海洋沉积物来源真菌嗜松青霉 SD-272 代谢产物研究

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摘要: 对来源于珠江口沉积物的一株海洋真菌嗜松青霉(*Penicillium pinophilum*)SD-272 的次生代谢产物, 进行了化学成分分离及其生物活性研究。采用常规硅胶柱层析、凝胶 Sephadex LH-20 柱层析、制备薄层层析等分离手段, 通过紫外、核磁共振技术、质谱技术等现代波谱学技术, 从其发酵液提取物中共分离并鉴定了 13 个化合物, 分别为: 4′-demethylvermistatin **(1)**, vermistatin **(2)**, penisimplicissin**(3)**, deoxyfunicone **(4)**, 5, 6-epoxy-3-deoxyfunicone **(5)**, 5′-methoxy-6-methyl-biphenyl-3, 4, 3′-triol **(6)**, altenusin **(7)**, 1-deoxyrubralactone**(8)**, kojic acid **(9)**, 7-hydroxy-2-(2-hydroxypropyl)-5-methylchromone **(10)**, dankasterone **(11)**, 4-hydroxy-2-methoxyacetanilide **(12)**, N-(2-hydroxypropanoyl)-2-aminobenzoic acid amide **(13)**。这些化合物均为首次从嗜松青霉中分离得到, 其中化合物 **11** 显示较好的卤虫致死活性, LD_{50} 值为 39.2 μmol/L。

关键词: 沉积物; 嗜松青霉(*Penicillium pinophilum*); 次生代谢产物; 卤虫致死活性

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海洋沉积物是在漫长的地质年代里, 由陆地径流、大气输入及人类活动带入海洋并沉降在海底的物质总称。海洋沉积物既不同于淡水沉积物和土壤等陆地环境, 又与海水环境相对独立, 长期处于高盐、低温和高压等特殊生态环境, 成为地球上最复杂的微生物栖息地[1-2]。海洋沉积物来源真菌作为海洋微生物重要组成部分, 蕴藏着许多具有潜在应用前景的活性物质, 是开发新抗菌、抗肿瘤药物等新药的重要资源[3]。近年来, 科学研究已在海洋沉积物来源真菌次生代谢产物中发现了大量结构新颖、活性多样的化合物[4-7]。在本课题组对海底沉积物来源真菌次生代谢产物研究的过程中[8-9], 我们对一株珠江口沉积物来源的真菌嗜松青霉(*Penicillium pinophilum*)进行了规模发酵, 从其发酵提取物中分离鉴定了 13 个化合物(图 1), 这些化合物均为首次从嗜松青霉中分离得到, 其中化合物 **11** 显示较好的卤虫致死活性, LD_{50} 值为 39.2 mol/L。

1　材料与方法

1.1　仪器与试剂

BrukerAvance 500 MHz 核磁共振仪; Dionex 分析型高效液相色谱仪; Lobar LiChroprer RP-18 硅胶(40~63 μm, Merck); 薄层色谱硅胶 GF_{254} 和柱色谱硅胶(200~300 目)为青岛海洋化工分厂产品; 显色剂为茴香醛硫酸溶液和碘; 所有有机溶剂均为重蒸工业级溶剂。

1.2　菌株发酵

(1) 菌株: 菌株 SD-272 是分离自珠江口沉积物中的真菌。

(2) 菌株发酵: 菌种以琼脂-麦芽膏培养基 4℃保存。发酵培养基成分为: 蔗糖 2%、蛋白胨 0.5%、酵母膏 0.3%、味精 1%、甘露醇 2%、土豆汁 20%, 培养基 pH 为 6.5。盛有发酵培养基的 1 L 三角瓶(60 瓶)在 116℃下高压灭菌 20 min, 待三角瓶冷却后接种, 常温静置培养 35 d。

