 4c

Yield = 33%, White solid, m.p. 67–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71–7.74 (m, 2H), 7.70 (d, J= 8.8 Hz, 1H), 7.32–7.34 (m, 2H), 6.84 (dd, J= 8.8, 2.4 Hz, 1H), 6.65 (d, J= 2.4 Hz, 1H), 3.78 (s, 3H), 2.46 (s, 6H). ESI-MS: m/z (%) 321 $[M+H]^+$ (100).

3.2.4. Data for 4d

Yield = 57%, White solid, m.p. 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74–7.78 (m, 2H), 7.70 (d, J= 8.8 Hz, 1H), 6.96–7.00 (m, 2H), 6.84 (dd, J= 8.8, 2.4 Hz, 1H), 6.66 (d, J= 2.4 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 2.47 (s, 3H). ESI-MS: m/z (%) 337 $[M+H]^+$ (100).

3.2.5. Data for 4e

Yield = 57%, White solid, m.p. 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76–7.79 (m, 2H), 7.71 (d, J= 8.8 Hz, 1H), 7.53–7.56 (m, 2H), 6.82–6.85 (m, 1H), 6.58–6.59 (m, 1H), 3.75 (s, 3H), 2.45 (s, 3H), 1.35 (s, 9H). ESI-MS: m/z (%) 363 $[M+H]^+$ (100).

3.2.6. Data for 4f

Yield = Yield = 49%, White solid, m.p. 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, J= 8.8 Hz, 1H), 7.02 (s, 2H), 6.83 (dd, J= 8.8, 2.4 Hz, 1H), 6.20 (d, J= 2.4 Hz,

1H), 3.64 (s, 3H), 2.57 (s, 3H), 2.56 (s, 6H), 2.34 (s, 3H). ESI-MS: *m/z* (%) 349 $[M+H]^+$ (100).

3.2.7. Data for 4g

Yield = 51%, White solid, m.p. 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, J= 8.8 Hz, 1H), 7.24 (s, 2H), 6.81 (dd, J= 8.8, 2.4 Hz, 1H), 6.04 (d, J= 2.4 Hz, 1H), 4.00–4.07 (m, 2H), 3.53 (s, 3H), 2.92–2.99 (m, 1H), 2.66 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.21 (s, 6H), 1.19 (s, 6H). ESI-MS: *m/z* (%) 433 $[M+H]^+$ (100).

3.2.8. Data for 4h

Yield = 42%, White solid, m.p. 78–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86–7.91 (m, 2H), 7.70 (d, J= 8.8 Hz, 1H), 7.20–7.25 (m, 2H), 6.87 (dd, J= 8.8, 2.4 Hz, 1H), 6.66 (d, J= 2.8 Hz, 1H), 3.80 (s, 3H), 2.46 (s, 3H). ESI-MS: *m/z* (%) 325 $[M+H]^+$ (100).

3.2.9. Data for 4i

Yield = 41%, White solid, m.p. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68–7.75 (m, 5H), 6.87 (dd, J= 8.8, 2.4 Hz, 1H), 6.65 (d, J= 2.4 Hz, 1H), 3.80 (s, 3H), 2.46 (s, 3H). ESI-MS: *m/z* (%) 384 $[M+H]^+$ (100).

3.2.10. Data for 4j

Yield = 34%, Turquoise oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J= 7.2 Hz, 1H), 7.85–7.89 (m, 2H), 7.74–7.79 (m, 2H), 6.90 (dd, J= 8.8, 2.4 Hz, 1H), 6.70 (d, J= 2.4 Hz, 1H), 3.79 (s, 3H), 2.54 (s, 3H). ESI-MS: *m/z* (%) 352 $[M+H]^+$ (100).

3.2.11. Data for 4k

Yield = 34%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (t, J= 2.0 Hz, 1H), 8.53–8.56 (m, 1H), 8.23–8.26 (m, 1H), 7.83 (t, J= 8.0 Hz, 1H), 7.70 (d, J= 8.8 Hz, 1H), 6.90 (dd, J= 8.8, 2.4 Hz, 1H), 6.74 (d, J= 2.4 Hz, 1H), 3.84 (s, 3H), 2.45 (s, 3H). ESI-MS: *m/z* (%) 352 $[M+H]^+$ (100).

