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Review 综述

海洋曲霉来源的新天然产物

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摘要：海洋真菌由于其遗传背景复杂、代谢产物种类多且产量高，已成为海洋微生物新天然产物的主要来源，从我们对2010–2013年初的海洋微生物来源新天然产物的统计来看，研究最多的是曲霉属(*Aspergillus*)真菌，占海洋真菌来源新天然产物的31%。本文从菌株来源、化合物结构及其生物活性等方面，综述了自1992年第一个海洋曲霉天然产物到2014年8月已报道的共512个海洋曲霉来源的新天然产物。这些海洋天然产物具有丰富的化学多样性，且36%的化合物表现出细胞毒、抑菌、抗氧化和抗寄生虫等生物活性；含氮化合物是其主要的结构类型、约占曲霉源海洋天然产物总数的52%，也是出现活性化合物比例最高的结构类型、约40%的含氮化合物具有生物活性，其中脱氢二酮哌嗪生物碱halimide的化学衍生物plinabulin已结束II期临床研究，并于2015年第三季度开始在美国和中国进行III期临床研究，用于治疗转移性的晚期非小细胞肺癌。

关键词：海洋真菌，曲霉，天然产物，化学结构，生物活性，来源

海洋真菌由于其遗传背景复杂、代谢产物种类多、产量高，成为海洋微生物新天然产物的主要来源，作者对2010–2013年初的海洋微生物来源新天然产物的统计表明，研究最多的真菌属是曲霉(*Aspergillus*)，占海洋真菌新天然产物的31%[1]。海洋曲霉源天然产物的研究始于1992年，Shinggu等报道了首例海洋曲霉来源的新天然产物fumiquinazolines A–C (**149–151**)[2]；截止到2014年8月，已报道512个海洋曲霉来源的新天然产物。其结构类型多样(包括聚酮、生物碱、萜类、甾体、卤代物、脂肪酸、肽类、糖苷等)，且有多种生物活性(包括抗癌、抑菌、自由基清除和抗寄生虫等)。值得一提的是，由海洋曲霉天然产物halimide(**301**)[3−4]衍生而来的plinabulin (NPI-2358)[5]是一种血管阻断剂，作用于肿瘤细胞，影响微管蛋白解聚；目前plinabulin已结束II期临床研究、开始在美国和中国进行III期临床研究，用于治疗转移性的晚期非小细胞肺癌(NSCLC)[6]，成为20个海洋药物之一，也是唯一的海洋曲霉菌来源的药物[7]。由此可见海洋曲霉是海洋天然产物

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乃至新药发现的重要资源，本文将综述这些海洋曲霉新天然产物的菌株来源、结构及其生物活性。

1 海洋动物来源的曲霉天然产物

1.1 海绵来源的曲霉天然产物

氯代物chlorocarolides A(**1**)和B(**2**)来源于赫曲霉*Aspergillus cf.ochraceus* 941026[8]。1株黑曲霉*Aspergillus niger*代谢产生二酮哌嗪(环缩二氨酸)的二聚体asperazine(**3**)，该化合物可以选择性抑制人白血病细胞L1210、C38以及人结肠癌细胞H116或者CX1细胞株[9]。化合物asperic acid(**4**)是从另外1株黑曲霉*A. niger* 94-1212的次生代谢产物中分离得到[10]。花斑曲霉*A. versicolor* (Vuill) Triab代谢产生六元色酮的衍生物aspergiones A-F(**5**–**10**)[11]以及aspergillone(**11**)、aspergillodiol(**12**)、aspergillol(**13**)和12-acetyl-aspergillol(**14**)[12]。3个含氯的抗生素**15**–**17**来自孔曲霉*A. ostianus* TUF 01F313，均对大西洋鲁杰氏菌*Ruegeria atlantica*有抑制活性，其中化合物**16**和**17**在25 μg/disc浓度下的抑菌圈直径分别为10.1 mm和10.5 mm，而化合物**15**在5 μg/disc时即表现出较好的抑制活性(抑菌圈直径为12.7 mm)，另外该化合物还有微弱的金黄色葡萄球菌抑制活性(25 μg/disc时抑菌圈直径为10.2 mm)[13]。进一步研究还分离到aspinotriols A(**18**)和B(**19**)、aspinonediol(**20**)[14]，aspergillides A–C(**22**–**24**)[15]及其七环生物碱化合物21-hydroxystephacidin A(**25**)[16](图1)。并确定了dihydroaspyrone(**21**)的绝对构型[14]，其中化合物**22**–**24**对L1210细胞的LD_{50}分别为2.1、71.0和2.0 μg/mL[15]。