1.3　提取分离

菌株规模发酵结束后, 发酵液采用乙酸乙酯萃取, 减压蒸干得到发酵液提取物; 菌丝体经细胞破碎仪破碎后, 采用 80%丙酮水溶液超声萃取 3 次, 减压浓缩去除丙酮后的剩余水相再用乙酸乙酯萃取 3 次, 减压蒸干有机相得到菌丝体粗提物, 经 HPLC 和

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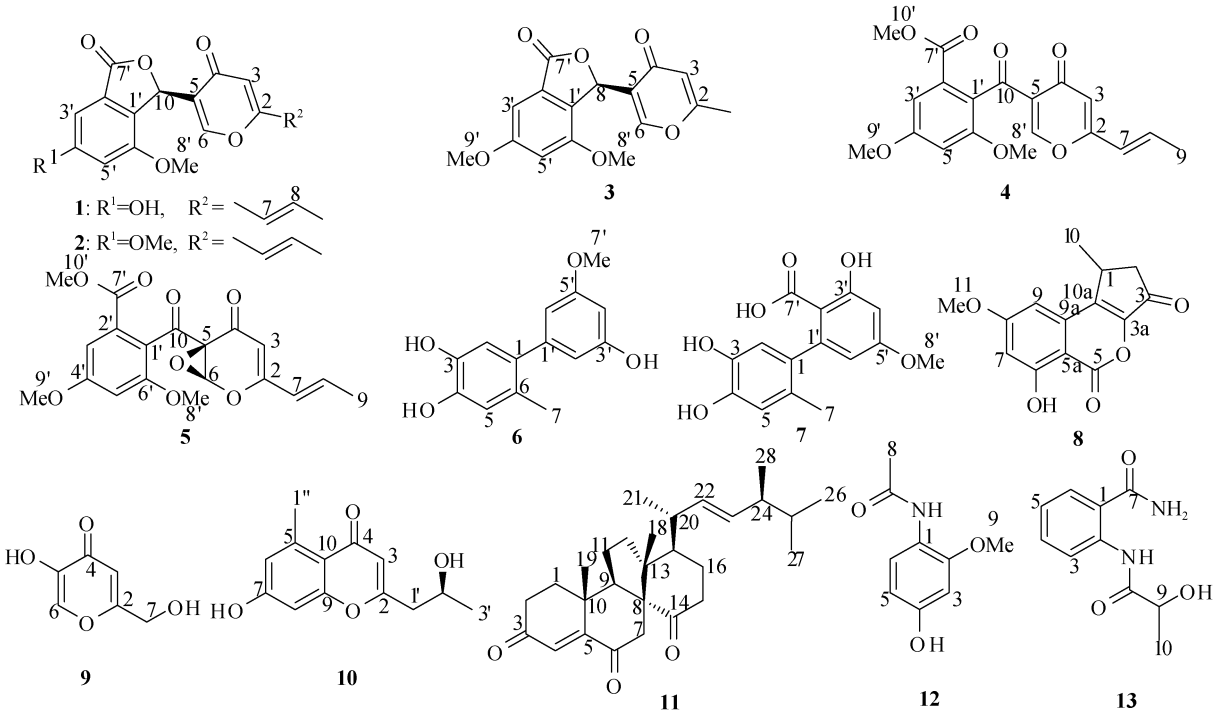