3.2.12. Data for 4l

Yield = 60%, White solid, m.p. 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38–8.42 (m, 2H), 8.10–8.14 (m, 2H), 7.72 (d, J= 8.8 Hz, 1H), 6.90 (dd, J= 8.8, 2.4 Hz, 1H), 6.73 (d, J= 2.4 Hz, 1H), 3.84 (s, 3H), 2.46 (s, 3H). ESI-MS: *m/z* (%) 352 $[M+H]^+$ (100).

3.2.13. Data for 4m

Yield = 40%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, J= 2.4 Hz, 1H), 8.09 (dd, J= 8.4, 2.0 Hz, 1H), 7.79 (d, J= 8.8 Hz, 1H), 7.73 (d, J= 8.8 Hz, 1H), 6.92 (dd, J= 8.8, 2.4 Hz, 1H), 6.78 (d, J= 2.4 Hz, 1H), 3.86 (s, 3H), 2.46 (s, 3H). ESI-MS: *m/z* (%) 386 $[M+H]^+$ (100).

3.2.14. Data for 4n

Yield = 33%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, J= 5.2 Hz, 1H), 7.71 (d, J= 8.8 Hz, 1H), 7.63 (d, J= 4.0 Hz, 1H), 7.14 (t, J= 4.0 Hz, 1H), 6.87 (dd, J= 8.8, 2.4 Hz, 1H), 6.70 (d, J= 2.4 Hz, 1H), 3.80 (s, 3H), 2.51 (s, 3H). ESI-MS: m/z (%) 335 $[M+Na]^+$ (70).

3.2.15. Data for 4o

Yield = 39%, White solid, m.p. 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77–8.80 (m, 1H), 8.18–8.21 (m, 1H), 8.16 (dd, J= 7.6, 1.2 Hz, 1H), 7.99–8.02 (m, 1H), 7.76–7.80 (m, 1H), 7.67–7.73 (m, 2H), 7.55 (dd, J= 8.4, 7.6 Hz, 1H), 6.78 (dd, J= 8.8, 2.4 Hz, 1H), 6.08 (d, J= 2.4 Hz, 1H), 3.50 (s, 3H), 2.54 (s, 3H). ESI-MS: m/z (%) 357 $[M+H]^+$ (100).

3.2.16. Data for 4p

Yield = 35%, White oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (dd, J= 4.4, 2.0 Hz, 1H), 8.46 (dd, J= 7.6, 1.6 Hz, 1H), 8.31 (dd, J= 8.4, 2.0 Hz, 1H), 8.18 (dd, J= 8.4, 1.6 Hz, 1H), 7.67 (d, J= 8.8 Hz, 1H), 6.66 (dd, J= 8.4, 7.6 Hz, 1H), 7.62 (q, J= 4.0 Hz, 1H), 6.76 (dd, J= 8.8, 2.4 Hz, 1H), 6.64 (d, J= 2.4 Hz, 1H), 3.66 (s, 3H), 2.58 (s, 3H). ESI-MS: m/z (%) 380 $[M+Na]^+$ (96).

3.2.17. Data for 5a

Yield = 54%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (dd, J= 7.6, 1.6 Hz, 1H), 7.52–7.56 (m, 1H), 7.37–7.43 (m, 2H), 3.42 (q, J= 7.6 Hz, 2H), 2.63 (s, 3H), 1.57 (t, J= 7.6 Hz, 3H). ESI-MS: m/z (%) 229 $[M+H]^+$ (100).

3.2.18. Data for 5b

Yield = 72%, Pale yellow solid, m.p. 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80–7.83 (m, 2H), 7.68–7.72 (m, 1H), 7.65 (dd, J= 7.6, 1.6 Hz, 1H), 7.52–7.56 (m, 2H), 7.42–7.46 (m, 1H), 7.32–7.36 (m, 1H), 7.10 (dd, J= 8.0, 1.2 Hz, 1H), 2.51 (s, 3H). ESI-MS: m/z (%) 277 $[M+H]^+$ (100).