Circumdatins D–F(**26**–**28**)分离自另外一株孔曲霉*A. ostianus* IBT 12704[17]。混源萜tropolactones A–D(**29**–**32**)由曲霉属*Aspergillus* sp. CNK-371代谢产生，其中化合物**29**–**31**对HCT-116细胞有微弱的抑制活性，IC_{50}分别为13.2、10.9和13.9 μg/mL[18]。棘孢曲霉*A. aculeatus* CRI323-04代谢产生aspergillusol A(**33**)[19]和asperaculin A(**34**)[20]，其中化合物**33**对酵母和嗜热脂肪芽孢杆菌来源的α-糖苷酶有抑制活性，IC_{50}值分别为465和1060 μmol/L[19]。化合物**35**–**37**来自另一株棘孢曲霉*A. aculeatus* CRI322-03[21]。曲霉*A. insuetus*代谢产生Terretonins E(**38**)和F(**39**)，均具有哺乳动物线粒体呼吸链抑制作用，IC_{50}值分别为3.90和2.97 μmol/L[22]。菌核曲霉*A. sclerotiorum* Huber SP080903f04代谢产生*N*-去甲棕曲菌素JBIR-15(**40**)[23]。焦曲霉*A. ustus* 8009代谢产生7个补身烷倍半萜化合物**41**–**47**，其中**44**、**45**对多种肿瘤细胞有细胞毒活性，尤其是**45**对L5178Y细胞株的EC_{50}值为0.6 μg/mL[24]。蛇孢甲壳素**48**–**52**及吡咯生物碱**53**、**54**也来自同一株菌[25]。脂肽fellutamide C(**55**)(图1)来自于*A. versicolor*，对SK-MEL-2、XF498和HCT15的IC_{50}分别为5.1、3.9和3.1 μmol/L[26]。

JBIR-74(**56**)和JBIR-75(**57**)来自*Aspergillus* sp. fs14[27]。混源萜insuetolides A–C(**58**–**60**)和补身烷倍半萜**61**来自奇突曲霉*A. insuetus* OY-207，其中化合物**58**有抑制粗糙链孢霉菌的活性、MIC为140 μmol/L，化合物**60**和**61**对人MOLT-4细胞有细胞毒活性、50 mg/mL时的抑制率分别为51%和55%[28]。脂肽fellutamide F(**62**)来自*A. versicolor* PF10M，对多株人癌细胞的EC_{50}为0.13–1.81 μg/mL[29]。*Aspergillus* sp.代谢产生4个没药烷倍半萜aspergiterpenoid A(**63**)、(–)-sydonol(**64**)、(–)-sydonic acid(**65**)和化合物**66**，其对金黄色葡萄球菌、枯草芽孢杆菌、蜡状芽孢杆菌等有抑菌活性(MIC为1.25–20.0 μmol/L)[30]。没药烷倍半萜二聚体disydonols A–C(**67**–**69**)也来自同一株菌，其中化合物**67**和**69**对HepG-2和Cashi细胞均有细胞毒活性(IC_{50}分别为9.31/12.40 μg/mL和2.91/10.20 μg/mL)[31]。缩酚酸环醚**70**–**72**、二芳基醚**73**及吡喃酮**74**来自爪甲曲霉*A. unguis* CRI282-03，其中化合物**70**–**72**均有芳香酶抑制活性(IC_{50}分别为2.2、