图 1　化合物 **1**–**13** 的结构

Fig.1　Structures of compounds **1**–**13**

TLC 检测发现与发酵液提取物基本一致，合并后得到总粗提物 50.2 g。

将上述粗提物进行硅胶 VLC 柱层析，根据极性从小到大(石油醚/乙酸乙酯到氯仿/甲醇)进行梯度洗脱，经 TLC 和 HPLC 检测，合并得到 9 个组分(Fr.1–9)。其中，Fr.2 经正相硅胶柱层析、凝胶 Sephadex LH-20(甲醇)柱层析和制备薄层层析分离得到化合物 **1**(6.3 mg)、**2**(25.1 mg)、**3**(5.8 mg)、**4**(10.1 mg)和化合物 **5**(6.7 mg)；Fr.3 经反相硅胶柱层析、凝胶 Sephadex LH-20(甲醇)柱层析和制备薄层层析分离得到化合物 **6**(9.4 mg)、**7**(14.8 mg)、**8**(5.2 mg)和化合物 **11**(8.1 mg)；Fr.4 经正相硅胶柱层析、凝胶 Sephadex LH-20(丙酮)柱层析、制备薄层层析和制备高效液相分离得到化合物 **9**(6.3 mg)、**10**(3.1 mg)、**12**(6.3 mg)和化合物 **13**(5.5 mg)。

1.4　卤虫致死活性筛选

(1) 材料：卤虫卵取自中国科学院烟台海岸带研究所。

(2) 卤虫致死活性筛选[10]：阳性对照药为秋水仙碱，阴性对照为 DMSO，空白对照为洁净海水。取适量虫卵放入洁净海水中，在室温下通气培养 48 min 后，吸取 195 μL 卤虫生长液依次加入 96 孔板中，再依次加入 5 μL 浓度为 4 mg/mL 的样品溶液，使样品终浓度达到 0.1 mg/mL，对每个样品分别做 3 组平行实验。24 h 后在解剖镜下记录每孔卤虫死亡数目和卤虫总数，计算致死率。

致死率 = 卤虫死亡数目/卤虫总数 × 100%

2　化合物结构鉴定

化合物**1**：白色无定形粉末，^{1}H-NMR (DMSO-d_6)δ_H: 6.22 (1H, s, H-3), 8.14 (1H, s, H-6), 6.26 (1H, dd, J = 15.8, 1.6 Hz, H-7), 6.63 (1H, m, H-8), 1.88 (3H, dd, J = 6.9, 1.5 Hz, H-9), 6.22 (1H, s, H-10), 6.74 (1H, d, J = 1.6 Hz, H-3'), 6.73 (1H, d, J = 1.6 Hz, H-5'), 3.73 (3H, s, H-8'); ^{13}C NMR (DMSO-d_6) δ_C: 161.7 (C-2, C), 112.3 (C-3, CH), 176.3 (C-4, C), 122.4 (C-5, C), 155.5 (C-6, CH), 122.9 (C-7, CH), 135.8 (C-8, CH), 18.1 (C-9, CH_3), 74.2 (C-10, CH), 124.7 (C-1', C), 128.6 (C-2', C), 101.8 (C-3', CH), 161.2 (C-4', C), 105.0 (C-5', CH), 154.7 (C-6', C), 169.8 (C-7', C), 55.7 (C-8', CH_3)。其波谱数据与4'-demethylvermistatin 的文献报道[11]一致，该化合物为首次从 *P.pinophilum* 中分离得到。当样品浓度为0.1 mg/mL 时，对卤虫有一定的致死活性，致死率为33%。

化合物**2**：白色无定形粉末，^{1}H-NMR ($CDCl_3$)δ_H: 6.15 (1H, s, H-3), 7.42 (1H, s, H-6), 6.05 (1H, d, J = 15.0 Hz, H-7), 6.60 (1H, m, H-8), 1.91 (3H, d, J = 6.8 Hz, H-9), 6.44 (1H, s, H-10), 6.97 (1H, s, H-3'), 6.67

(1H, s, H-5'), 3.78 (3H, s, H-8'), 3.86 (3H, s, H-9'); ^{13}C NMR ($CDCl_3$) δ_C: 163.1 (C-2, C), 112.8 (C-3, CH), 177.2 (C-4, C), 123.4 (C-5, C), 153.8 (C-6, CH), 123.1 (C-7, CH), 135.9 (C-8, CH), 18.5 (C-9, CH_3), 73.5 (C-10, CH), 127.7 (C-1', C), 129.3 (C-2', C), 99.0 (C-3', CH), 162.1 (C-4', C), 105.1 (C-5', CH), 154.9 (C-6', C), 169.9 (C-7', C), 55.7 (C-8', CH_3), 55.9 (C-9', CH_3)。其波谱数据与 vermistatin 的文献报道[12]一致，该化合物为首次从 *P.pinophilum* 中分离得到。当样品浓度为0.1 mg/mL 时，对卤虫有一定的致死活性，致死率为41%。