3.2.19. Data for 5c

Yield = 51%, White solid, m.p. 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66–7.70 (m, 2H), 7.65 (dd, J= 7.6, 1.6 Hz, 1H), 7.41–7.46 (m, 1H), 7.30–7.35 (m, 3H), 7.10 (dd, J= 8.0, 1.2 Hz, 1H), 2.52 (s, 3H), 2.46 (s, 3H). ESI-MS: m/z (%) 291 $[M+H]^+$ (100).

3.2.20. Data for 5d

Yield = 74%, Yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.74 (m, 2H), 7.65 (dd, J= 7.6, 1.6 Hz, 1H), 7.41–7.46 (m, 1H), 7.31–7.35 (m, 1H), 7.10 (dd, J= 8.0, 1.2 Hz, 1H), 6.94–6.99 (m, 2H), 3.89 (s, 3H), 2.53 (s, 3H). ESI-MS: m/z (%) 307 $[M+H]^+$ (100).

3.2.21. Data for 5e

Yield = 81%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71–7.75 (m, 2H), 7.65 (dd, J= 7.6, 1.6 Hz, 1H), 7.52–7.55 (m, 2H), 7.42–7.47 (m, 1H), 7.31–7.36 (m, 1H), 7.13 (dd, J= 8.0, 1.2 Hz, 1H), 2.49 (s, 3H), 1.35 (s, 9 H). ESI-MS: m/z (%) 333 $[M+H]^+$ (100).

3.2.22. Data for 5f

Yield = 67%, Pale yellow solid, m.p. 96–97 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.72 (m, 1H), 7.26–7.36 (m, 2H), 7.00 (s, 2H), 6.71–6.74 (m, 1H), 2.60 (s, 3H), 2.52 (s, 6H), 2.34 (s, 3H). ESI-MS: m/z (%) 319 $[M+H]^+$ (100).

3.2.23. Data for 5g

Yield = 56%, Pale yellow solid, m.p. 78–79 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76–7.79 (m, 1H), 7.30–7.33 (m, 2H), 7.22 (s, 2H), 6.65–6.67 (m, 1H), 3.96–4.03 (m, 2H), 2.91–2.98 (m, 1H), 2.68 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 1.19 (s, 6H), 1.17 (s, 6H). ESI-MS: m/z (%) 403 $[M+H]^+$ (100).

3.2.24. Data for 5h

Yield = 66%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83–7.86 (m, 2H), 7.66 (dd, J= 7.6, 1.6 Hz, 1H), 7.44–7.48 (m, 1H), 7.34–7.38 (m, 1H), 7.20–7.24 (m, 2H), 7.12 (dd, J= 8.0, 1.2 Hz, 1H), 2.53 (s, 3H). ESI-MS: m/z (%) 295 $[M+H]^+$ (100).

3.2.25. Data for 5i

Yield = 78%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J= 0.8 Hz, 4H), 7.67 (dd, J= 7.6, 1.6 Hz, 1H), 7.44–7.48 (m, 1H), 7.38 (t, J= 7.6 Hz, 1H), 7.09 (dd, J= 8.0, 1.2 Hz, 1H), 2.53 (s, 3H). ESI-MS: m/z (%) 356 $[M+H]^+$ (100).

3.2.26. Data for 5j

Yield = 71%, Yellow solid, m.p. 56–57 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96–8.02 (m, 1H), 7.87–7.91 (m, 2H), 7.69–7.75 (m, 2H), 7.38–7.51 (m, 2H), 7.25 (t, J= 8.4 Hz, 1H), 2.60 (s, 3H). ESI-MS: m/z (%) 322 ($[M+H]^+$ (100).

3.2.27. Data for 5k

Yield = 56%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (t, J= 4.0 Hz, 1H), 8.54–8.57 (m, 1H), 8.18–8.21 (m, 1H), 7.82 (t, J= 8.0 Hz, 1H), 7.67 (dd, J= 7.6, 1.6 Hz, 1H), 7.49–7.53 (m, 1H), 7.38–7.42 (m, 1H), 7.20 (dd, J= 8.0, 1.2 Hz, 1H), 2.52 (s, 3H). ESI-MS: m/z (%) 322 $[M+H]^+$ (100).

