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北部湾海洋真菌 *Aspergillus fumigatus* DL-p0m-g2 的化学成分及药理活性研究

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摘要: 为获得具有生物活性的化合物, 对一株分离于北部湾钉螺菌株 *Aspergillus fumigatus* DL-p0m-g2 的化学成分及药理活性进行研究。综合应用反相 ODS (octadecylsilyl) 柱色谱、半制备液相等多种色谱学方法进行分离纯化, 根据化合物理化性质、质谱和核磁共振波谱学数据进行结构鉴定, 并对分离得到的化合物进行细胞毒活性、抑菌活性和胆固醇转运蛋白 NPC1L1 (NPC1-like intracellular cholesterol transporter 1)蛋白结合等生物活性评价。实验共分离得到 21 个生物碱类化合物和 1 个甾体, 分别鉴定为 6-methoxyspirotryprostatin B (**1**)、spirotryprostatin A (**2**)、fumitremorgin C (**3**)、cyclotryprostatin A (**4**)、fumitremorgin B (**5**)、pseurotin A (**6**)、azaspirofuran A (**7**)、azaspirofuran B (**8**)、cephalimysin C (**9**)、cephalimysin B (**10**)、fumiquinazoline C (**11**)、fumiquinazoline B (**12**)、fumiquinazoline A (**13**)、fumiquinazoline D (**14**)、fumiquinazoline F (**15**)、tryprostatin B (**16**)、verruculogen (**17**)、chaetominine (**18**)、bisdethiobis(methylthio)glitoxin (**19**)、helvolic acid (**20**)、7-deacetylpyripyropene A (**21**)、terezine D (**22**)。其中化合物 **6** 对人肝癌细胞(HepG2)、人肺癌细胞(A549)、人直肠癌细胞(HCT116)有一定的细胞毒活性; 化合物 **1**、**3** 和 **20** 对金黄色葡萄球菌表现出抑菌活性; 化合物 **14** 与 NPC1L1 蛋白具有较好的结合, 显示其在降脂药物开发中的研究潜力。

关键词: *Aspergillus fumigatus*; 化学成分; 细胞毒活性; 抑菌活性; NPC1L1 蛋白结合

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Study on the chemical constituents and pharmacological activity of the marine-derived fungus *Aspergillus fumigatus* DL-p0m-g2 in the Beibu Gulf

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Abstract: The chemical constituents and their bioactivities of *Aspergillus fumigatus* DL-p0m-g2 from the Beibu Gulf were studied in order to obtain bioactive compounds. The compounds were isolated and purified by reversed-phase ODS column chromatography, semi-preparative liquid chromatography and other chromatographic methods. Their structures were identified by physicochemical

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properties, mass spectrometry and nuclear magnetic resonance spectroscopy. The cytotoxic, antibacterial and cholesterol transporter NPC1L1 protein binding activities of the isolated compounds were evaluated. As a result, a total of 21 alkaloids and one steroid were isolated and identified as 6-methoxyspirotryprostatin B (**1**), spirotryprostatin A (**2**), fumitremorgin C (**3**), cyclotryprostatin A (**4**), fumitremorgin B (**5**), pseurotin A (**6**), azaspirofuran A (**7**), azaspirofuran B (**8**), cephalimysin C (**9**), cephalimysin B (**10**), fumiquinazoline C (**11**), fumiquinazoline B (**12**), fumiquinazoline A (**13**), fumiquinazoline D (**14**), fumiquinazoline F (**15**), tryprostatin B (**16**), verruculogen (**17**), chaetominine (**18**), bisdethiobis(methylthio)glitoxin (**19**), helvolic acid (**20**), 7-deacetylpyripyropene A (**21**), terezine D (**22**). Compound **6** showed moderate cytotoxic activity against human hepatoma cells (HepG2), human lung cancer cells (A549) and human rectal cancer cells (HCT116). Compounds **1**, **3** and **20** showed antibacterial activity against *Staphylococcus aureus*. Compound **14** showed a good binding with NPC1L1 protein, indicating its potential in the development of lipid-lowering drugs.

Key words: *Aspergillus fumigatus*; chemical constituents; cytotoxic activity; anti-bacteria activity; NPC1L1 protein binding

海洋是生命起源的地方, 占据地球表面积的 70%, 有 80%的生物栖息于此, 拥有着丰富多彩的生物资源。海洋微生物资源丰富, 优势独特, 高压、高盐、低光照的特殊环境使得生存于此的微生物能够产生更多有别于陆地微生物的结构新颖、活性独特的天然产物, 是新的活性次生代谢产物的主要来源(Liu et al, 2018; Wang et al, 2020)。尤其是海洋真菌, 因其代谢产物高于海洋放线菌且种类更为丰富, 也成为国内外近十几年来研究的焦点(罗明和 等, 2015)。近年来, 从海洋真菌中发现了很多活性次级代谢产物, 包括生物碱类、萜类、大环内酯类以及聚酮类等多种天然活性物质, 并且发现这些物质具有抗肿瘤、抗癌、抗病毒、抗菌等多种活性(Newman et al, 2020)。自 Cephalosporin C 从海洋真菌中分离出来后, 越来越多的活性代谢产物被分离鉴定(张金新 等, 2023)。我国南海海域广阔, 生物种类资源繁多, 生态系统类型多样。全世界发现的超过 3.5 万种海洋天然产物中有 20%来自中国南海(王庆琳 等, 2020)。Ye 等(2018)从南海软珊瑚 *Sarcophyton infundibuliforme* 中分离得到两个新的骨架为三环[6.3.1.$0^{1,5}$]十二烷含氮二萜化合物 sarinfacetamides A 和 B, sarinfacetamides A 对 ConA 诱导的 T 淋巴细胞增殖具有明显的促进作用。Zhang 等(2021)从海绵岩藻分离的 *Nocardiopsis dassonvillei* SCSIO 40065 中得到两个多环硫代生物碱 dassonmycins A 和 B, 两种化合物均表现出中等的抗菌和细胞毒性活性。Yao 等(2021)从南海来源的曲霉属真菌中分离得到三个新的环戊烯酮衍生物, 和五个新的环己烯酮衍生物。Cai 等(2019)从红树林内生真菌 *Aspergillus sp.* SK-28 中分离得到具有 6/5/4/5/6 五环骨架的吲哚二酮哌嗪生物碱二聚体(+)-Asperginulin A 对藤壶 *Balanus reticulatus* 具有防污活性。Jiao 等(2020)从中国南海永兴岛分离的 *Aspergillus flavipes* 164013 菌株中得到三种氯化 PKS-NRPS 杂合代谢物 flavipesides A-C 均具有有效的胰脂肪酶抑制活性, IC_{50} 值 (half maximal inhibitory concentration) 为 0.07~0.23μmol·L^{-1},。

北部湾位于我国南海西北部海域, 拥有丰富的海洋生物资源。至 2020 年, 从北部湾发现 197 种海洋真菌(徐新亚 等, 2020); 对北部湾的 477 种新报道的海洋天然产物进行来源归属发现微生物来源占 52%, 其中从真菌中分离的海洋天然产物占微生物的 91%(Wang et al, 2023)。从北部湾海洋真菌中分离得到的生物碱、萜类等化合物都表现出一定的抗肿瘤、抑菌等生物活性, 具有被应用开发的强大潜在价值(徐新亚 等, 2020)。Wang 等(2021)从北部湾分离得到的珊瑚共生真菌 *Cladosporium halotolerans* GXIMD 02502 中发现 Coniochaetone K 对在 10μmol·L^{-1} 的浓度下显示出显著的细胞毒性活性。Lin 等(2023)从 *Trichoderma* sp. GXIMD 01001 中分离得到的 7 个新的 18-residue peptaibols 均显示出显著的细胞毒性, 对四种人类癌细胞系的最低 IC_{50} 值为 0.46~4.7μmol·L^{-1}。高谕康等(2020)从一株海洋曲霉 *Aspergillus fumigatus* MDCW-15 的次级代谢产物中分离出一种新的烟曲霉酸对白色念珠菌有抑制活性, 最小抑菌浓度(minimal inhibition concentration, MIC)为 32.0μg·mL^{-1}。本次在对我国北部湾来源真菌 *Aspergillus fumigatus* DL-p0m-g2 的活性次生代谢产物的研究中, 获得了一系列生物碱类次生代谢产物(图 1), 部分代谢产物对多种肿瘤细胞和金黄色葡萄球菌具有抑制活性, 且发现一个化合物与胆固醇转运蛋白 NPC1L1 具有良好的结合活性。