化合物**3**：白色无定形粉末，^{1}H-NMR (DMSO-d_6)δ_H: 6.17 (1H, s, H-3), 8.22 (1H, s, H-6), 1.75 (3H, s, H-7), 6.27 (1H, s, H-8), 6.92 (1H, d, J = 1.7 Hz, H-3'), 6.87 (1H, d, J = 1.7 Hz, H-5'), 3.86 (3H, s, H-8'), 3.76 (3H, s, H-9'); ^{13}C NMR (DMSO-d_6) δ_C: 166.5 (C-2, C), 114.4 (C-3, CH), 176.0 (C-4, C), 121.9 (C-5, C), 156.2 (C-6, CH), 18.9 (C-7, CH_3), 74.3 (C-8, CH), 127.5 (C-1', C), 128.8 (C-2', C), 99.0 (C-3', CH), 162.3 (C-4', C), 104.9 (C-5', CH), 154.7 (C-6', C), 169.6 (C-7', C), 55.9 (C-8', CH_3), 56.0 (C-9', CH_3)。其波谱数据与 penisimplicissin 的文献报道[12]一致，该化合物为首次从 *P.pinophilum* 中分离得到。当样品浓度为0.1 mg/mL 时，对卤虫有一定的致死活性，致死率为20%。

化合物**4**：白色无定形粉末，^{1}H-NMR ($CDCl_3$)δ_H: 6.09 (1H, s, H-3), 8.51 (1H, s, H-6), 6.07 (1H, d, J = 14.8Hz, H-7), 6.68 (1H, m, H-8), 1.94 (3H, d, J = 5.5 Hz, H-9), 7.08 (1H, s, H-3'), 6.64 (1H, s, H-5'), 3.86 (3H, s, H-8'), 3.78 (3H, s, H-9'), 3.78 (3H, s, H-10'); ^{13}C NMR ($CDCl_3$) δ_C: 161.4 (C-2, C), 115.0 (C-3, CH), 175.9 (C-4, C), 126.0 (C-5, C), 160.9 (C-6, CH), 122.7 (C-7, CH), 136.3 (C-8, CH), 18.6 (C-9, CH_3), 191.7 (C-10, C), 126.1 (C-1', C), 129.9 (C-2', C), 105.3 (C-3', CH), 160.7 (C-4', C), 103.0 (C-5', CH), 157.4 (C-6', C), 166.4 (C-7', C), 55.6 (C-8', CH_3), 56.1 (C-9', CH_3), 52.4 (C-10', CH_3)。其波谱数据与 deoxyfunicone 的文献报道[13]一致，该化合物为首次从 *P.pinophilum* 中分离得到。当样品浓度为0.1 mg/mL 时，对卤虫有一定的致死活性，致死率为35%。

化合物**5**：无色晶体，^{1}H-NMR ($CDCl_3$)δ_H: 5.48 (1H, s, H-3), 5.60 (1H, s, H-6), 5.93 (1H, d, J = 15.0 Hz, H-7), 6.67 (1H, m, H-8), 1.91 (3H, d, J = 6.9 Hz, H-9), 6.87 (1H, s, H-3'), 6.54 (1H, s, H-5'), 3.86 (3H, s, H-8'), 3.76 (3H, s, H-9'), 3.86 (3H, s, H-10'); ^{13}C NMR ($CDCl_3$) δ_C: 161.4 (C-2, C), 104.1 (C-3, CH), 185.3 (C-4, C), 62.6 (C-5, C), 81.6 (C-6, CH), 124.1 (C-7, CH), 137.7 (C-8, CH), 18.6 (C-9, CH_3), 190.8 (C-10, C), 119.8 (C-1', C), 134.2 (C-2', C), 101.5 (C-3', CH), 163.0 (C-4', C), 106.2 (C-5', CH), 159.1 (C-6', C), 167.6 (C-7', C), 55.8 (C-8', CH_3), 56.1 (C-9', CH_3), 52.9 (C-10', CH_3)。其波谱数据与5, 6-epoxy- 3-deoxyfunicone 的文献报道[14]一致，该化合物为首次从 *P.pinophilum* 中分离得到。当样品浓度为0.1 mg/mL 时，对卤虫有一定的致死活性，致死率为39%。