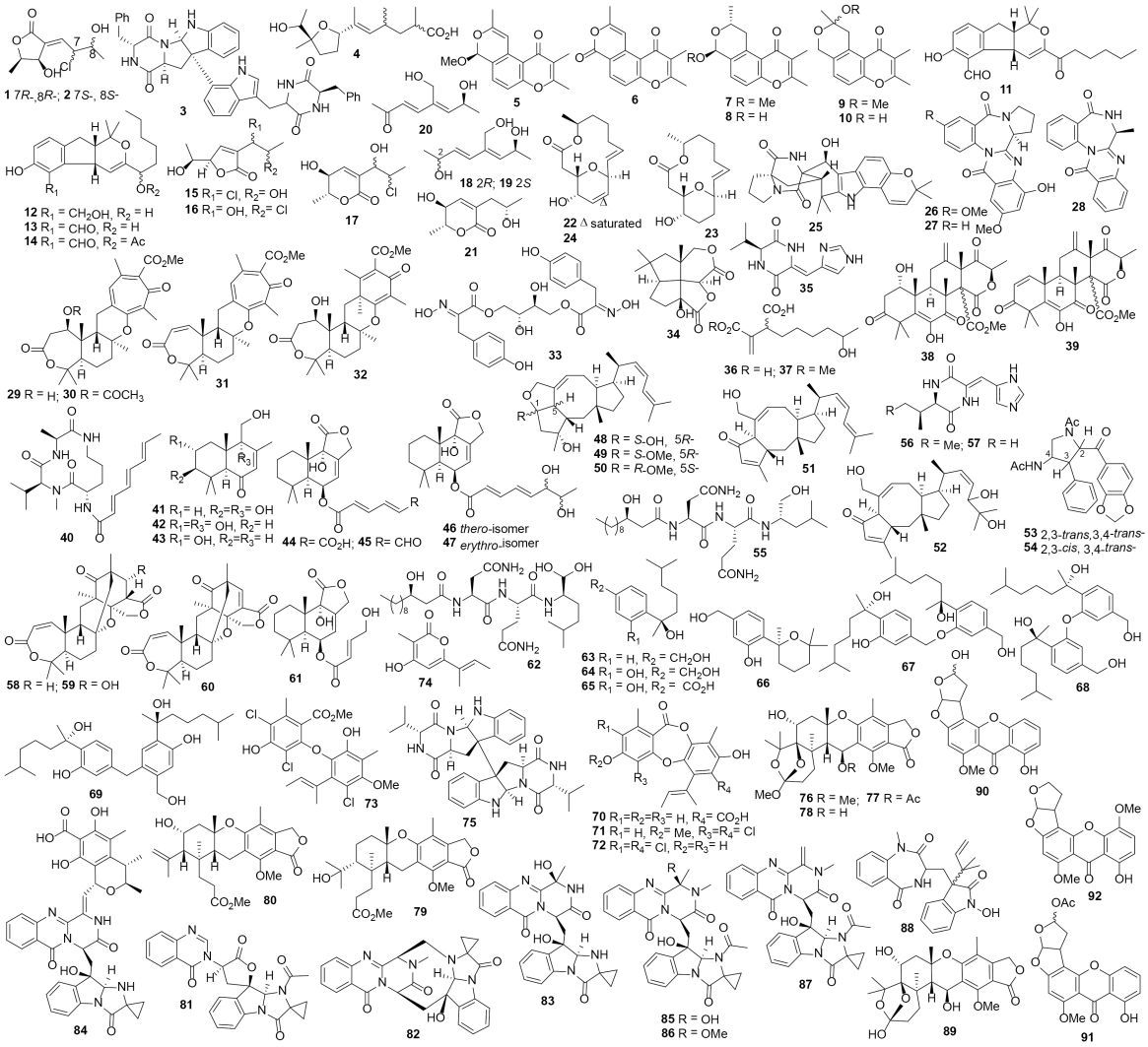

图 1. 化合物1–92的结构

Figure 1. Structures of compounds **1–92**.

4.1和0.7 μmol/L)，且**70**和**71**在黄嘌呤氧化测试中表现出自由基清除活性(IC_{50}分别为16.0和<15.6 μmol/L)[32]。二酮哌嗪二聚体eurocristatine(**75**)产自冠突散囊菌*Eurotium cristatum* KUFC 7356[33]，*E. cristatum*是小冠曲霉*A. cristatellus*的有性型。1株*Aspergillus* sp.代谢产生austalides M–Q(**76**–**80**)[34]、tryptoquivaline K (**81**)和 fumiquinazolines K–P (**82**–**87**)[35]以及生物碱**88**和混源萜austalide R(**89**)[36](图1)。其中化合物**81**在10 μg/mL浓度下对小鼠淋巴瘤细胞L5178Y的抑制率为23%[35]，化合物**88**能选择性抑制弧菌(*Vibrio* sp.)生长，而**89**则广谱抗菌、其对*Vibrioharveyi*、*V. proteolyticus*、*V. carchariae*、*Shewanella putrefaciens*、*Roseobacter litoralis*、*Pseudoalteromonas elyakovii*、*P. irgensii*和*Halomonas aquamarina*均有抑制作用[36]。

杂色曲霉*A. versicolor* MF359代谢产生3个柄曲霉素**90**–**92**(图1)，其中化合物**92**对金黄色葡萄球菌和枯草芽孢杆菌均有抑制活性，MIC分别为12.500 μg/mL和3.125 μg/mL[37]。黑曲霉*A. niger*代谢产生3,3-bicoumarin bicoumanigrin(**93**)、

aspernigrins A和B(**94**、**95**)以及pyranonigrins A–D(**96**–**99**)(图2)；化合物**93**在浓度1–20 μg/mL时具有人肿瘤细胞毒活性，化合物**94**、**95**在浓度为50 μg/mL有轻微的肿瘤细胞毒活性；化合物**95**具有神经保护作用[38]。Nafuredin(**100**)产自黑曲霉*Aspergillus niger* FT–0554，表现出猪蛔虫*Ascarissuum*延胡索酸还原酶(NFRD)抑制活性，其IC_{50}为12 nmol/L[39]。

1.2 珊瑚来源的曲霉天然产物

土曲霉*A. terreus*HKI0499代谢产生aspernolides A、B(**101**、**102**)[40]。(+)-methyl sydowate(**103**)、7-deoxy-7,14-didehydrosydonic acid(**104**)和7-deoxy-7,8-didehydrosydonic acid(**105**)(图2)来自一株*Aspergillus* sp.，其中化合物**103**可抑制金黄色葡萄球菌、100 μg/mL浓度下抑菌圈直径为11 mm[41]。Aspergilones A、B(**106**、**107**)来自同一株菌，其中化合物**106**对HL-60、MCF-7和A549细胞的IC_{50}分别为3.2、25.0和27.0 μg/mL，且有抗污损作用、EC_{50}为7.7 μg/mL[42]。*A. sydowii* PSU-F154代谢产生倍半萜aspergillusenes A (**108**)、B (**109**)和