1 仪器与材料

1.1 仪器与试剂

HCB-1300V 洁净工作台(青岛海尔特种电器有限

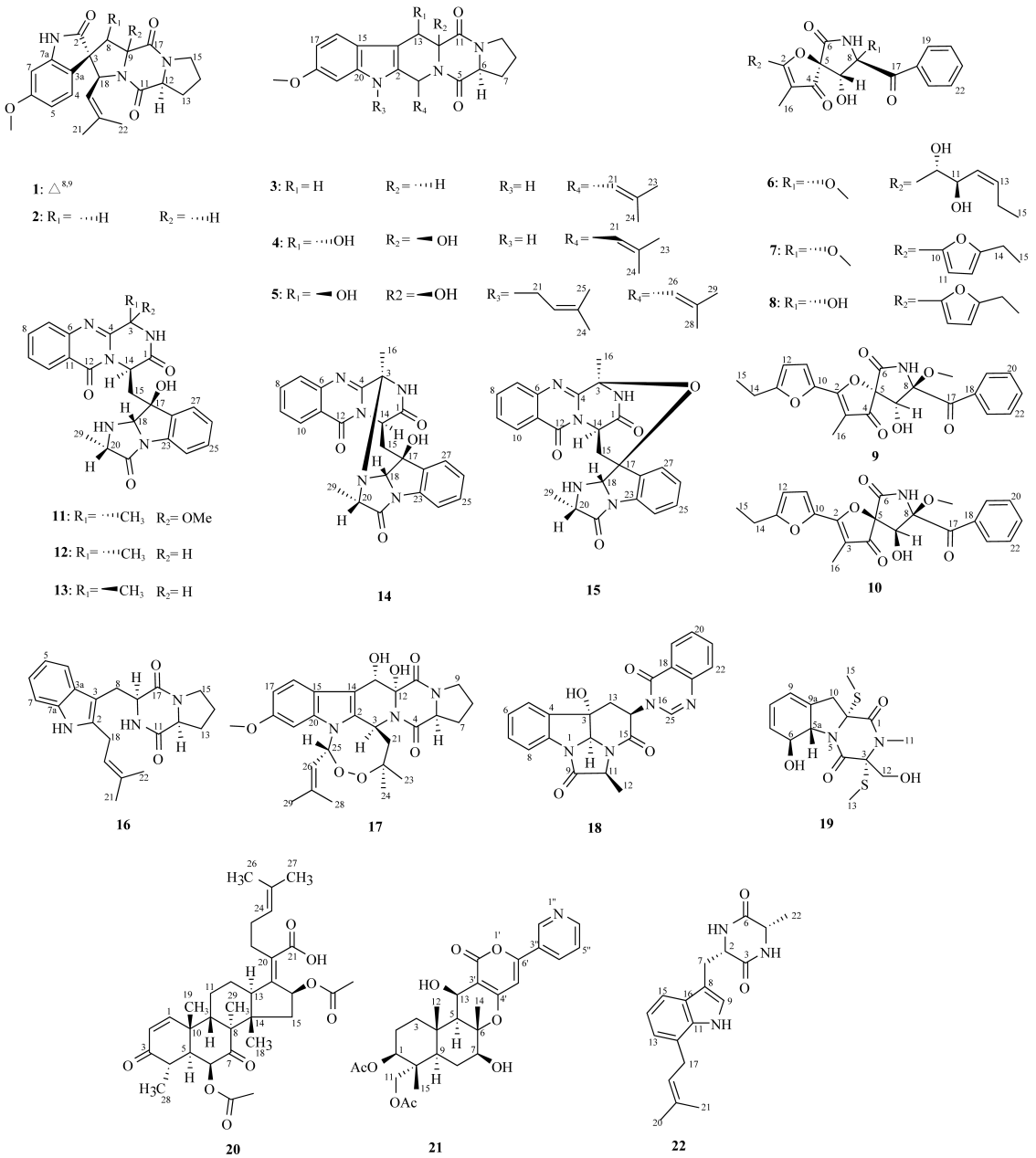

图 1 化合物 **1**—**22** 的化学结构

Fig. 1 The chemical structures of compounds **1**—**22**

公司)、LRH-500A 型生化培养箱(广东泰宏君科学仪器股份有限公司)、YXQ-LS-75SII 型高压灭菌锅(上海博迅实业有限公司医疗设备厂)、CR-080R 型春霖超声波清洗机(深圳市春霖清洗设备有限公司); Agilent 1260 高效液相色谱仪(美国 Agilent 公司)、AL104 型分析天平(瑞士梅特勒公司)、Brucker AVANCE 400MHz 核磁共振仪(德国 Brucker 公司)、Agilent InfinityLab LC/MSD 质谱仪(Agilent 公司)、赛默飞高分辨质谱仪, 日立分析高效液相色谱, 兰博 series III制备型高效液相色谱, Nicolet is 10 傅里叶变换红外光谱仪(美国赛默飞世尔科技公司), Agilent Cary60 紫外–可见分光光度计(美国 Agilent Technology 公司)。分析高效液相色谱柱为 $5C_{18}$–MS-II (C_{18}, 250mm×4.6mm, 5μm, Nacalai tesque, 日本), 5PFP (250mm×4.6mm, 5μm, Nacalai tesque, 日本); 制备型高效液相色谱柱 $5C_{18}$–MS-II (C_{18}, 250mm×10mm, 5μm, Nacalai tesque, 日本), 5PFP (250mm×10mm, 5μm, Nacalai tesque, 日本), 反相硅胶 YMC*GEL ODS-A-HG (日本 YMC Group)。提取分离用乙酸乙酯、甲醇、二氯甲烷等均为工业用化学纯产品。

1.2 菌株来源与发酵培养

海洋菌株分离于北海钉螺(*Oncomelania hupensis*), 经对比生长形态与基因序列, 此菌株鉴定为 *Aspergillus fumigatus*, 其系统发育树见图 2。

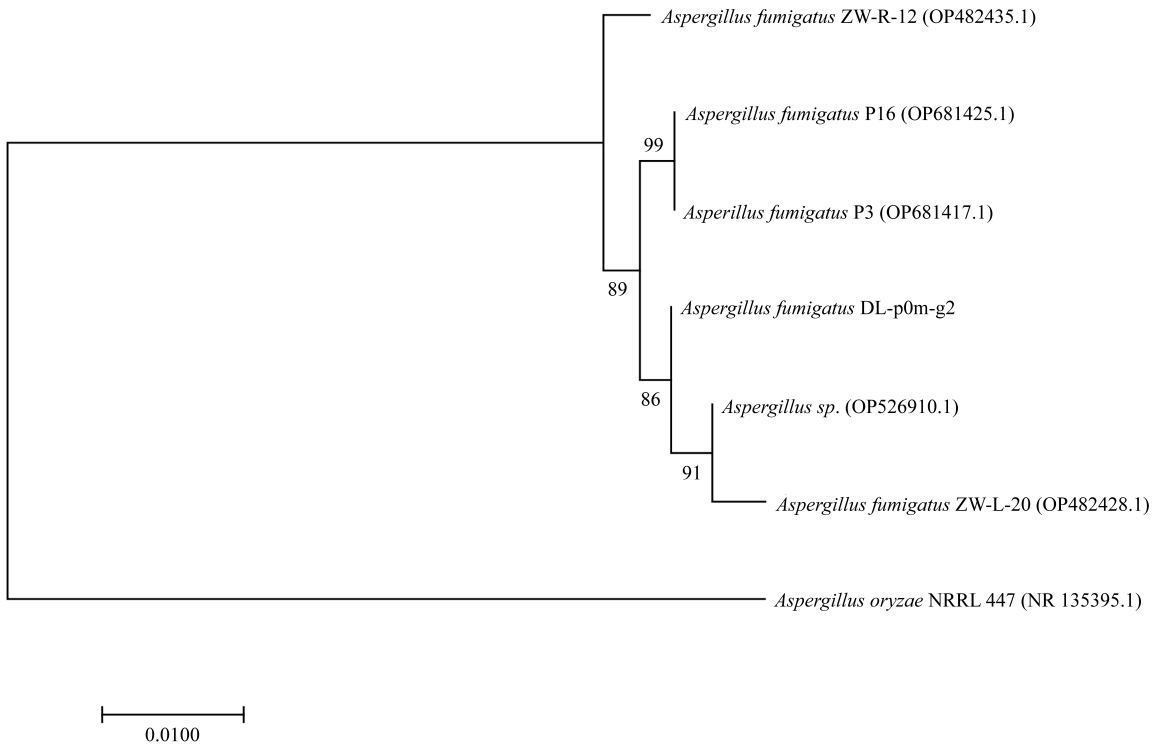

图 2 菌株 *Aspergillus fumigatus* DL-p0m-g2 的系统发育树

Fig. 2 Phylogenetic tree of strain *Aspergillus fumigatus* DL-p0m-g2

实验使用培养基包括真菌二号培养基: 葡萄糖 1%, 甘露醇 2%, 酵母膏 0.3%, 麦芽糖 2%, 味精 1%, 磷酸二氢钾 0.05%, 海水素 0.33‰; 马铃薯土豆培养基: 马铃薯 20.0%, 葡萄糖 2%, 琼脂 2.0%, 海水素 0.33‰。