3.2.28. Data for 5l

Yield = 84%, Pale yellow solid, m.p. 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38–8.41 (m, 2H), 8.05–8.09 (m, 2H), 7.69 (dd, J= 7.6, 1.6 Hz, 1H), 7.48–7.52 (m, 1H), 7.38–7.43 (m, 1H), 7.16 (dd, J= 8.0, 1.2 Hz, 1H), 2.53 (s, 3H). ESI-MS: m/z (%) 322 $[M+H]^+$ (100).

3.2.29. Data for 5m

Yield = 67%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (d, J= 2.0 Hz, 1H), 8.02 (dd, J= 8.4, 2.0 Hz, 1H), 7.79 (d, J= 8.4 Hz, 1H), 7.70 (dd, J= 7.6, 1.6 Hz, 1H), 7.51–7.55 (m, 1H), 7.40–7.44 (m, 1H), 7.22 (dd, J= 8.0, 1.2 Hz, 1H), 2.54 (s, 3H). ESI-MS: m/z (%) 356 $[M+H]^+$ (100).

3.2.30. Data for 5n

Yield = 89%, Pale red oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (dd, J= 5.2, 3.6 Hz, 1H), 7.65 (dd, J= 7.6, 1.6 Hz, 1H), 7.19 (dd, J= 4.4, 2.4 Hz, 1H), 7.45–7.49 (m, 1H), 7.34–7.38 (m, 1H), 7.19 (dd, J= 8.0, 1.2 Hz, 1H), 7.11–7.13 (m, 1H), 2.56 (s, 3H). ESI-MS: m/z (%) 305 $[M+Na]^+$ (79).

3.2.31. Data for 5o

Yield = 59%, White solid, m.p. 126–127 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (dd, J= 8.4, 0.8 Hz, 1H), 8.19 (d, J= 8.4 Hz, 1H), 8.09 (dd, J= 7.2, 1.2 Hz, 1H), 8.02 (d, J= 8.0 Hz, 1H), 7.76–7.80 (m, 1H), 7.63–7.71 (m, 2H), 7.52 (dd, J= 8.0, 7.2 Hz, 1H), 7.21–7.29 (m, 2H), 6.63 (dd, J= 7.6, 1.6 Hz, 1H), 2.55 (s, 3H). ESI-MS: m/z (%) 327 $[M+H]^+$ (100).

3.2.32. Data for 5p

Yield = 68%, White solid, m.p. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (dd, J= 4.4, 1.6 Hz, 1H), 8.41 (dd, J= 7.6, 1.6 Hz, 1H), 8.31 (dd, J= 8.4, 1.6 Hz, 1H), 8.17 (dd, J= 8.4, 1.6 Hz, 1H), 7.58–7.63 (m, 3H), 7.30–7.34 (m, 1H), 7.22–7.26 (m, 1H), 7.13 (dd, J= 8.0, 1.2 Hz, 1H), 2.61 (s, 3H). ESI-MS: m/z (%) 350 $[M+Na]^+$ (98).

3.2.33. Data for 6a

Yield = 60%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (t, J= 8.0 Hz, 1H), 6.82–6.88 (m, 3H), 3.81 (s, 3H), 3.31 (q, J= 7.2 Hz, 2H), 1.55 (t, J= 7.2 Hz, 3H). ESI-MS: m/z (%) 217 $[M+H]^+$ (100).

3.2.34. Data for 6b

Yield = 81%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84–7.86 (m, 2H), 7.65–7.68 (m, 1H), 7.51–7.55 (m, 2H), 7.14–7.19 (m, 1H), 6.77–6.80 (m, 1H), 6.52–6.56 (m, 2H), 3.71 (s, 3H). ESI-MS: m/z (%) 265 $[M+H]^+$ (100).

3.2.35. Data for 6c

Yield = 96%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.73 (m, 2H), 7.30–7.32 (m, 2H), 7.18 (t, J= 8.0 Hz, 1H), 6.76–6.79 (m, 1H), 6.52–6.56 (m, 2H), 3.72 (s, 3H), 2.44 (s, 3H). ESI-MS: m/z (%) 279 $[M+H]^+$ (100).