化合物**6**：黄色油状物，^{1}H NMR (DMSO-d_6)δ_H: 6.55 (1H, s, H-2), 6.60 (1H, s, H-5), 2.05 (3H, s, H-7), 6.22 (1H, d, J = 2.0 Hz, H-2'), 6.25 (1H, d, J = 0.5 Hz, H-4'), 6.19 (1H, d, J = 0.8 Hz, H-6'), 3.69 (3H, s, H-7'); ^{13}C NMR (DMSO-d_6) δ_C: 132.2 (C-1, C), 116.7 (C-2, CH), 144.4 (C-3, C), 143.6 (C-4, C), 117.5 (C-5, CH), 124.7 (C-6, C), 19.3 (C-7, CH_3), 142.9 (C-1', C), 108.8 (C-2', CH), 159.9 (C-3', C), 99.2 (C-4', CH), 158.0 (C-5', C), 105.7 (C-6', CH), 54.8 (C-7', CH_3)。其波谱数据与5'-methoxy-6-methyl-biphenyl-3, 4, 3'-triol 的文献报道[15]一致，该化合物为首次从 *P.pinophilum* 中分离得到。

化合物**7**：白色无定形粉末，^{1}H NMR (DMSO-d_6)δ_H: 6.42 (1H, s, H-2), 6.53 (1H, s, H-5), 1.85 (3H, s, H-7), 6.43 (1H, d, J = 2.4 Hz, H-4'), 6.10 (1H, d, J = 2.4 Hz, H-6'), 3.76 (3H, s, H-8'); ^{13}C NMR (DMSO-d_6) δ_C: 132.4 (C-1, C), 116.6 (C-2, CH), 145.0 (C-3, C), 143.9 (C-4, C), 115.9 (C-5, CH), 124.9 (C-6, C), 18.8 (C-7, CH_3), 142.1 (C-1', C), 108.7 (C-2', C), 161.5 (C-3', C), 99.6 (C-4', CH), 162.0 (C-5', C), 108.9 (C-6', CH), 171.5 (C-7', C), 55.3 (C-8', CH_3)。其波谱数据与 altenusin 的文献报道[16]一致，该化合物为首次从 *P.pinophilum* 中分离得到。

化合物**8**：黄色无定形粉末，^{1}H-NMR (DMSO-d_6) δ_H: 3.42 (1H, m, H-1), 2.92 (1H, d, J = 19.0, 6.4 Hz, H_a-2), 2.21 (1H, d, J = 19 Hz, H_b-2), 6.80 (1H, s, H-7), 6.74 (1H, s, H-9), 1.34 (3H, d, J = 6.9 Hz, H-10), 3.92 (3H, s, H-11); ^{13}C NMR (DMSO-d_6) δ_C: 27.7 (C-1, CH), 42.4 (C-2, CH_2), 195.6 (C-3, C), 147.5 (C-3a, C), 165.2 (C-5, C), 100.5 (C-5a, C), 163.8 (C-6, C), 103.9 (C-7, CH), 166.2 (C-8, C), 101.9 (C-9, CH), 134.7 (C-9a, C), 144.6 (C-10a, C), 20.5 (C-10, CH_3), 56.1 (C-11, CH_3)。其波谱数据与1-deoxyrubralactone 的文献报道[17]一致，该化合物为首次从 *P.pinophilum* 中分离得到。