将保存于斜面中的菌株接种于马铃薯培养基, 置于 28℃培养 3d。挑取长有菌株的培养基于真菌二号培养基中, 室温培养 30d。

1.3 化合物的提取与分离

对菌株 *Aspergillus fumigatus* DL-p0m-g2 进行真菌 2 号培养基发酵(33L, 室温, 30d), 用乙酸乙酯(EtOAc)对发酵物浸提 3 次, 过滤和减压浓缩后得到 20.84g 粗提物(图 3)。采用石油醚、90%甲醇–水对粗提物进行萃取, 得到石油醚层萃取物 7.76g, 甲醇层萃取物 14.49g。取甲醇萃取部位, 经反相 ODS 色谱柱, 依次用 20%、 40%、 60%、 80%、 100%甲醇–水梯度洗脱, 每个梯度分 3 次收集。得 Fr.1.1~ Fr.5.3 共 15 个组分。Fr.3.2 (3.6g)经中压制备液相得 Fr.3.2.1~ Fr.3.2.12 共 12 个组分。Fr.3.2.5 (346.5mg)经半制备型液相色谱(HPLC) [50%甲醇–水] 纯化得到化合物 **1** (5.5mg, t_R=34.2min)、化合物 **2** (2.0mg, t_R=25.6min)和化合物 **18** (5.1mg, t_R=28.4min)。Fr.3.2.7 (376.9mg)经半制备型液相色谱 [45%甲醇–水] 纯化得到化合物 **6** (17.3mg, t_R=18.5min) 与化合物 **19** (47.8mg, t_R=25.2min)。Fr.4.1 (654.9mg)经半制备型液相色谱 [55%乙腈–水] 纯化得到化合物 **3** (17.7mg, t_R = 10.7min)、化合物 **7**(10.6mg, t_R=18.7min) 和化合物 **8** (2.0mg, t_R=19.5min)。Fr.4.3 (600.9mg)经半制备型液相色谱 [55%乙腈–水] 纯化得到化合物 **5** (3.3mg, t_R=29.7min)、化合物 **17** (6.8mg, t_R=18.8min)和化合物 **20** (3.7mg, t_R=27.8min)。Fr.3.3 (1111.9mg)经反相 ODS 色谱柱, 依次用 40%, 50%, 60%, 70%, 100%甲醇–水梯度洗脱, 得 Fr.3.3.1~ Fr. 3.3.9 共 9 个组分。Fr.3.3.6 (78.9mg)经半制备型液相色谱 [45%乙腈–水] 纯化得到化合物 **11** (3mg, t_R=11.8min)和化合物 **14** (9.1mg, t_R=15.9min)。Fr.3.3.5 (347.7mg)经半制备型液相色谱 [60%甲醇–水] 得到组分 Fr.3.3.5.1~ Fr.3.3.5.5。Fr.3.3.5.3 (70mg) 经半制备型液相色谱 [40%乙腈–水] 纯化得到化合物 **9** (5.2mg, t_R=24.1min) 、化合物 **10** (7mg, t_R=26.0min)和化合物 **21** (4.4mg, t_R=9.5min)。Fr.3.3.5.4 (95.6mg) 经半制备型液相色谱 [46%乙腈–水] 纯化得到组分 Fr.3.3.5.4.2、化合物 **4** (5.7mg, t_R=18.6min)、化合物 **12** (3.5mg, t_R=11.7min) 、化合物 **15** (1.7mg, t_R=16.4min) 和化合物 **16** (1.9mg, t_R=20.5min)。组分 Fr.3.3.5.4.2 (6.0mg) 经半制备型液相色谱 [55%甲醇–水] 纯化得到化合物 **13** (2.5mg, t_R=19.8min)和化合物 **22** (1.7mg, t_R=18.7min)。

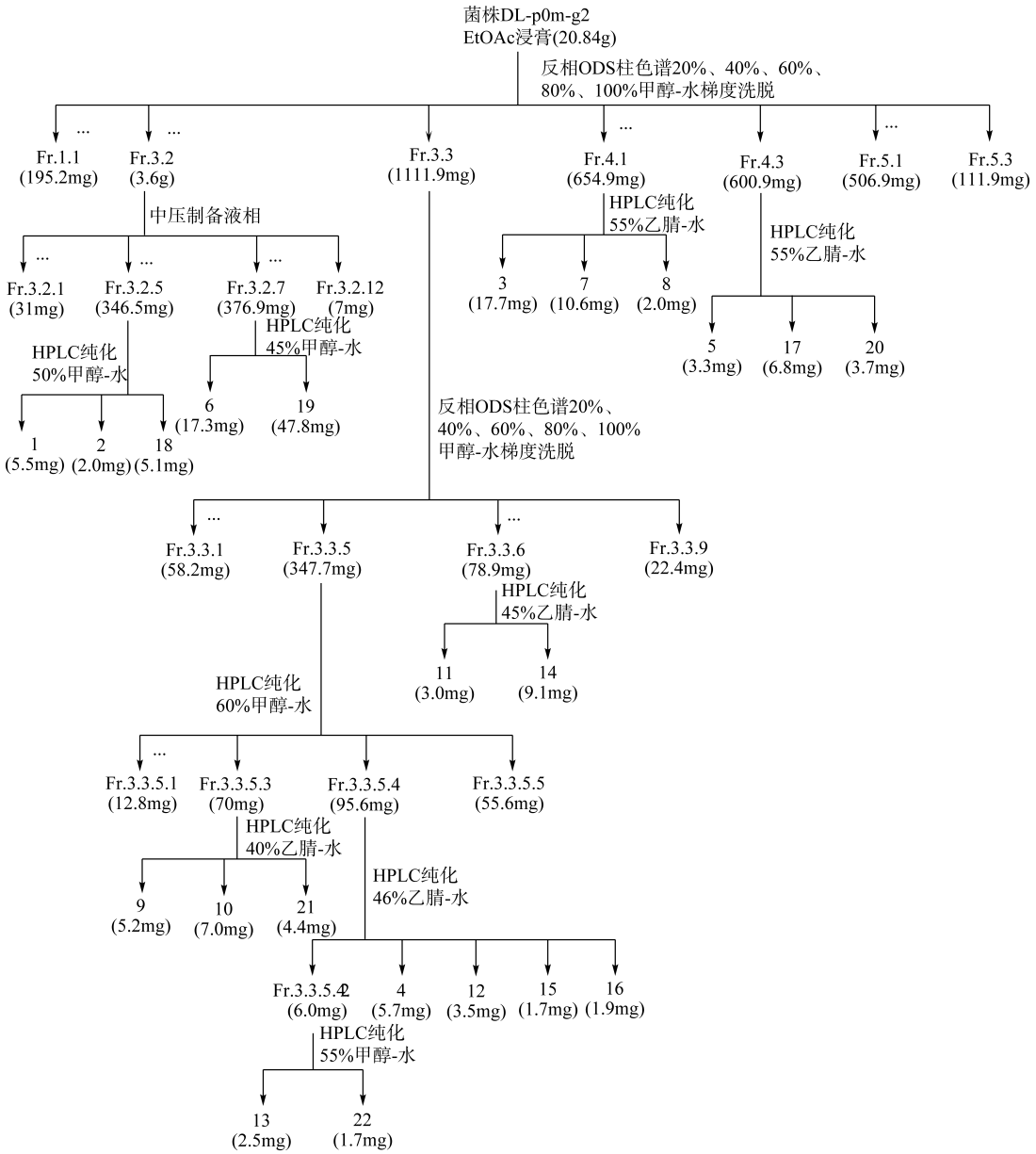

图 3 菌株 *Aspergillus fumigatus* DL-p0m-g2 化合物 **1**—**22** 分离流程图

Fig. 3 The flowing chart of compounds **1**—**22** from *Aspergillus fumigatus* DL-p0m-g2

1.4 活性试验

1.4.1 细胞增殖抑制试验

实验参照 CCK-8 (cell counting kit-8)法(王聪 等, 2017), 样品用 DMSO (dimethyl sulfoxide)溶解, 母液浓度为 20mmol·L^{-1}。取对数生长期的肿瘤细胞, 稀释成 8×10^{3}ind.·mL^{-1} 的细胞悬液, 96 孔板中每孔接种 100μL 后于二氧化碳培养箱中培养 24h, 去除原有培养基并加入 100μL 化合物稀释液后, 培养箱中培养 48h, 再次去除培养基, 加入含有 10% CCK-8 增强型溶液的培养基培养 4h, 在 450nm 处检测其吸光度并测量其抑制率。若化合物在 50μmol·L^{-1} 浓度时, 抑制率大于 50%, 则说明该化合物对肿瘤细胞有较好抑制活性, 将对其进行半抑制浓度(IC_{50})测定。实验过程中, 每个测量浓度均设 3 个平行。

1.4.2 最小抑菌浓度测定

实验使用二倍稀释法(吴萌萌 等, 2021), 用 96 孔板对 22 个化合物进行细菌活性试验研究, 在 96 孔板中加入 100μL 金黄色葡萄球菌液, 药物浓度为 0.5μg·mL^{-1}~256μg·mL^{-1}。同时设置阳性药组, 阴性对照组, 每个药物浓度设置 3 个复孔。在 18h 后观察记录细菌生长情况, 测定最小抑菌浓度。

1.4.3 硫氧还蛋白还原酶活性测试实验

实验参照硫氧还蛋白还原酶活性检测试剂盒说明书, 样品用 DMSO 溶解, 母液浓度为 20mmol·L^{-1}。将样品与试剂混合配置成 500μL 待测样品, 先在 96 孔板中加入 200μL 待测样品在 405nm 处测定 10s 时吸光