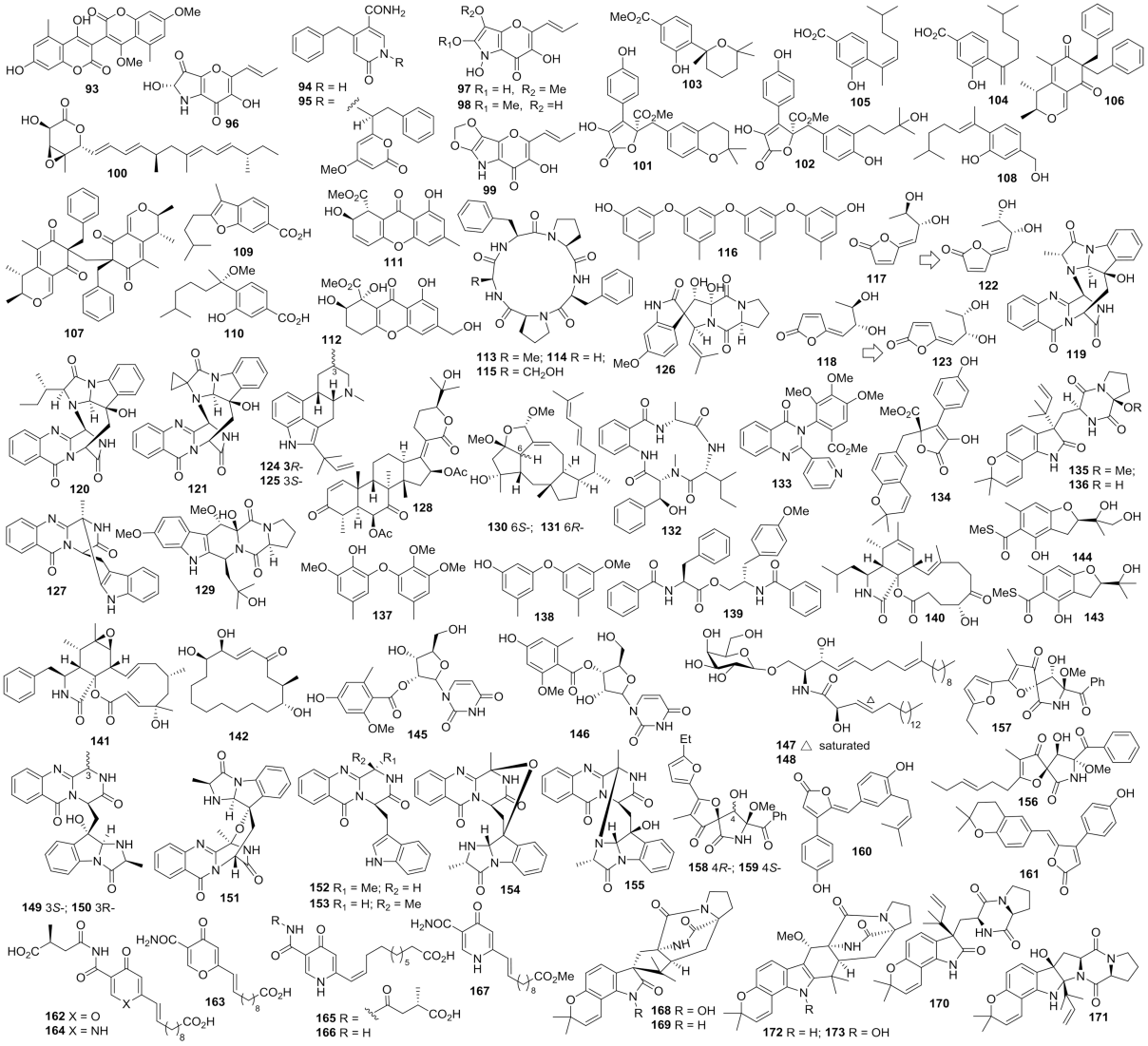

图 2. 化合物93–173的结构

Figure 2. Structures of compounds **93–173**.

methylsydonic acid (**110**)，以及氧杂蒽酮aspergillusones A(**111**)和B(**112**)[43]。*A. versicolor* LCJ-5-4代谢产生环五肽versicoloritides A–C (**113**–**115**)、地衣酚四聚体tetraorcinol A(**116**)、内酯versicolactones A、B(**117**、**118**)[44]以及喹唑啉酮生物碱cottoquinazolines B–D(**119**–**121**)[45]，其中化合物**116**有弱的DPPH自由基清除活性(IC_{50}为67 μmol/L)，化合物**121**对白色念珠菌有中等抑菌活性(MIC 22.6 μmol/L)；化合物**116**[46]、**121**[47]被NPR选为热点化合物；经过全合成研究，化合物versicolactones A和B的结构分别修正为**122**和**123**[48]。烟曲霉*A. fumigates*代谢产生新吲哚生物碱**124**和**125**[49]。二酮哌嗪生物碱spirotryprostatin F(**126**)[50]和fumiquinazoline K(**127**)以及萜类化合物**128**[51]来自另一株烟曲霉*A. fumigatus* KMM 4631，其中化合物**126**在较低浓度(0.1–1.0 μmol/L)时可以促进大豆、荞麦和小麦发芽[50]。吲哚生物碱cyclotryprostatin E(**129**)来自萨氏曲霉*A. sydowii* SCSIO 00305[52]。内生曲霉*Aspergillus* sp.代谢产生二倍半萜ophiobolin *O*(**130**)和6-*epi*-ophiobolin *O*(**131**)，对P388均有较强的细胞毒活性，IC_{50}分别为4.7和9.3 μmol/L[53]，且化合物**130**可以使MCF-7周期停滞于G_0/G_1期(IC_{50}为17.86 μmol/L)、并通过MAPK途径使MCF-7呈现时间和剂量依赖的细胞凋亡[54]。土曲霉菌*A. terreus* SCSGAF0162代谢产生asperterrestide A(**132**)、terremide C(**133**)和aspernolide E(**134**)(图2)，化合物**132**对组织细胞淋巴瘤细胞U937和急性淋巴母细胞白血病细胞MOLT-4的IC_{50}值分别是6.4和6.2 μmol/L，对流感病毒H1N1和H3N2的IC_{50}值分别是15.0 μmol/L和8.1 μmol/L[55]。