化合物**9**：白色无定形粉末，^{1}H-NMR (DMSO-d_6)δ_H: 6.33 (1H, s, H-3), 8.02 (1H, s, H-6), 4.29 (2H, s, H-7), 5.65 (1H, br s, 7-OH), 9.04 (1H, br s, 5-OH); ^{13}C NMR (DMSO-d_6) δ_C: 168.0 (C-2, C), 109.8 (C-3, CH), 173.9 (C-4, C), 145.7 (C-5, C), 139.2 (C-6, CH), 59.4 (C-7, CH_2)。其波谱数据与 kojic acid 的文献报道[18]一致，该化合物为首次从 *P.pinophilum* 中分离得到。

化合物**10**：黄色油状物，^{1}H-NMR (DMSO-d_6)δ_H: 5.97 (1H, s, H-3), 6.61 (1H, s, H-6), 6.64 (1H, s, H-8), 2.58 (2H, m, H-1'), 4.17 (1H, m, H-2'), 1.13 (3H, d, J =

6.3 Hz, H-3'), 2.65 (3H, s, H-1"); ^{13}C NMR (DMSO-d_6) δ_C: 164.4 (C-2, C), 111.4 (C-3, CH), 178.1 (C-4, C), 141.2 (C-5, C), 116.3 (C-6, CH), 160.9 (C-7, C), 100.3 (C-8, CH), 158.8 (C-9, C), 114.2 (C-10, C), 42.6 (C-1', CH_2), 63.9 (C-2', CH), 23.3 (C-3', CH_3), 21.9 (C-1", CH_3)。其波谱数据与 7-hydroxy-2-(2-hydroxypropyl)-5-methylchromone 的文献报道[19]一致，该化合物为首次从 *P.pinophilum* 中分离得到。

化合物**11**：白色无定形粉末，^{1}H NMR (DMSO-d_6)δ_H: 6.36 (1H, s, H-4), 2.01~2.62 (6H, m, H-1, 2, 7), 2.81 (1H, m, H-9), 2.48 (2H, m, H-15), 1.69~2.02 (6H, m, H-11, 12, 16), 1.48 (1H, m, H-17), 0.98 (3H, s, H-18), 1.26 (3H, s, H-19), 2.42 (1H, m, H-20), 1.09 (3H, d, J = 6.8 Hz, H-21), 5.22 (1H, d, J = 15.3 Hz, H-22), 5.18 (1H, dd, J = 15.3, 7.7 Hz, H-23), 1.88 (1H, m, H-24), 1.47 (1H, d, J = 6.8, H-25), 0.82 (3H, d, J = 7.2 Hz, H-26), 0.83 (3H, d, J = 7.2 Hz, H-27), 0.92 (3H, d, J = 7.2 Hz, H-28); ^{13}C NMR (DMSO-d_6) δ_C: 38.9 (C-1, CH_2), 34.2 (C-2, CH_2), 198.8 (C-3, C), 124.5 (C-4, CH), 157.3 (C-5, C), 199.9 (C-6, C), 40.8 (C-7, CH_2), 62.2 (C-8, C), 49.4 (C-9, CH), 36.0 (C-10, C), 25.1 (C-11, CH_2), 38.3 (C-12, CH_2), 53.9 (C-13, C), 215.1 (C-14, C), 37.9 (C-15, CH_2), 23.2 (C-16, CH_2), 49.4 (C-17, CH), 17.1 (C-18, CH_3), 24.0 (C-19, CH_3), 37.3 (C-20, CH), 23.6 (C-21, CH_3), 132.8 (C-22, CH), 133.6 (C-23, CH), 43.2 (C-24, CH), 33.1 (C-25, CH), 20.0 (C-26, CH_3), 19.7 (C-27, CH_3), 17.6 (C-28, CH_3)。其波谱数据与 dankasterone 的文献报道[20]一致，该化合物为首次从 *P.pinophilum* 中分离得到，并对卤虫有较好的致死活性，LD_{50}值为39.2 μmol/L，而阳性对照 LD_{50}值为92.1μmol/L。