度; 然后将 200μL 待测样品放入 37℃水浴 5min 后混匀测定 10s 吸光度。阳性药为姜黄素, 实验过程设置 3 个复孔。

1.4.4 NPC1L1 蛋白活性测试实验

实验方法参考文献(Zhang et al, 2021)完成, 使用 Biacore.T200 T200(Cytia)进行表面等离子共振(surface plasmon resonance, SPR)实验。用 Amine Coupling Kit 将 NPC1L1 蛋白偶联到 CM5 芯片表面, 首先将 CM5 芯片按照标准仪器程序进行安装和启动后, 将 N-羟基琥珀酰亚胺和 1-乙基（3-二甲基氨基丙基）碳酰氯)以 1:1 的比例混合并运行混合物, 总体积为 200μL, 流速为 10μL·min^{-1}, 时间为 600s。然后将 NPC1L1 蛋白在 pH 值为 4.6 的醋酸钠溶液中稀释至 20μg·mL^{-1}, 蛋白溶液总体积 800μL, 流速 10μL·min^{-1}, 时间为 3000s。最后, 乙醇胺溶液总体积 200μL, 流速 10μL·min^{-1}, 时间为 420s。然后, 使用含 1% DMSO 的磷酸盐缓冲液(phosphate buffer solution, PBS, pH 7.4)对 CM5 芯片进行预处理。用含 DMSO 的 PBS-P 将化合物稀释至 0.1μmol·L^{-1}, 确保 DMSO 终浓度为 1%, 流速 30μL·min^{-1}, 结合时间 60s, 解离时间 120s。最终结果采用 Biacore.T200 进行分析。

2 实验结果

2.1 结构鉴定

化合物 **1**: 淡黄色粉末状物, 分子式为 $C_{22}H_{23}N_3O_4$, HRESIMS *m/z* 394.1761 $[M + H]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 7.02 (1H, d, *J* = 8.3 Hz, H-4), 6.56 (1H, dd, *J* = 2.3, 8.3 Hz, H-5), 6.50 (1H, d, *J* = 2.3 Hz, H-7), 5.74 (1H, s, H-8), 5.28 (1H, overlap, H-19), 5.28 (1H, overlap, H-18), 4.45 (1H, dd, *J* = 6.2, 11.3 Hz, H-12), 3.79 (3H, s, OMe-6), 3.79 (1H, m, H-15), 3.75 (1H, m, H-15), 1.97, 2.41 (2H, m, H-13), 1.97, 2.11 (2H, m, H-14), 1.59 (3H, s, H-21), 1.27 (3H, s, H-22); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 181.1 (C-2), 164.9 (C-11), 162.4 (C-6), 156.9 (C-17), 144.2 (C-7a), 139.0 (C-20), 138.9 (C-9), 129.5 (C-4), 122.2 (C-19), 120.3 (C-3a), 118.6 (C-8), 108.1 (C-5), 98.2 (C-7), 65.3 (C-18), 63.0 (C-12), 62.9 (C-3), 55.9 (OMe-6), 46.0 (C-15), 30.0 (C-13), 25.3 (C-14), 22.9 (C-21), 18.3 (C-22)。以上数据与文献(王亚楠 等, 2019)报道对照基本一致, 化合物 **1** 鉴定为 6-methoxyspirotryprostatin B。

化合物 **2**: 淡黄色油状物, 分子式为 $C_{22}H_{25}N_3O_4$, HRESIMS *m/z* 418.1736 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 7.02 (1H, d, *J* = 8.4 Hz, H-4), 6.53 (1H, dd, *J* = 2.4, 8.4 Hz, H-5), 6.48 (1H, d, *J* = 2.4 Hz, H-7), 5.08 (1H, m, H-19), 5.02 (1H, m, H-9), 4.71 (1H, d, *J* = 9.2 Hz, H-18), 4.43 (1H, t, *J* = 7.8 Hz, H-12), 3.78 (3H, s, OMe-6), 3.55 (2H, m, H-15), 2.58 (1H, dd, *J* = 10.7, 13.3 Hz, H-8), 2.34 (1H, dd, *J* = 7.2, 13.3 Hz, H-8), 2.32 (1H, m, H-13), 2.11 (1H, m, H-13), 1.65 (3H, d, *J* = 0.9 Hz, H-22), 1.18 (3H, d, *J* = 1.1 Hz, H-21); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 183.2 (C-2), 169.4 (C-11), 168.9 (C-17), 162.2 (C-6), 144.4 (C-7a), 139.1 (C-20), 128.2 (C-4), 122.7 (C-19), 120.1 (C-3a), 107.7 (C-5), 97.7 (C-7), 62.3 (C-9), 61.8 (C-12), 59.8 (C-18), 57.1 (C-3), 55.9 (OMe-6), 46.2 (C-15), 35.3 (C-8), 28.5 (C-13), 25.6 (C-22), 24.5 (C-14), 18.1 (C-21)。以上数据与文献(陈雷等, 2017)报道对照基本一致, 化合物 **2** 鉴定为 spirotryprostatin A。

化合物 **3**: 白色粉末状物, 分子式为 $C_{22}H_{25}N_3O_3$, HRESIMS *m/z* 402.1794 $[M + Na]^+$。^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.94 (1H, s, H-1), 7.43 (1H, d, *J* = 8.6 Hz, H-16), 6.85 (1H, d, *J* = 1.9 Hz, H-19), 6.81 (1H, dd, *J* = 2.1, 8.6 Hz, H-17), 5.98 (1H, d, *J* = 9.6 Hz, H-3), 4.90 (1H, d, *J* = 9.5 Hz, H-21), 4.17 (1H, dd, *J* = 4.8, 11.4 Hz, H-12), 4.10 (1H, dd, *J* = 8.3, 8.3 Hz, H-6), 3.82 (3H, s, OMe-18), 3.63 (2H, overlap, H-9), 3.51 (1H, dd, *J* = 5.1, 16.0 Hz, H-13a), 3.09 (1H, dd, *J* = 11.7, 15.9 Hz, H-13b), 2.40 (1H, m, H-7a), 2.23 (1H, m, H-7b), 2.05 (1H, m, H-8a), 1.98 (3H, s, H-24), 1.91 (1H, m, H-8b), 1.64 (3H, s, H-23); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 169.6 (C-5), 165.9 (C-11), 156.6 (C-18), 137.1 (C-20), 134.1 (C-22), 132.3 (C-2), 124.3 (C-21), 120.8 (C-15), 119.0 (C-16), 109.6 (C-17), 106.3 (C-14), 95.4 (C-19), 59.3 (C-6), 56.9 (C-12), 55.9 (OMe-18), 51.1 (C-3), 45.5 (C-9), 28.7 (C-7), 25.8 (C-23), 23.2 (C-8), 22.1 (C-13), 18.2 (C-24)。以上数据与文献(任虹 等, 2011)报道对照基本一致, 化合物 **3** 鉴定为 fumitremorgin C。

化合物 **4**: 白色粉末状物, 分子式为 $C_{22}H_{25}N_3O_5$, HRESIMS *m/z* 434.1695 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 7.73 (1H, d, *J* = 8.7 Hz, H-16), 6.86 (1H, d, *J* = 2.2 Hz, H-19), 6.66 (1H, dd, *J* = 2.3, 8.7 Hz, H-17), 5.93 (1H, d, *J* = 9.6 Hz, H-3), 5.67 (1H, s, H-13), 4.78 (1H, dt, *J* = 1.2, 9.6 Hz, H-21), 4.49 (1H, d, *J* = 9.6 Hz, H-21), 3.80 (3H, s, OMe-18), 3.59 (2H, overlap, H-9), 2.00 (3H, d, *J* = 1.0 Hz, H-24), 1.65 (1H, d, *J* = 1.0 Hz, H-23); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 173.2 (C-

11), 168.1 (C-5), 157.5 (C-18), 139.5 (C-20), 135.7 (C-22), 131.2 (C-2), 124.9 (C-21), 122.2 (C-15), 121.9 (C-16), 110.0 (C-17), 106.6 (C-14), 95.7 (C-19), 84.9 (C-12), 69.7 (C-13), 60.1 (C-6), 55.9 (OMe-18), 51.4 (C-3), 46.5 (C-9), 30.2 (C-7), 25.9 (C-23), 23.5 (C-8), 18.4 (C-24)。以上数据与文献(赵欢 等, 2018)报道对照基本一致, 化合物 **4** 鉴定为 cyclotryprostatin A。

