Potential antiviral sclerotiorin amine derivatives and their preliminary structure-activity relationship

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Abstract: Objective To evaluate antiviral activity of the natural compound, (+)-sclerotiorin and its semisynthetic derivatives. **Methods** (+)-Sclerotiorin (**1**) and its semisynthetic derivatives (**2**～**31**) were evaluated for their antiviral activities against RSV, EV71, HSV-1, H1N1, and Cox-B3 by the CPE inhibition assay. **Results** Compounds **3** and **11** showed potent and selective antiviral activity against EV71, and had very high selectivity index values (SI 37.8 and 38.0, respectively). **Conclusion** Compounds **3** and **11** are potent antiviral candidates.

Key words: antiviral activity; sclerotiorin amine derivative; structure-activity relationship
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Sclerotiorin 的胺类衍生物的潜在抗病毒活性及其初步构效关系研究*

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摘 要: 目的 为了评价天然产物(+)-sclerotiorin 及其半合成衍生物的抗病毒活性。**方法** 通过 CPE 法评价(+)-sclerotiorin (**1**)及其半合成衍生物(**2**～**31**)对 RSV、EV71、HSV-1、H1N1 和 Cox-B3 的抗病毒活性。**结果** 化合物 **3** 和 **11** 显示出对 EV71 的抗病毒活性, 并且具有非常高的选择性指数值(SI 值分别为 37.8 和 38.0)。**结论** 化合物 **3** 和 **11** 是潜在的抗病毒先导化合物。

关键词: 抗病毒活性; Sclerotiorin 的胺类衍生物; 构效关系

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Infectious diseases account for about 20% of global mortality, and viruses are responsible for about one-third of these deaths[1]. As a result, it is imperative to develop new and effective antiviral drugs against viruses infections. Marine natural products have been proven to be rich sources of structurally novel and biologically active compounds for drug discovery. Azaphilones are a family of fungal polyketide metabolites, which showed potential activities including cytotoxic[2], antimicrobial[3], antiviral, and anti-inflammatory activities[4].

1 Experimental Section

As our ongoing researching for bioactive natural compounds and their semisynthetic derivatives[5-8], a series of sclerotioramine derivatives of the natural compound, (+)-sclerotiorin (**1**), has been successfully semi-synthesized with high yields. Most of them showed potent antifouling activity against the larval settlement of the barnacle *Balanus amphitrite*[9]. (+)-Sclerotiorin (**1**) was isolated from the fungal strain *Penicillium sclerotiorum* (CHNSCLM-0013) which was isolated from a piece of gorgonian coral fresh tissue. A series of sclerotioramine derivatives (**2～31**) was semisynthesized by a one-step reaction with high yields(Fig. 1). Their structures were established by extensive spectroscopic methods and single-crystal X-ray diffraction analysis [9].

2 Results and Discussion

To evaluate the biological activity of these antifouling reagents, (+)-sclerotiorin (**1**) and its semisynthetic derivatives (**2～31**) were further evaluated for their antiviral activities and preliminary structure-activity relationship. As shown in Table 1, only compounds **3～8**, containing the aliphatic N-terminus, and **11** with the hydroxylamine group, showed potent antiviral activity against EV71 with IC_{50} values of 2.03～63.83 μmol/L. By contrast, the corresponding derivatives with the aromatic N-substituted group were completely inactive in this screen. This suggested that the aromatic group had a disadvantage effect on the antiviral activity. Intriguingly, the most potent compound **11**, showed promising activity against EV71 with an IC_{50} value of 2.03 μmol/L, which was approximately 206-fold more potent than that of ribavirin (IC_{50} = 418 μmol/L). It should be emphasized that toxicity profile was a major concern of the development of antiviral drugs. Fortunately, the active compounds **3** and **11** had very high selectivity index values (TC_{50}/IC_{50} 37.79 and 38.01, respectively) which were lower than that of the positive control, ribavirin (TC_{50}/IC_{50} = 24), suggesting that they were potent low-toxicity or non-toxic candidates.