曲霉菌*Aspergillus* sp. XS-20090066代谢产生吲哚生物碱17-*epi*-notoamidesQ、M(**135**、**136**)和苯醚衍生物cordyols D、E(**137**、**138**)[56]。曲霉菌*A. elegans*ZJ-2008010代谢产生4′-OMe-asperphenamate (**139**)和细胞松弛素aspochalasins A_1和Z_{24}(**140**、**141**)，其中化合物**139**对表皮葡萄球菌*S. epidermidis*表现出了选择性的抑制活性(MIC值为10 μmol/L)[57]。曲霉菌*Aspergillus* sp. SCSGAF 0076代谢产生了大环内酯aspergillide D(**142**)[58]。赤散囊菌*Eurotium rubrum* SH-823代谢产生硫代物eurothiocins A和B(**143**和**144**)，抑制α-糖苷酶的IC_{50}值分别为17.1 μmol/L和42.6 μmol/L[59]。杂色曲霉*A. versicolor*代谢产生核苷类化合物**145**和**146**，对表皮葡萄球菌有选择性抑制作用、MIC值为12.5 μmol/L，对卤虫有致死活性，LC_{50}值为8.4 μg/mL[60]。曲霉菌*A. flavipes*代谢产生脑苷脂flavicerebrosides A和B(**147**和**148**)(图2)，均对KB细胞有细胞毒活性，IC_{50}值分别为20.7 μg/mL和14.3 μg/mL[61]。

1.3 其它动物来源的曲霉天然产物

Fumiquinazolines A–C(**149**–**151**)来自烟曲霉*A. fumigatus* OUPS-T106B-5，有中等细胞毒活性[2] (Numata et al. 1992)，其结构通过全合成确证[62-63]；该菌株还产生fumiquinazolines D–G(**152**–**155**)[64]、cephalimysin A(**156**)[65]及cephalimysins B–D(**157**–**159**)[66]，其中化合物**149**、**150**及**152**–**155**对P388细胞有细胞毒活性，ED_{50}分别为6.1、16.0、13.5、13.8、14.6和17.7 μg/mL[64]，化合物**156**对P388和HL-60细胞的IC_{50}值分别为15.0 nmol/L和9.5 nmol/L[65]，化合物**158**和**159**对HL-60的IC_{50}分别为58.4和48.7 μmol/L[66]。曲霉*A. terreus* OUCMDZ-1925代谢产生rubrolides R(**160**)和S(**161**)，抑制K562细胞的IC_{50}分别为12.8和10.9 μmol/L，化合物**161**还具有抗H1N1病毒的活性、IC_{50}为87.1 μmol/L，化合物**160**具有ABTS和DPPH自由基清除活性，IC_{50}分别为1.33 mmol/L和43.4 μmol/L[67]。曲霉*Aspergillus* sp. MF275代谢产生himeic acids A–C(**162**–**164**)[68]和himeic acids E–G(**165**–**167**)[69] (图2)，其中化合物**162**具有泛素激活酶E1抑制活性，50 μmol/L时的抑制率为65%[68]。

曲霉*Aspergillus* sp. MF297-2代谢产生notoamides A–D(**168**–**171**)(图2)，化合物**168**–**170**对Hela及

L1210细胞的IC_{50}值为22–52 μg/mL[70]；该菌株还代谢产生notoamides F–K(**172**–**177**)(图3)，其中**175**对Hela有弱活性、IC_{50}为21 μg/mL[71]。随后，又从该菌株的代谢产物中相继分离鉴定了notoamide E(**178**)和notoamides E_2–E_4(**179**–**181**)[72]、(–)-versicolamide B(**182**)和notoamides L–N(**183**–**185**)[73]、notoamides O–R(**186**–**189**)[74]以及notoamide S(**190**)[75]。具有倍半萜母核的吡啶生物碱pileotin A(**191**)则来自烟曲霉*A. fumigatus* OUPS-N138[76]。变色曲霉*A. versicolor* OUPS-N136代谢产生吲哚二萜anthcolorins A–F(**192**–**197**)(图3)，其中**193**–**195**对P388细胞的IC_{50}值在2.2–8.5 μmol/L之间[77]。

Spiculisporic acids B–D(**198**–**200**)来自内生曲霉*Aspergillus* sp. HDf2[78]。环肽clavatustides A、B(**201**、**202**)[79]和C(**203**)[80]来自1株棒曲霉*A. clavatus* C2WU，其中**201**和**202**呈现剂量依赖的肝癌细胞系(HCC)增殖抑制活性。此外，**201**、**202**还可将人肝癌细胞HepG-2的细胞周期阻滞在