化合物 **5**: 白色粉末状物, 分子式为 $C_{27}H_{33}N_3O_5$, HRESIMS *m/z* 502.2311 $[M + Na]^+$。^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.84 (1H, d, *J* = 8.7 Hz, H-16), 6.80 (1H, dd, *J* = 2.3, 8.7 Hz, H-17), 6.69 (1H, d, *J* = 2.3 Hz, H-19), 5.97 (1H, d, *J* = 10.0 Hz, H-26), 5.77 (1H, s, H-13), 5.03 (1H, t, *J* = 5.2 Hz, H-22), 4.70 (1H, m, H-3), 4.54 (2H, d, *J* = 5.6 Hz, H-21), 4.45 (1H, d, *J* = 7.0, 9.8 Hz, H-6), 3.84 (3H, s, OMe-18), 3.64 (2H, overlap, H-9), 2.47 (1H, m, H-7a), 2.09 (2H, m, H-8), 1.99 (3H, d, *J* = 1.0 Hz, H-29), 1.95 (1H, m, H-7b), 1.85 (3H, s, H-24), 1.70 (3H, d, *J* = 0.9 Hz, H-25), 1.63 (3H, d, *J* = 1.1 Hz, H-28); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 170.6 (C-5), 166.4 (C-11), 156.4 (C-18), 138.1 (C-20), 135.4 (C-27), 134.8 (C-23), 131.3 (C-2), 123.1 (C-26), 121.5 (C-16), 120.7 (C-15), 120.4 (C-22), 109.5 (C-17), 104.5 (C-14), 94.0 (C-19), 83.1 (C-12), 69.1 (C-13), 58.9 (C-6), 55.9 (OMe-18), 49.2 (C-3), 45.4 (C-9), 41.9 (C-21), 29.1 (C-7), 25.9 (C-25), 25.7 (C-29), 22.8 (C-8), 18.5 (C-24), 18.4 (C-28)。以上数据与文献(任虹 等, 2011)报道对照基本一致, 化合物 **5** 鉴定为 fumitremorgin B。

化合物 **6**: 白色晶状结晶, 分子式为 $C_{22}H_{25}NO_8$, HRESIMS *m/z* 454.1472 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 8.35 (2H, d, *J* = 8.5 Hz, H-19, H-23), 7.65 (1H, t, *J* = 7.4 Hz, H-21), 7.50 (2H, t, *J* = 7.9 Hz, H-20, H-22), 5.62 (1H, dt, *J* = 11.1, 7.4 Hz, H-13), 5.46 (1H, dd, *J* = 11.1, 9.0 Hz, H-12), 4.67 (1H, dd, *J* = 8.9, 7.0 Hz, H-10), 4.60 (1H, brs, H-7), 4.54 (1H, s, H-9), 4.50 (1H, d, *J* = 6.6 Hz, H-11), 3.34 (3H, s, OMe-8), 2.14 (2H, m, H-14), 1.76 (3H, s, H-16), 0.98 (3H, t, *J* = 7.52 Hz, H-15); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 199.2 (C-4), 197.1 (C-17), 188.7 (C-6), 169.2 (C-2), 137.3 (C-13), 135.1 (C-21), 134.9 (C-18), 131.7 (C-19, 23), 129.5 (C-20, 22), 128.8 (C-12), 114.4 (C-3), 93.9 (C-5), 93.6 (C-8), 76.3 (C-9), 72.9 (C-10), 69.5 (C-11), 52.5 (OMe-8), 22.2 (C-14), 14.5 (C-15), 5.8 (C-16)。以上数据与文献(陈雷 等, 2017)报道对照基本一致, 化合物 **6** 鉴定为 pseurotin A。

化合物 **7**: 黄色油状物, 分子式为 $C_{22}H_{21}NO_7$, HRESIMS *m/z* 434.1212 $[M + Na]^+$。^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.32 (2H, d, *J* = 7.9 Hz, H-19, H-23), 7.61 (2H, dd, *J* = 7.3, 14.7 Hz, 7-NH, H-21), 7.48 (2H, t, *J* = 7.8 Hz, H-20, H-22), 7.03 (1H, d, *J* = 3.4 Hz, H-11), 6.22 (1H, d, *J* = 3.4 Hz, H-12), 4.69 (1H, d, *J* = 12.0 Hz, H-9), 4.19 (1H, d, *J* = 8.6 Hz, OH-9), 3.40 (3H, s, OMe-8), 2.74 (2H, q, *J* = 7.6 Hz, H-14), 2.00 (3H, s, H-16), 1.27 (3H, d, *J* = 7.6 Hz, H-15); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 195.8 (C-4), 194.8 (C-17), 172.7 (C-2), 166.4 (C-6), 163.9 (C-13), 143.5 (C-10), 134.6 (C-21), 132.6 (C-18), 130.7 (C-19, 23), 128.8 (C-20, 22), 118.4 (C-11), 108.1 (C-3), 107.9 (C-12), 91.7 (C-5), 89.9 (C-8), 74.4 (C-9), 51.8 (OMe-8), 21.9 (C-14), 11.9 (C-15), 6.3 (C-16)。以上数据与文献(Ren et al, 2010)报道对照基本一致, 化合物 **7** 鉴定为 azaspirofuran A。

化合物 **8**: 黄色油状物, 分子式为 $C_{21}H_{19}NO_7$, HRESIMS *m/z* 420.1054 $[M + Na]^+$。^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.29 (2H, qd, *J* = 1.3, 9.8 Hz, H-19, H-23), 7.63 (1H, t, *J* = 7.3 Hz, H-21), 7.50 (2H, t, *J* = 7.7, 8.0 Hz, H-20, H-22), 7.20 (1H, d, *J* = 3.6 Hz, H-11), 7.09 (1H, s, NH-7), 6.30 (1H, d, *J* = 3.6 Hz, H-12), 5.01 (1H, s, H-9), 2.79 (1H, q, *J* = 7.6 Hz, OMe-8), 2.05 (3H, s, H-16), 1.30 (3H, t, *J* = 7.6 Hz, H-15); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 197.8 (C-4), 192.4 (C-17), 174.8 (C-2), 165.1 (C-13), 164.5 (C-6), 143.3 (C-10), 134.4 (C-21), 133.2 (C-18), 130.7 (C-19, C-23), 128.9 (C-20, C-22), 120.2 (C-11), 108.4 (C-12), 108.0 (C-3), 93.2 (C-5), 87.8 (C-8), 72.7 (C-9), 51.8, (OMe-8), 22.0 (C-14), 11.9 (C-15), 6.4 (C-16)。以上数据与文献(Ren et al, 2010)报道对照基本一致, 化合物 **8** 鉴定为 azaspirofuran B。

化合物 **9**: 黄色油状物, 分子式为 $C_{22}H_{21}NO_7$, HRESIMS *m/z* 434.1214 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 8.26 (2H, d, *J* = 8.0 Hz, H-19, H-23), 7.61 (1H, t, *J* = 7.41 Hz, H-21), 7.48 (2H, t, *J* = 7.8 Hz, H-20, H-22), 7.01 (1H, d, *J* = 3.6 Hz, H-11), 6.17 (1H, d, *J* = 3.5 Hz, H-12), 4.66 (1H, d, *J* = 4.2 Hz, H-9), 3.35 (3H, s, OMe-8), 3.15 (1H, d, *J* = 4.5 Hz, 9-OH), 2.74 (2H, q, *J* = 7.6 Hz, H-14), 2.02 (3H, s, H-16), 1.27 (3H, t, *J* = 7.6 Hz, H-15); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 196.0 (C-4), 193.6 (C-17), 170.3 (C-2), 168.3 (C-6), 163.9 (C-13), 143.3 (C-10), 134.2 (C-21), 134.0 (C-18),

129.9 (C-19, 23), 128.8 (C-20, 22), 118.1 (C-11), 108.2 (C-3), 107.8 (C-12), 95.2 (C-8), 88.0 (C-5), 76.9 (C-9), 51.6 (OMe-8), 21.9 (C-14), 11.9 (C-15), 6.3 (C-16)。以上数据与文献 (Yamada et al, 2010)报道对照基本一致, 化合物 **9** 鉴定为 cephalimysin B。

化合物 **10**: 黄色油状物, 分子式为 $C_{22}H_{21}NO_7$, HRESIMS *m/z* 434.1217 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) δ: 8.32 (2H, d, J = 8.4 Hz, H-19, H-23), 7.63 (1H, t, J = 7.5 Hz, H-21), 7.45 (3H, t, J = 7.9 Hz, H-20, H-22, H-7), 7.10 (1H, d, J = 3.5 Hz, H-11), 6.26 (1H, d, J = 3.5 Hz, H-12), 4.59 (1H, d, J = 12.4 Hz, H-9), 3.40 (1H, d, J = 12.4 Hz, 9-OH), 3.36 (3H, s, OMe-8), 2.78 (2H, q, J = 7.6 Hz, H-14), 2.02 (3H, s, H-16), 1.31 (3H, t, J = 7.6 Hz, H-15); ^{13}C-NMR (100 MHz, CD_3OD) δ: 198.3 (C-4), 194.0 (C-17), 171.4 (C-2), 167.3 (C-6), 163.9 (C-13), 143.6 (C-10), 134.7 (C-21), 133.1 (C-18), 130.8 (C-19, 23), 128.7 (C-20, 22), 117.9 (C-11), 109.5 (C-3), 107.8 (C-12), 92.6 (C-8), 86.8 (C-5), 73.6 (C-9), 51.8 (OMe-8), 21.9 (C-14), 11.9 (C-15), 6.4 (C-16)。以上数据与文献 (Yamada et al, 2010)报道对照基本一致, 化合物 **10** 鉴定为 cephalimysin C。