3.2.36. Data for 6d

Yield = 86%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74–7.78 (m, 2H), 7.18 (t, J= 8.0 Hz, 1H), 6.94–6.98 (m, 2H), 6.76–6.79 (m, 1H), 6.52–6.57 (m, 2H), 3.88 (s, 3H), 3.72 (s, 3H). ESI-MS: m/z (%) 295 $[M+H]^+$ (100).

3.2.37. Data for 6e

Yield = 89%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75–7.78 (m, 2H), 7.51–7.54 (m, 2H), 7.19 (t, J= 8.0 Hz, 1H), 6.77–6.80 (m, 1H), 6.57–6.60 (m, 1H), 6.52 (t, J= 2.4 Hz, 1H), 3.69 (s, 3H), 1.34 (s, 9 H). ESI-MS: m/z (%) 321 $[M+H]^+$ (100).

3.2.38. Data for 6f

Yield = 97%, White solid, m.p. 71–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (t, J= 8.0 Hz, 1H), 6.97 (s, 2H), 6.75–6.78 (m, 1H), 6.51–6.53 (m, 2H), 3.70 (s, 3H), 2.56 (s, 6H), 2.32 (s, 3H). ESI-MS: m/z (%) 307 $[M+H]^+$ (100).

3.2.39. Data for 6g

Yield = 60%, White solid, m.p. 55–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (s, 2H), 7.19 (t, J= 8.0 Hz, 1H), 6.76–6.79 (m, 1H), 6.57–6.60 (m, 1H), 6.50 (t, J= 2.4 Hz, 1H), 4.03–4.10 (m, 2H), 3.66 (s, 3H). 2.89–2.96 (m, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.19 (s, 6H), 1.18 (s, 6H). ESI-MS: m/z (%) 391 $[M+H]^+$ (100).

3.2.40. Data for 6h

Yield = 85%, White solid, m.p. 52–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84–7.89 (m, 2H), 7.16–7.23 (m, 3H), 6.78–6.81 (m, 1H), 6.52–6.56 (m, 2H), 3.73 (s, 3H). ESI-MS: m/z (%) 283 $[M+H]^+$ (100).

3.2.41. Data for 6i

Yield = 91%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65–7.72 (m, 4H), 7.20 (d, J= 8.0 Hz, 1H), 6.79–6.82 (m, 1H), 6.57 (t, J= 2.4 Hz, 1H), 6.51–6.54 (m, 1H), 3.74 (s, 3H). ESI-MS: m/z (%) 344 $[M+H]^+$ (100).

3.2.42. Data for 6j

Yield = 64%, Yellow solid. m.p. 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94–7.97 (m, 1H), 7.82–7.84 (m, 2H), 7.66–7.70 (m, 1H), 7.24 (t, J= 8.0 Hz, 1H), 6.81–6.84 (m, 1H), 6.75–6.78 (m, 2H), 3.75 (s, 3H). ESI-MS: m/z (%) 310 $[M+H]^+$ (100).

3.2.43. Data for 6k

Yield = 61%, Pale yellow solid, m.p. 70–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (q, J= 2.0 Hz, 1H), 8.51–8.54 (m, 1H), 8.16–8.19 (m, 1H), 7.80 (t, J= 8.0 Hz, 1H), 7.22 (t, J= 8.0 Hz, 1H), 6.81–6.84 (m, 1H), 6.59–6.61 (m, 1H), 6.53–6.56 (m, 1H), 3.75 (s, 3H). ESI-MS: m/z (%) 310 $[M+H]^+$ (100).

3.2.44. Data for 6l

Yield = 93%, White solid, m.p. 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36–8.39 (m, 2H), 8.03–8.07 (m, 2H), 7.22 (t, J= 8.0 Hz, 1H), 6.81–6.84 (m, 1H), 6.60 (t, J= 2.4 Hz, 1H), 6.50–6.53 (m, 1H), 3.75 (s, 3H). ESI-MS: m/z (%) 310 $[M+H]^+$ (100).