化合物**12**：白色无定形粉末，^{1}H-NMR (DMSO-d_6)δ_H: 6.42 (1H, d, J = 2.4 Hz, H-3), 6.27 (1H, dd, J = 8.5, 2.4 Hz, H-5), 7.44 (1H, d, J = 8.5 Hz, H-6), 1.99 (3H, s, H-8), 3.73 (3H, s, H-9), 8.86 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 118.7(C-1, C), 151.6 (C-2, C), 99.2 (C-3, CH), 154.9 (C-4, C), 106.0 (C-5, CH), 124.4 (C-6, CH), 167.8 (C-7, C), 23.4 (C-8, CH_3), 55.3 (C-9, CH_3)。其波谱数据与4-hydroxy-2-methoxyacetanilide的文献报道[21]一致，该化合物为首次从 *P.pinophilum* 中分离得到。

化合物**13**：无色油状物，^{1}H-NMR (DMSO-d_6)δ_H: 8.57 (1H, dd, J = 8.3, 0.8 Hz, H-3), 7.47 (1H, td, J = 7.7, 1.0 Hz, H-4), 7.11 (1H, td, J = 7.7, 1.0 Hz, H-5), 7.74 (1H, dd, J = 7.7, 1.0 Hz, H-6), 4.10 (1H, q, J = 6.8Hz, H-9), 1.30 (3H, d, J = 6.8 Hz, H-10), 12.0 (1H, br s, NH), 6.09 (1H, br s, 9-OH), 8.56 (1H, br s, $CONH_a$), 7.56 (1H, br s, $CONH_b$);^{13}C NMR (DMSO-d_6) δ_C: 120.9 (C-1, C), 138.7 (C-2, C), 119.8 (C-3, CH), 131.7 (C-4, CH), 122.3 (C-5, CH), 128.4 (C-6, CH), 170.2 (C-7, C), 174.0 (C-8, C), 67.8 (C-9, CH), 20.8 (C-10, CH_3)。其波谱数据与 N-(2-hydroxypropanoyl)-2-aminobenzoic acid amide 的文献报道[22]一致，该化合物为首次从 *P.pinophilum* 中分离得到。

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Study of metabolites from *Penicillium pinophilum* SD-272, a marine sediment-derived fungus

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Abstract: In this paper, thirteen compounds were isolated from the zymotic fluid extract of the fungal strain *Penicillium pinophilum* SD-272by a combination of silica gel, Sephadex LH-20, and Lobar LiChroprep RP-18 column chromatography as well as the preparative thin layer chromatography. SD-272was isolated from sediment sample collected from the estuary of the Pearl River in South China Sea. The structures of these compounds were elucidated mainly based on the analysis of the UV, MS, 1D and 2D NMR as 4′-demethylvermistatin (**1**), vermistatin (**2**), penisimplicissin(**3**), deoxyfunicone (**4**), 5, 6-epoxy-3-deoxyfunicone (**5**), 5′-methoxy-6- methyl-biphenyl-3, 4, 3′-triol (**6**), altenusin (**7**), 1-deoxyrubralactone(**8**), kojic acid (**9**), 7-hydroxy-2-(2-hydroxypropyl)-5-methylchromone (**10**), dankasterone (**11**), 4-hydroxy-2-methoxyacetanilide (**12**), and N-(2-hydroxypropanoyl)- 2-aminobenzoic acid amide (**13**). All the compounds were firstly reported to be isolated from *P.pinophilum*. Compound **11** displayed potent brine shrimp lethality with a LD_{50} of 39.2 μmol/L.

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