化合物 **11**: 淡黄色油状物, 分子式为 $C_{25}H_{25}N_5O_5$, HRESIMS *m/z* 498.1753 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) δ: 8.19 (1H, dd, J = 1.4, 8.0 Hz, H-10), 7.83 (1H, m, H-8), 7.75 (1H, d, J = 7.8 Hz, H-7), 7.58 (1H, d, J = 7.7 Hz, H-27), 7.54 (1H, m, H-24), 7.49 (1H, d, J = 8.1 Hz, H-9), 7.34 (1H, td, J = 1.2, 7.7 Hz, H-25), 7.17 (1H, td, J = 1.2, 7.7 Hz, H-26), 5.95 (1H, dd, J = 6.9, 7.8 Hz, H-14), 5.40 (1H, d, J = 1.8 Hz, H-18), 4.20 (1H, q, J = 6.6 Hz, H-20), 3.40 (3H, s, OMe-3), 2.61 (1H, dd, J = 7.9, 14.3 Hz, H-15b), 2.41 (1H, dd, J = 6.8, 14.3 Hz, H-15a), 1.93 (3H, s, H-16), 1.30 (3H, d, J = 6.7 Hz, H-29); ^{13}C-NMR (100 MHz, CD_3OD) δ: 173.8 (C-1), 173.7 (C-21), 162.9 (C-12), 151.0 (C-4), 147.9 (C-6), 141.0 (C-28), 137.9 (C-23), 135.8 (C-8), 130.4 (C-25), 128.8 (C-7), 128.7 (C-9), 127.6 (C-10), 126.4 (C-26), 126.3 (C-27), 121.9 (C-11), 115.8 (C-24), 87.8 (C-18), 86.2 (C-3), 81.1 (C-17), 60.4 (C-20), 54.8 (C-14), 50.7 (OMe-3), 39.5 (C-15), 20.7 (C-16), 18.3 (C-29)。以上数据与文献 (Takahashi et al, 1995)报道对照基本一致, 化合物 **11** 鉴定为 fumiquinazoline C。

化合物 **12**: 淡黄色油状物, 分子式为 $C_{24}H_{25}N_5O_4$, HRESIMS *m/z* 468.1649 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) δ: 8.19 (1H, dd, J = 1.1, 7.9 Hz, H-10), 7.81 (1H, td, J = 1.5, 7.8 Hz, H-8), 7.64 (1H, d, J = 8.5 Hz, H-7), 7.62 (1H, dd, J = 8.5 Hz, H-27), 7.51 (1H, td, J = 0.9, 7.6 Hz, H-24), 7.48 (1H, d, J = 8.5 Hz, H-9), 7.34 (1H, m, H-25), 7.20 (1H, m, H-26), 5.78 (1H, dd, J = 5.6, 10.0 Hz, H-14), 5.39 (1H, d, J = 1.7 Hz, H-18), 4.21 (1H, q, J = 6.7 Hz, H-20), 2.57 (1H, dd, J = 10.0, 13.9 Hz, H-15b), 2.35 (1H, dd, J = 5.6, 13.9 Hz, H-15a), 1.82 (3H, d, J = 7.2 Hz, H-16), 1.28 (3H, d, J = 6.7 Hz, H-29); ^{13}C-NMR (100 MHz, CD_3OD) δ: 173.5 (C-1), 171.4 (C-21), 162.3 (C-12), 153.8 (C-4), 148.4 (C-6), 140.7 (C-28), 137.9 (C-23), 136.1 (C-8), 130.5 (C-25), 128.2 (C-7), 127.7 (C-9), 127.6 (C-10), 126.5 (C-26), 126.4 (C-27), 121.3 (C-11), 115.8 (C-24), 87.8 (C-18), 81.2 (C-17), 60.3 (C-20), 53.5 (C-14), 53.5 (C-3), 39.2 (C-15), 24.7 (C-16), 18.4 (C-29)。以上数据与文献 (Takahashi et al, 1995) 报道对照基本一致, 化合物 **12** 鉴定为 fumiquinazoline B。

化合物 **13**: 淡黄色油状物, 分子式为 $C_{24}H_{23}N_5O_4$, HRESIMS *m/z* 468.1646 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) δ: 8.20 (1H, dd, J = 1.3, 8.0 Hz, H-10), 7.81 (1H, ddd, J = 1.5, 7.2, 8.2 Hz, H-8), 7.71 (1H, d, J = 7.9 Hz, H-27), 7.58 (1H, d, J = 7.5 Hz, H-7), 7.52 (1H, ddd, J = 1.1, 7.0, 8.0 Hz, H-24), 7.45 (1H, d, J = 7.8 Hz, H-9), 7.32 (1H, td, J = 1.2, 7.7 Hz, H-25), 7.18 (1H, td, J = 1.0, 7.6 Hz, H-26), 5.98 (1H, t, J = 7.9 Hz, H-14), 5.41 (1H, d, J = 1.7 Hz, H-18), 4.99 (1H, q, J = 6.6 Hz, H-3), 4.21 (1H, q, J = 6.6 Hz, H-20), 2.52 (1H, dd, J = 8.3, 14.1 Hz, H-15b), 2.23 (1H, dd, J = 7.5, 14.1 Hz, H-15a), 1.74 (3H, d, J = 6.6 Hz, H-16), 1.29 (3H, d, J = 6.6 Hz, H-29); ^{13}C-NMR (100 MHz, CD_3OD) δ: 173.5 (C-1), 172.4 (C-21), 162.7 (C-12), 153.8 (C-4), 148.7 (C-6), 141.0 (C-28), 137.7 (C-23), 135.8 (C-8), 130.5 (C-25), 128.5 (C-7), 128.2 (C-9), 127.6 (C-10), 126.5 (C-26), 126.3 (C-27), 121.6 (C-11), 115.8 (C-24), 87.8 (C-18), 81.2 (C-17), 60.2 (C-20), 54.7 (C-14), 50.3 (C-3), 37.0 (C-15), 18.5 (C-29), 16.8 (C-16)。以上数据与文献 (Takahashi et al, 1995)报道对照基本一致, 化合物 **13** 鉴定为 fumiquinazoline A。

化合物 **14**: 淡黄色粉末状物, 分子式为 $C_{24}H_{21}N_5O_4$, HRESIMS *m/z* 466.1486 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) δ: 8.20 (1H, d, J = 7.9 Hz, H-10), 7.82 (1H, t, J = 7.8 Hz, H-8), 7.72 (1H, d, J = 8.1

Hz, H-7), 7.54 (1H, t, *J* = 7.5 Hz, H-9), 7.43 (2H, overlap, H-27, H-24), 7.31 (1H, t, *J* = 7.6 Hz, H-25), 7.18 (1H, t, *J* = 7.6 Hz, H-26), 5.67 (1H, d, *J* = 1.6 Hz, H-14), 5.46 (1H, d, *J* = 9.7 Hz, H-18), 4.25 (1H, q, *J* = 6.4 Hz, H-20), 3.18 (1H, dd, *J* = 10.2, 15.2 Hz, H-15b), 2.23 (1H, d, *J* = 15.1 Hz, H-15a), 2.09 (3H, s, H-16), 1.09 (3H, d, *J* = 6.5 Hz, H-29); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 174.0 (C-1), 172.0 (C-21), 162.4 (C-12), 154.3 (C-4), 148.0 (C-5), 139.8 (C-22), 139.0 (C-28), 136.0 (C-8), 130.7 (C-25), 128.8 (C-7), 128.7 (C-9), 127.6 (C-10), 126.7 (C-26), 125.3 (C-27), 121.6 (C-11), 116.3 (C-24), 87.2 (C-18), 84.5 (C-17), 72.1 (C-3), 60.3 (C-20), 54.6 (C-14), 44.5 (C-15), 19.0 (C-16), 18.0 (C-29)。以上数据与文献(朱伟明等, 2015)报道对照基本一致, 化合物 **14** 鉴定为 fumiquinazoline D。

化合物 **15**: 淡黄色油状物, 分子式为 $C_{24}H_{21}N_5O_4$, HRESIMS *m/z* 466.1486 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 8.30 (1H, dd, *J* = 1.1, 8.0 Hz, H-10), 7.91 (1H, td, *J* = 1.5, 8.3 Hz, H-2), 7.85 (1H, dd, *J* = 0.9, 8.3 Hz, H-8), 7.66 (1H, ddd, *J* = 1.3, 7.5, 7.5 Hz, H-9), 7.36 (3H, m, H-24, H-25, H-27), 7.24 (1H, ddd, *J* = 1.9, 7.2, 7.2 Hz, H-26), 5.57 (1H, dd, *J* = 1.0, 7.3 Hz, H-14), 5.29 (1H, s, H-18), 3.70 (1H, q, *J* = 7.0 Hz, H-20), 2.97 (1H, dd, *J* = 7.3, 15.1 Hz, H-15b), 2.09 (1H, dd, *J* = 0.9, 15.1 Hz, H-15a), 2.02 (3H, s, H-16), 1.02 (3H, d, *J* = 6.9 Hz, H-29); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 173.7 (C-1), 172.7 (C-21), 161.7 (C-12), 151.9 (C-4), 148.2 (C-6), 140.6 (C-28), 136.0 (C-8), 131.0 (C-25), 129.7 (C-9), 129.4 (C-7), 127.6 (C-10), 127.4 (C-26), 126.1 (C-27), 122.6 (C-11), 116.2 (C-24), 89.0 (C-17), 87.8 (C-18), 85.4 (C-3), 60.1 (C-20), 53.0 (C-14), 32.3 (C-15), 24.4 (C-16), 18.9 (C-29)。以上数据与文献 (Takahashi et al, 1995) 报道对照基本一致, 化合物 **15** 鉴定为 fumiquinazoline F。