3.2.45. Data for 6m

Yield = 82%, Pale yellow solid, m.p. 66–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (d, J= 2.4 Hz, 1H), 7.97 (dd, J= 8.4, 2.0 Hz, 1H), 7.76 (d, J= 8.4 Hz, 1H), 7.25 (t, J= 8.0 Hz, 1H), 6.83–6.86 (m, 1H), 6.63 (t, J= 2.4 Hz, 1H), 6.54–6.57 (m, 1H), 3.77 (s, 3H). ESI-MS: m/z (%) 344 $[M+H]^+$ (100).

3.2.46. Data for 6n

Yield = 97%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (dd, J= 5.2, 1.2 Hz, 1H), 7.61 (dd, J= 4.0, 1.6 Hz, 1H), 7.21 (t, J= 8.0 Hz, 1H), 7.12 (dd, J= 5.2, 4.0 Hz, 1H), 6.80–6.83 (m, 1H), 6.58–6.63 (m, 2H), 3.73 (s, 3H). ESI-MS: m/z (%) 293 $[M+Na]^+$ (86).

3.2.47. Data for 6o

Yield = 82%, Pale yellow solid, m.p. 49–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, J= 8.8 Hz, 1H), 8.13 (t, J= 7.6 Hz, 2H), 7.99 (d, J= 8.4 Hz, 1H), 7.76–7.80 (m, 1H), 7.65–7.69 (m, 1H), 7.49 (t, J= 8.0 Hz, 1H), 7.07 (t, J= 8.0 Hz, 1H), 6.68–6.71 (m, 1H), 6.40–6.43 (m, 2H), 3.58 (s, 3H). ESI-MS: m/z (%) 315 $[M+H]^+$ (100).

3.2.48. Data for 6p

Yield = 96%, Pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.27 (dd, J= 4.4, 2.0 Hz, 1H), 8.41 (dd, J= 7.6, 1.2 Hz, 1H), 8.31 (dd, J= 8.4, 2.0 Hz, 1H). 8.14 (dd, J= 8.4, 1.6 Hz, 1H), 7.58–7.63 (m, 2H), 7.10 (t, J= 8.0 Hz, 1H), 6.69–6.72 (m, 1H), 6.58–6.63 (m, 2H), 3.64 (s, 3H). ESI-MS: m/z (%) 338 $[M+Na]^+$ (89).

3.3. Anti-oomycete activity of compounds 4a–p, 5a–p, and 6a–p against P. capsici

Forty-eight sulfonate derivatives of paeonol (**4a–p**, **5a–p**, and **6a–p**) were screened *in vitro* for their anti-oomycete activity against *P. capsici*. Potato dextrose agar (PDA) medium was prepared in the flasks and sterilized. Paeonol (**1**), 2-hydroxy acetophenone (**2**), 3-methoxyphenol (**3**), **4a–p**, **5a–p**, and **6a–p** and zoxamide (used as a positive control) were dissolved in acetone before mixing with PDA. The ranges of **1**, **2**, **3**, **4a–p**, **5a–p**, **6a–p** and zoxamide concentrations for the assays were defined in preliminary experiments, and the final concentrations in medium were 5, 25, 50, 75, 100 mg/L. Pure acetone mixed with PDA was served as the control, while zoxamide, a commercially available agricultural fungicide, was used as a positive control. The medium was then poured into sterilized Petri dishes. Mycelial plugs (5-mm diameter) were cut from the growing edge of a 7-day-old colony and then placed on the PDA plates, and incubated at 28 °C in the dark, respectively. Colony growth rate (mm/7 days) was determined on PDA medium. Three plates were evaluated for each compounds and an average colony diameter was calculated. The radial growths of the colonies were measured and the data were statistically analyzed. Mean colony diameter (minus the diameter of the plug) was measured for each treatment and expressed as a percentage of growth inhibition. The median effective concentration (EC_{50}) of **1**, **2**, **3**, **4a–p**, **5a–p**, **6a–p** and zoxamide for *P. capsici* isolate was calculated by linear regression of relative percentage of growth inhibition against log transformed samples concentration.

Disclosure statement

No potential conflict of interest was reported by the authors.

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