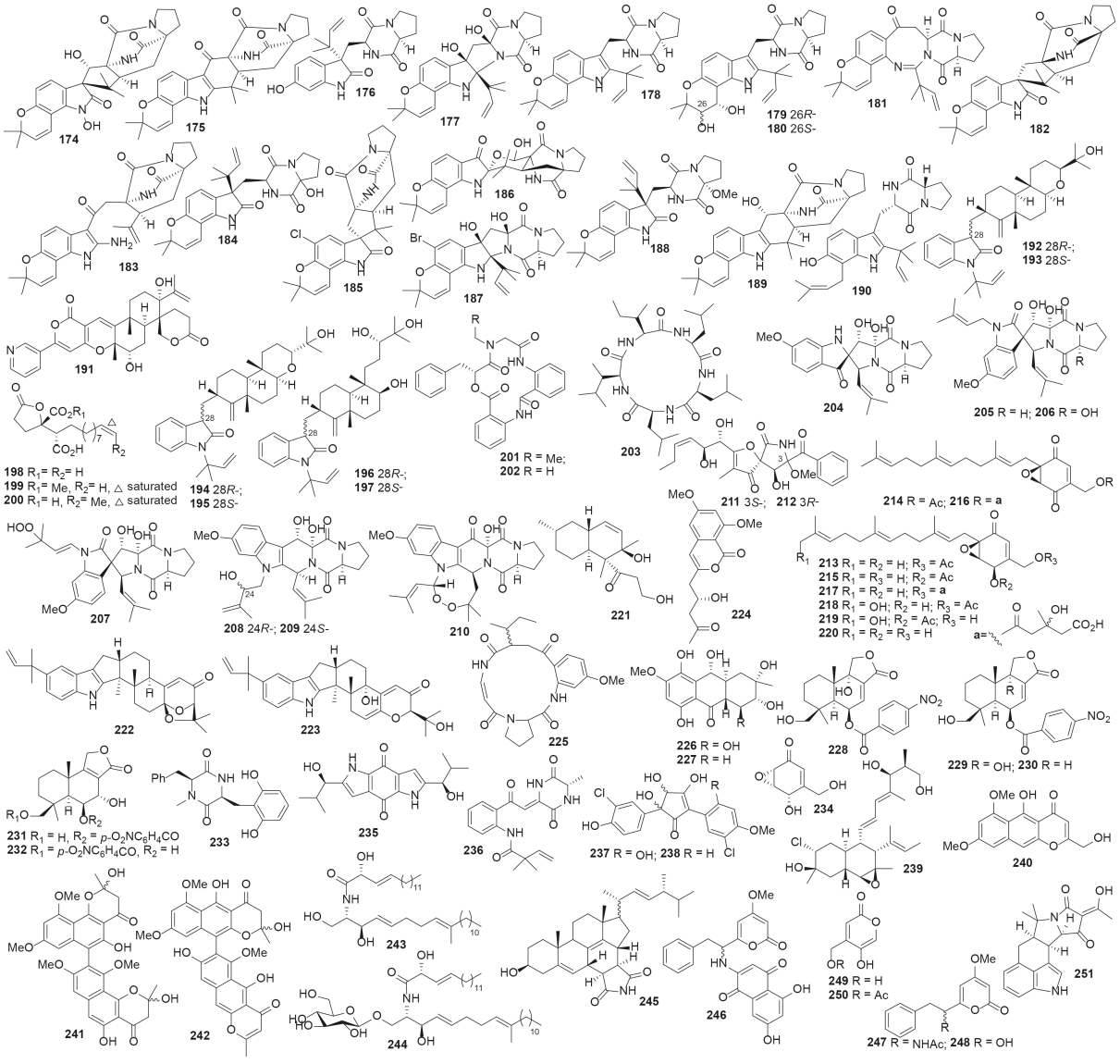

图 3. 化合物174–251的结构

Figure 3. Structures of compounds **174–251**.

G_1期[79]。化合物**204**、spirotryprostatins C–E (**205–207**)、fumitremorgin B的衍生物(**208**、**209**)和13-oxoverruculogen(**210**)来自一株烟曲霉 *A. fumigatus*，均有细胞毒活性，尤其是化合物**207**对MOLT-4、HL-60和A549细胞的IC_{50}分别为3.1、2.3、3.1 μmol/L，**208**对HL-60、BEL-7402细胞的IC_{50}分别为3.4、7.0 μmol/L，**209**和**210**对HL-60细胞的IC_{50}分别为5.4 μmol/L和1.9 μmol/L[81]。另一株烟曲霉*A. fumigatus* WFZ–25代谢产生螺内酰胺pseurotins A_1和A_2(**211**和**212**)[82]。Yanuthones A–E(**A213**–**A217**)、1-hydroxyyanuthones A、C(**218**、**219**)及22-deacetylyanuthone A(**220**)(图3)产自黑曲霉*A. niger* F97S11[83]。

曲霉菌*Aspergillus* sp. MF297代谢产生多聚乙酰aspermytin A(**221**)，在50 μmol/L时**221**可诱导小鼠嗜铬细胞瘤PC-12细胞神经轴突生长[84]。黄曲霉*A. flavus* OUCMDZ-2205代谢产生吲哚二萜**222**、**223**和异香豆素**224**，其中化合物**222**对金黄色葡萄菌的MIC值为20.5 μmol/L，**在**10 μmol/L时**222**和**223**可将A549细胞阻滞在S期，化合物**222**对PKC-β的IC_{50}值为15.6 μmol/L[85]。柄曲霉*A. flavipes* Z-4代谢产生环肽**225**[86](图3)。