化合物 **16**: 白色粉末状物, 分子式为 $C_{21}H_{25}N_3O_2$, HRESIMS *m/z* 374.1845 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 7.48 (1H, d, *J* = 7.8 Hz, H-4), 7.31 (1H, d, *J* = 7.9 Hz, H-7), 7.16 (1H, td, *J* = 1.1, 7.2 Hz, H-6), 7.09 (1H, td, *J* = 0.9, 7.9 Hz, H-5), 5.64 (1H, brs, H-10), 5.32 (1H, tt, *J* = 1.3, 7.2 Hz, H-19), 4.37 (1H, dd, *J* = 3.3, 11.5 Hz, H-12), 4.06 (1H, t, *J* = 7.9 Hz, H-9), 3.68 (2H, m, H-8, H-15a), 3.59 (1H, ddd, *J* = 3.2, 8.7, 11.7 Hz, H-15b), 3.48 (2H, t, *J* = 7.2 Hz, H-18), 2.96 (1H, dd, *J* = 11.4, 15.1 Hz, H-8), 2.33 (1H, m, H-13a), 2.06 (1H, m, H-13b), 1.91 (2H, m, H-14), 1.79 (3H, s, H-19), 1.75 (3H, s, H-20); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 170.3 (C-11), 167.5 (C-17), 138.8 (C-7a), 137.3 (C-20), 134.7 (C-2), 129.5 (C-3a), 122.1 (C-6), 121.9 (C-19), 119.8 (C-5), 119.1 (C-4), 111.7 (C-7), 104.4 (C-3), 60.1 (C-12), 57.2 (C-9), 46.0 (C-15), 29.0 (C-13), 28.6 (C-21), 26.2 (C-8), 25.9 (C-18), 22.5 (C-14), 18.0 (C-22)。以上数据与文献(赵文英 等, 2006)报道对照基本一致, 化合物 **16** 鉴定为 tryprostatin B。

化合物 **17**: 淡黄色粉末, 分子式为 $C_{28}H_{35}N_3O_7$, HRESIMS *m/z* 534.2253 $[M + Na]^+$。^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.90 (1H, d, *J* = 8.7 Hz, H-16), 6.83 (1H, dd, *J* = 2.2, 8.7 Hz, H-17), 6.64 (1H, d, *J* = 8.2 Hz, H-25), 6.59 (1H, d, *J* = 2.2 Hz, H-19), 6.05 (1H, d, *J* = 10.2 Hz, H-3), 5.66 (1H, s, H-13), 5.04 (1H, dt, *J* = 1.3, 8.1 Hz, H-26), 4.48 (1H, dd, *J* = 7.1, 9.6 Hz, H-6), 3.84 (3H, s, OMe-18), 3.64 (2H, overlap, H-9), 2.50 (1H, m, H-7), 2.00 (3H, s, H-29), 1.74 (3H, s, H-28), 1.72 (3H, s, H-24), 1.01 (3H, s, H-23); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 170.8 (C-11), 166.3 (C-5), 156.5 (C-18), 143.3 (C-27), 136.4 (C-20), 131.7 (C-2), 121.8 (C-16), 121.1 (C-15), 118.6 (C-26), 109.5 (C-17), 105.7 (C-14), 94.1 (C-19), 86.0 (C-25), 82.7 (C-12), 82.3 (C-22), 68.8 (C-13), 58.9 (C-6), 55.9 (OMe-18), 51.3 (C-9), 49.0 (C-3), 45.5 (C-21), 29.2 (C-7), 27.2 (C-24), 25.8 (C-23), 24.3 (C-29), 22.8 (C-8), 19.0 (C-28)。以上数据与文献(王聪 等, 2019)报道对照基本一致, 化合物 **17** 鉴定为 verruculogen。

化合物 **18**: 白色粉末状, 分子式为 $C_{22}H_{18}N_4O_4$, HRESIMS *m/z* 403.1399 $[M + H]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 8.23 (1H, brs, H-25), 7.85 (1H, td, *J* = 1.5, 7.6 Hz, H-21), 7.71 (1H, d, *J* = 8.1 Hz, H-22), 7.58 (2H, overlap, H-20, H-5), 7.48 (2H, d, *J* = 7.5 Hz, H-8), 7.42 (1H, td, *J* = 1.2, 7.6 Hz, H-7), 7.25 (1H, td, *J* = 1.0, 7.6 Hz, H-6), 5.6 (1H, brs, H-2), 4.59 (1H, q, *J* = 6.9 Hz, H-11), 3.28 (1H, overlap, H-13), 2.61 (1H, dd, *J* = 3.1, 13.0 Hz, H-13), 1.71 (3H, d, *J* = 7.0 Hz, H-12); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 173.6 (C-10), 162.4 (C-17), 148.7 (C-23), 140.4 (C-9), 137.4 (C-21), 136.0 (C-4), 131.3 (C-7), 128.7 (C-20), 128.0 (C-22), 127.7 (C-19), 127.0 (C-6), 125.7 (C-5), 123.7 (C-18), 116.2 (C-8), 84.6 (C-2), 78.0 (C-3), 61.4 (C-11), 40.3 (C-13), 14.7 (C-12)。以上数据与文献(王宇 等, 2017)报道对照基本一

致, 化合物 **18** 鉴定为 chaetominine。

化合物 **19**: 棕黄色油状物, 分子式为 $C_{22}H_{25}NO_8$, HRESIMS *m/z* 379.0767 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 5.99 (1H, m, H-9), 5.93 (1H, m, H-8), 5.68 (1H, d, *J* = 9.5 Hz, H-7), 4.94 (1H, d, *J* = 13.7 Hz, H-5a), 4.88 (1H, m, H-6), 4.26 (1H, d, *J* = 11.5 Hz, H-12), 3.87 (1H, d, *J* = 11.5 Hz, H-12), 3.12 (3H, s, H-11), 3.12 (1H, d, *J* = 15.8 Hz, H-10), 2.94 (1H, d, *J* = 15.8 Hz, H-10), 2.28 (3H, s, H-15), 2.25 (3H, s, H-13); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 168.4 (C-4), 167.8 (C-1), 134.0 (C-9a), 130.7 (C-7), 124.8 (C-8), 120.8 (C-9), 75.7 (C-6), 74.3 (C-3), 73.1 (C-10a), 70.5 (C-5a), 64.6 (C-12), 39.7 (C-10), 29.1 (C-11), 15.2 (C-13), 13.5 (C-15)。以上数据与文献 (Xu et al, 2017)报道对照基本一致, 化合物 **19** 鉴定为 bisdethiobis(methylthio)glitoxin。

化合物 **20**: 无色针状物, 分子式为 $C_{33}H_{44}O_8$, HRESIMS *m/z* 591.2935 $[M + Na]^+$。^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.31 (1H, d, *J* = 10.1 Hz, H-1), 5.92 (1H, d, *J* = 8.4 Hz, H-16), 5.86 (1H, d, *J* = 10.0 Hz, H-2), 5.23 (1H, brs, H-6), 5.11 (1H, t, *J* = 6.5 Hz, H-24), 2.77 (1H, m, H-4), 2.61 (1H, dd, *J* = 2.2, 12.9 Hz, H-9), 2.56 (1H, d, *J* = 12.3 Hz, H-13), 2.45 (3H, m, H-12, H-22), 2.26 (1H, d, *J* = 12.4 Hz, H-5), 2.21 (1H, dd, *J* = 9.1, 15.0 Hz, H-15), 2.11 (3H, s, $OCOCH_3$-6), 1.96 (3H, m, $OCOCH_3$-16), 1.90 (1H, d, *J* = 15.0 Hz, H-15), 1.69 (3H, m, H-27), 1.60 (3H, m, H-26), 1.44 (3H, m, H-19), 1.28 (3H, d, *J* = 6.9 Hz, H-28), 1.17 (3H, m, H-29), 0.93 (3H, m, H-18); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 209.0 (C-7), 201.5 (C-3), 174.0 (C-21), 170.9 ($OCOCH_3$-16), 169.0 ($OCOCH_3$-6), 157.4 (C-1), 147.8 (C-17), 132.8 (C-25), 130.4 (C-20), 128.0 (C-2), 123.1 (C-24), 73.9 (C-6), 73.5 (C-16), 52.8 (C-8), 49.4 (C-13), 47.4 (C-5), 46.8 (C-14), 41.9 (C-9), 40.8 (C-15), 40.5 (C-4), 38.3 (C-10), 28.9 (C-22), 28.4 (C-23), 27.7 (C-19), 26.1 (C-12), 25.9 (C-27), 24.1 (C-11), 20.9 ($OCOCH_3$-6), 20.8 ($OCOCH_3$-16), 18.5 (C-29), 18.1 (C-18), 17.9 (C-26), 13.2 (C-28)。以上数据与文献 (Fujimoto et al, 1996)报道对照基本一致, 化合物 **20** 鉴定为 helvolic acid。