Moreover, compounds **5**, **17**, **21**, **29**, and **31** showed pronounced antiviral activity against H1N1 with IC_{50} values of 3.84～10.33 μmol/L, which were stronger than that of the positive control ribavirin (IC_{50} = 156 μmol/L). Additionally, compounds **17**, **29**, and **31** had relatively higher selectivity index values (TC_{50}/IC_{50} 7.89, 7.46 and 4.12, respectively) than that of the positive control, ribavirin (TC_{50}/IC_{50}=4). Compounds **1**, **3**, **7～9**, and **23** showed strong antiviral activity against HSV-1 with IC_{50} values of 2.40～55.11 μmol/L. Intriguingly, the most potent compound **23**, showed promising activity against HSV-1 with an IC_{50} value of 2.40 μmol/L, which was approximately 130-fold more potent than that of ribavirin (IC_{50}=313 μmol/L).

Additionally, **1**, **5**, **6**, **10**, **11**, **18**, **24**, **27**, **28**, and **31** showed strong antiviral activity against RSV with IC_{50} values of 10.56～76.85 μmol/L. Especially, compounds **5**, **10**, and **31**, showed promising activity against RSV, which were approximately 5-fold more potent than that of ribavirin (IC_{50} = 78 μmol/L).

Unfortunately, all the active compounds had a relative lower selectivity index values. Compounds **7**, **11**, **18**, **25**, and **31** showed strong antiviral activity against Cox-B3 with IC_{50} values of 9.27～59.37 μmol/L. Unfortunately, all the active compounds had relative lower selectivity index values.