2 植物来源的曲霉天然产物

2.1 海藻来源的曲霉天然产物

Tetrahydrobostrycin(**226**)和1-deoxytetrahydrobostrycin (**227**)来自曲霉*Aspergillus* sp. 05F16[87]。倍半萜insulicolide A(**228**)来自胰岛曲霉*A. insulicola*[88]。杂色曲霉*A. versicolor* CNC 327代谢产生化合物**229**–**232**(图3)，其中**229**表现出较强细胞毒活性，对HCC-2998、HCT-116、BT-549和SNB-75细胞的LC_{50}分别为0.53、0.44、0.27和0.44 μg/mL，其对5株肾肿瘤细胞(786-0、ACHN、CAK-1、TK-10和UO-31)表现出选择性抑制活性、LC_{50}约为0.47–0.57 μg/mL[89]。曲霉*Aspergillu* sp.代谢产生mactanamide(**233**)，具有抑制白色念珠菌活性[90]。Parasitenone(**234**)来自一株曲霉*A. parasiticus* MFA153[91]。手性双吡咯并蒽terreusinone(**235**)产自土曲霉*A. terreus* MFA 460，具有防护紫外线A的活性，ED_{50}值为70 μmol/L[92]。曲霉菌*Aspergillus* sp. MFA 212代谢产生二酮哌嗪golmaenone(**236**)，具有防护紫外线A的活性(ED_{50}值为90 μmol/L)和DPPH自由基清除活性，IC_{50}值为20 μmol/L[93]。Sydowins A、B(**237**、**238**)来自萨氏曲霉*A. sydowii*[94]。从曲霉*Aspergillus* sp. MFB024的代谢产物中发现1个多氧萘氢衍生物**239**(chlorofusarielin B)，其对金黄色葡萄球菌、甲氧西林耐药葡萄球菌、多药耐药葡萄球菌具有一定的抑制作用，其MIC均为62.5 μg/mL [95]。Nigerasperones A–C(**240**–**242**)为黑曲霉*A. niger* EN-13的产物，化合物**242**对白色念珠菌的抑菌圈为9 mm(两性霉素的抑菌圈为12 mm)、对DPPH自由基的清除率为41.6%[96]。此菌还代谢产生asperamides A和B(**243**和**244**)[97]、ergosterimide (**245**)[98]、**246**[99]、isopyrophen(**247**)和aspergillusol (**248**)[100]，其中化合物**243**对白色念珠菌的抑菌圈为12 mm[97]。

化合物**249**、**250**[101]和*iso*-α-CPA(**251**)(图3)[102]产自黄曲霉*A. flavus*c-f-3，化合物**251**对A549细胞的IC_{50}值为42.2 μmol/L[102]。赭曲霉*A. ochraceus* EN-31代谢产生2-hydroxycircumdatin C(**252**)[103]、7-nor-ergosterolide(**253**)和化合物**254**、**255**[104](图4)，化合物**252**具有明显的DPPH自由基清除作用，其IC_{50}值为9.9 μmol/L[103]。吲哚二萜asporyzin A–C(**256**–**258**)[105]和甾类asporyergosterol (**259**)[106]来自米曲霉*A. oryzae*cf-2，其中化合物**A258**有较强的大肠杆菌抑制作用(每孔30 μg给药时，抑菌圈为8 mm)[105]。JBIR-81(**260**)和JBIR-82(**261**)来自曲霉*Aspergillus* sp. SpD081030G1f1，是有效的自由基清除剂(对N18–RE–105细胞的L-谷氨酸毒性的EC_{50}分别为0.7和1.5 μmol/L，强于对照组的8.8 μmol/L)[107]。脑苷脂类flavusides