化合物 **21**: 淡黄色油状物, 分子式为 $C_{29}H_{35}NO_9$, HRESIMS *m/z* 542.2370 $[M + H]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 9.03 (1H, d, *J* = 1.6 Hz, H-2′), 8.64 (1H, dd, *J* = 1.2, 4.8 Hz, H-6"), 8.28 (1H, dt, *J* = 1.8, 8.1 Hz, H-4"), 7.57 (1H, dd, *J* = 4.9, 8.1 Hz, H-5"), 6.83 (1H, s, H-5'), 4.96 (1H, d, *J* = 3.6 Hz, H-13), 4.78 (1H, dd, *J* = 5.1, 11.4 Hz, H-1), 3.84 (2H, overlap, H-11), 3.73 (1H, dd, J = 4.8, 11.3 Hz, H-7), 2.14 (1H, dt, *J* = 3.2, 13.1 Hz, H-3), 2.04 (3H, s, $OCOCH_3$-1), 2.03 (3H, s, $OCOCH_3$-11), 1.64 (3H, s, H-14), 1.45 (3H, s, H-12), 0.93 (3H, s, H-15); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 172.5 ($OCOCH_3$-1, $OCOCH_3$-11), 165.3 (C-2'), 164.6 (C-2"), 158.1 (C-4'), 151.9 (C-6"), 147.3 (C-5"), 134.9 (C-4"), 129.3 (C-6'), 125.5 (C-3"), 104.4 (C-3'), 101.1 (C-5'), 86.7 (C-6), 78.3 (C-7), 75.2 (C-1), 66.1 (C-11), 60.4 (C-13), 55.3 (C-5), 46.8 (C-9), 41.8 (C-10), 39.2 (C-4), 37.1 (C-3), 28.8 (C-8), 23.8 (C-2), 21.0 ($OCOCH_3$-1), 20.7 ($OCOCH_3$-11), 18.0 (C-12), 15.9 (C-14), 13.4 (C-15)。以上数据与文献(Lan et al, 2016)报道对照基本一致, 化合物 **21** 鉴定为 7-deacetylpyripyropene A。

化合物 **22**: 白色粉末状物, 分子式为 $C_{19}H_{23}N_3O_2$, HRESIMS *m/z* 348.1682 $[M + Na]^+$。^{1}H-NMR (400 MHz, CD_3OD) *δ*: 7.43 (1H, d, *J* = 7.9 Hz, H-15), 7.07 (1H, s, H-9), 6.93 (1H, t, *J* = 7.5 Hz, H-14), 6.86 (1H, d, *J* = 7.0 Hz, H-13), 5.39 (1H, m, H-18), 4.26 (1H, td, *J* = 1.1, 4.2 Hz, H-2), 3.69 (1H, dq, *J* = 1.2, 7.0 Hz, H-5), 3.52 (2H, d, *J* = 7.2 Hz, H-17), 3.44 (1H, dd, *J* = 4.0, 14.6 Hz, H-7), 3.14 (1H, dd, *J* = 4.4, 14.6 Hz, H-7), 1.74 (3H, s, H-20), 1.73 (3H, s, H-21), 0.35 (3H, d, *J* = 7.1 Hz, H-22); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 170.7 (C-6), 169.5 (C-3), 136.5 (C-11), 133.7 (C-19), 129.2 (C-16), 125.7 (C-12), 125.7 (C-9), 123.4 (C-18), 121.7 (C-13), 120.5 (C-15), 117.8 (C-14), 109.7 (C-8), 57.5 (C-2), 51.8 (C-5), 30.9 (C-7), 30.5 (C-17), 25.9 (C-21), 19.9 (C-22), 17.9 (C-20)。以上数据与文献(Wang et al, 1995)报道对照基本一致, 化合物 **22** 鉴定为 terezine D。

2.2 活性测试结果

2.2.1 细胞毒活性测试结果

对化合物进行抗肿瘤活性筛选发现化合物 **6** 对人肝癌细胞(HepG2)、人肺癌细胞(A549)、人直肠癌细胞(HCT116)都具有一定的细胞毒活性, IC_{50} 值如表 1 所示。

表 1 化合物 6 细胞毒活性结果

Tab. 1 Cytotoxic activity results of compound 6

编号	名称	IC_{50} /(μmol·L^{-1})			
		HepG2	A549	HCT116	L02
1	**6**	35.86 ± 1.43	8.26 ± 1.89	17.04 ± 0.68	27.51 ± 2.84
P1	苏尼替尼	12.6 ± 3.14	9.4 ± 0.76	3.79 ± 0.2	20.6 ± 0.48
P2	盐酸阿霉素	0.66 ± 0.03	1.46 ± 0.72	0.03 ± 0.01	15.23 ± 1.24

2.2.2 抑菌活性测试结果

对 22 个单体化合进行抑菌活性筛选, 发现除化合物 **1**、**3**、**20** 外其他单体化合物对金黄色葡萄球菌均没有抑菌活性, 且所有化合物对耐甲氧西林的金黄色葡萄球菌均无明显抑制活性。化合物 **1**、**3**、**20** 的最小抑菌浓度(minimal inhibitory concentration, MIC)如表 2 所示。

表 2 化合物 1、3、20 抑制金黄色葡萄球菌活性结果
Tab. 2 Inhibition of *Staphylococcus aureus* activity results of compound 1, 3 and 20

名称	MIC/ (μg·mL^{-1})
1	64.0
3	8.0
20	1.0
环丙沙星	0.4

2.2.3 NPC1L1 蛋白结合活性测试结果

NPC1L1 作为胆固醇的特异性转运蛋白, 越来越受到人们的关注。对化合物 **1**—**20** 和化合物 **22** 进行 NPC1L1 蛋白结合活性测试, 使用阳性药为依折麦布, 结果显示化合物 **14** 与 NPC1L1 蛋白具有相互作用(图 4)。

3 讨论

目前, 从 *Aspergillus fumigatus* 中分离得到的化合物种类多为生物碱类、喹啉类衍生物和烟曲霉素类等。除此之外, 还从此菌株中首次分离得到吡喃酮类化合物(郭思雨 等, 2020)、酚酸类(钱诗筠 等, 2020)和肽类化合物(李基兴 等, 2020)。本文从海洋动物内生菌 *Aspergillus fumigatus* DL-p0m-g2 中分离得到 22 个

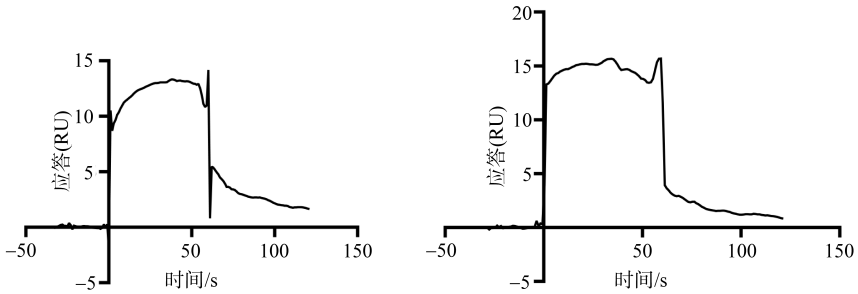

图 4 化合物 **14** 和依折麦布(ezetimibe)与 NPC1L1 相互作用的结合传感图
Fig. 4 Binding sensorgram for compound 14 and ezetimibe interaction with immobilized NPC1L1

化合物, 其中主要为生物碱类化合物, 丰富了烟曲霉代谢产物的种类。

据文献报道, 化合物 **19** 对 P388 小鼠白血病细胞有细胞毒活性, IC_{50} 值为 0.11μmol·L^{-1} (Sun et al, 2012); 化合物 **18** 对人类白血病 K562 和结肠癌 SW1116 细胞系的细胞毒性大于联合检测的阳性药–氟尿嘧啶 (Jiao et al, 2006)。除此外, 还发现化合物 **3**、**17** 和 **20** 有抑制植物致病菌的活性等 (Li et al, 2012)。本文对分离得到的 22 个单体化合物进行抑菌活性测试发现所有化合物对耐甲氧基西林金黄色葡萄球菌均无明显活性, 但化合物 **1**、**3** 和 **20** 对金黄色葡萄球菌均有抑菌活性, 其中化合物 **20** 已经作为抑菌药物被开发利用, 化合物 **1** 和化合物 **3** 的最小抑菌浓度(MIC)分别为 64μg·mL^{-1} 和 8μg·mL^{-1}。对所有化合物进行硫氧还蛋白还原酶活性测试发现所有化合物均无相应活性。化合物 **6** 在本次研究中对其进行细胞毒活性实验中首次发现其具有一定的人肝癌细胞 (HepG2)、人肺癌细胞(A549)、人直肠癌细胞(HCT116)抑制活性, IC_{50} 值分别为(35.86±1.43)μmol·L^{-1}、(8.26±1.89)μmol·L^{-1}和(17.04± 0.68)μmol·L^{-1}, 其对 A549 的抑制活性与阳性药苏尼替尼相当。同时测试发现化合物 **6** 对于人正常肝细胞的 IC_{50} 值要高于苏尼替尼和盐酸阿霉素, 这表明其安全性可能要优于这两种阳性药, 这使得其为后续药用价值的开发提供一定的参考。此外, 表面等离子共振测试显示化合物 **14** 和 NPC1L1 之间的相互作用, 这表明化合物 **14** 可能是潜在的 NPC1L1 抑制剂, 显示出其在抑制胆固醇吸收方面的潜力。

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