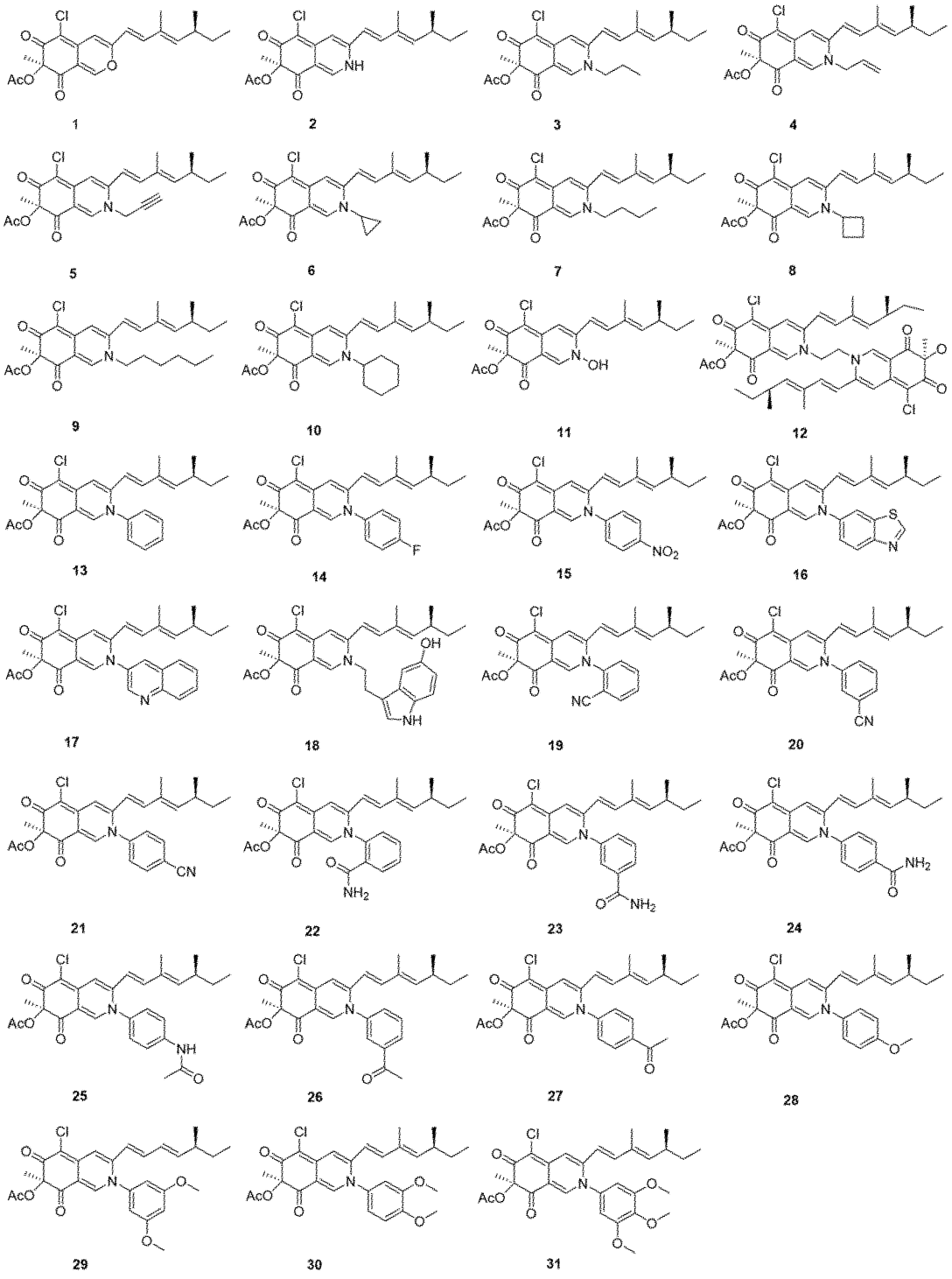

Fig. 1　Chemical structures of compounds **1～31**

Table 1 Antiviral Activities of compounds 1～31 against EV71, H1N1, RSV, HSV and Cox-B3

Compd*	EV71		H1N1		RSV		HSV-1		Cox-B3	
	IC_{50}/μmol·L^{-1}	SI**	IC_{50}/μmol·L^{-1}	SI	IC_{50}/μmol·L^{-1}	SI	IC_{50}/μmol·L^{-1}	SI	IC_{50}/μmol·L^{-1}	SI
1	—	—	—	—	76.85	3.0	28.16	8.3	—	—
3	7.32	37.8	—	—	—	—	23.85	12.2	—	—
4	62.20	4.3	—	—	—	—	—	—	—	—
5	17.34	2.1	4.78	3.8	16.17	2.6	—	—	—	—
6	63.83	4.4	—	—	71.42	4.1	—	—	—	—
7	10.34	24.2	—	—	—	—	34.80	7.0	59.37	4.1
8	53.52	2.5	—	—	—	—	55.11	5.1	—	—
9	—	—	—	—	—	—	14.16	2.3	—	—
10	—	—	—	—	13.86	2.8	—	—	—	—
11	2.03	38.0	—	—	32.94	2.5	—	—	27.61	3.0
17	—	—	3.84	7.9	—	—	—	—	—	—
18	—	—	—	—	31.87	3.3	—	—	24.15	4.3
21	—	—	5.13	3.7	—	—	—	—	—	—
23	—	—	—	—	—	—	2.40	5.3	—	—
24	—	—	—	—	26.43	2.2	—	—	—	—
25	—	—	—	—	—	—	—	—	9.27	2.3
27	—	—	—	—	18.81	2.4	—	—	—	—
28	—	—	—	—	24.15	2.0	—	—	—	—
29	—	—	7.98	7.5	—	—	—	—	—	—
31	—	—	10.33	4.1	10.56	6.1	—	—	13.44	4.8
Ribavirin***	418	24	156	4	78	128	313	32	39	256

Note: * Compounds **2**, **12～16**, **19**, **20**, **22**, **26** and **30** were inactive at their maximal nontoxic concentration against all the virus strains mentioned above. The Sign "-" indicates no activity; ** Selectivity index (SI) value equaled TC_{50}/IC_{50}; *** Positive control.

3 Conclusion

(+)-Sclerotiorin (**1**) and its semisynthetic derivatives (**2～31**) were evaluated for their antiviral activities. Fortunately, **3** and **11** showed potent and selective antiviral activity against EV71, and had very high selectivity index values, suggesting that they were potent antiviral candidates.

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