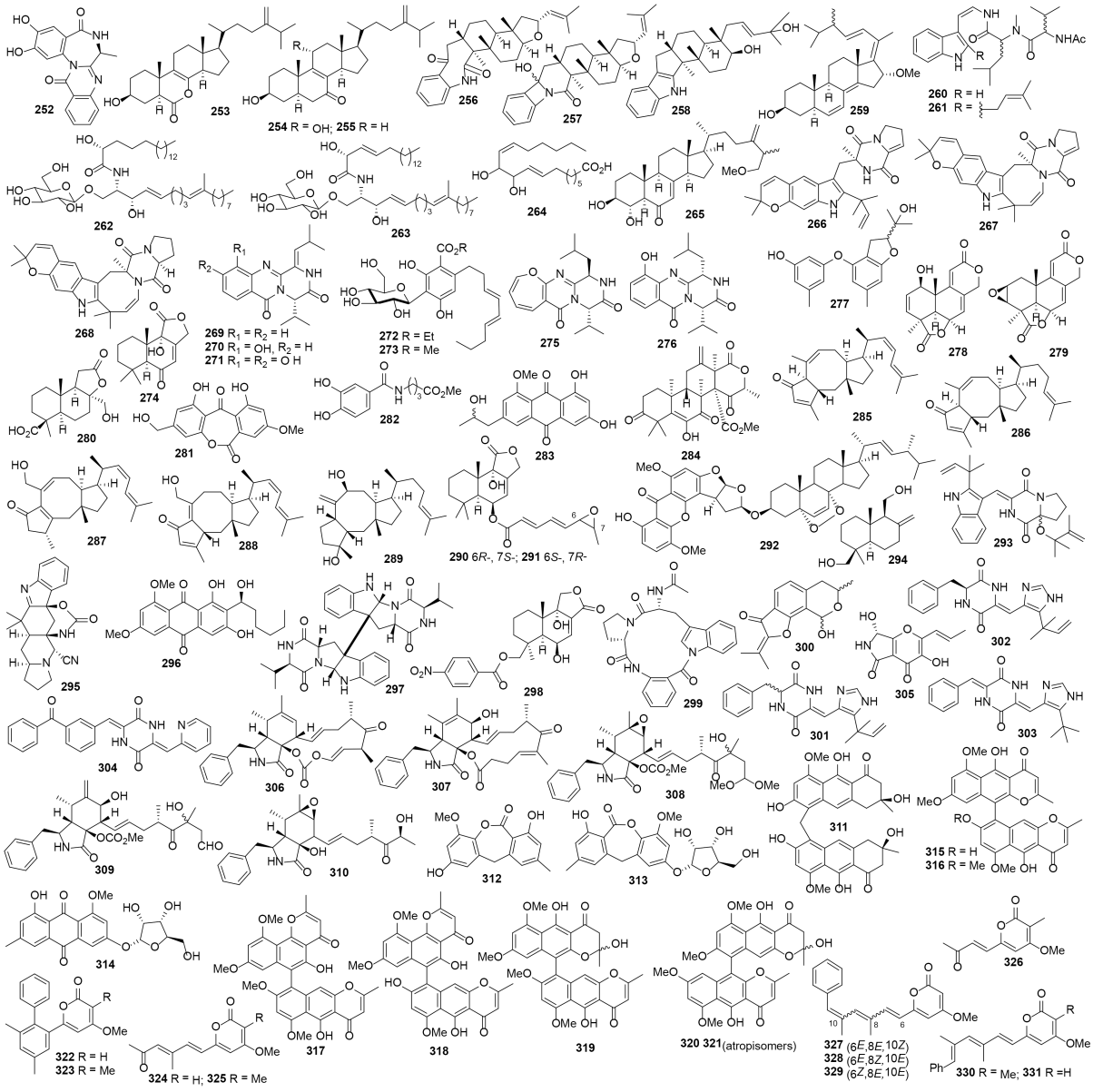

图 4. 化合物252–331的结构

Figure 4. Structures of compounds **252–331**.

A(**262**)和B(**263**)来自黄曲霉*A. flavus*，抑制金黄色葡萄球菌的MIC为15.6 μg/mL，对MRSA的MIC约为31.2 μg/mL[108]。脂肪酸**264**和甾体**265**来自另一株黄曲霉*A. flavus* cf-5[109]。肉色曲霉*A. carneus* KMM4638代谢产生吲哚生物碱carneamides A–C(**266–268**)、喹唑酮生物碱carnequinazolines A–C(**269–271**)、芳基糖苷carnemycins A、B(**272**、**273**)及倍半萜**274**[110]。喹唑啉酮衍生物**275**、**276**和二苯醚衍生物**277**也来自该菌[111]。二萜asperolides A–C(**278–280**)[112]、wentiquinone C(**281**)和**282**[113](图4)来自温特曲霉*A. wentii* EN-48，其中化合物**278**和**279**对多种肿瘤细胞有弱的细胞毒活性(IC_{50}为35–97 μmol/L)、化合物**282**有明显的DPPH自由基清除活性(IC_{50}为5.2 μg/mL)。

化合物**283**来自一株变色曲霉*A. versicolor*，对枯草芽孢杆菌、蜡状芽孢杆菌和金黄色葡萄球

菌有中等强度的抑菌活性(每孔100 μg给药时的抑菌圈分别为11、12和14 mm)[114]。萜类化合物1,2-dihydroterretonin F(**284**)、(6α)-21-deoxyophiobolin G(**285**)、(6α)-16,17-dihydro-21-deoxyophiobolin G(**286**)、ophiobolin U(**287**)、ophiobolin V(**288**)、ophiobolinW(**289**)和**290**、**291**(图4)来自焦曲霉*A. ustus* cf42，其中化合物**287**对大肠杆菌和金黄色葡萄球菌均有抑菌活性、每孔30 μg给药时的抑菌圈分别为15和10 mm[115]。Asperversin A(**292**)和**293**产自变色曲霉*A. versicolor* pt20[116]。花斑曲霉*A. versicolor* dl29代谢产生倍半萜albican-11,14-diol(**294**)[117]和生物碱aspeverin(**295**)[118]，其中化合物**294**对卤虫的LC_{50}为35.0 μg/mL，且为大肠杆菌和金黄色葡萄球菌的抑制剂、30 μg/孔时的抑菌圈分别为7和10.3 mm[117]，而化合物**295**对赤潮异弯藻*Heterosigma akashiwo*的EC_{50}值分别为6.3 μg/mL(24h)和3.4 μg/mL(96h)[118]。蒽醌6,8-di-*O*-methylaverantin(**296**)来自变色曲霉*A. versicolor* EN-7[119]。蜡叶散囊菌*E. herbariorum* HT-2代谢产生了吲哚二酮哌嗪二聚体cristatumin E(**297**)，其对K562细胞的IC_{50}值为8.3 μmol/L，对产气杆菌*Enterobacter aerogenes*和大肠杆菌*Escherichia coli*的MIC值分别为44.0和44.0 μmol/L[120]。赭曲霉*A. ochraceus* Jcma1F17代谢产生倍半萜6β,9α-dihydroxy-14-*p*-nitrobenzoylcinnamolide(**298**)，对10种人体肿瘤细胞(H1975、U937、K562、BGC-823、Molt-4、MCF-7、A549、Hela、HL60和Huh-7)的IC_{50}为1.95–6.12 μmol/L，对H3N2病毒和EV71病毒的IC_{50}分别为17.0和9.4 μmol/L[121]。2株曲霉菌*Aspergillus* sp. BM-05和BM-05ML共培养产生环三肽psychrophilin E(**299**)(图4)，对HCT-116细胞的IC_{50}值为28.5 μmol/L[122]。曲霉菌*A. pseudodeflectus*代谢产生pseudodeflectusin(**300**)，对NUGC-3、HeLA-S3和HL-60均有细胞毒活性，其中对HL-60细胞的IC_{50}值为39 μmol/L[123]。

1997年，Fenical等从曲霉*Aspergillus* sp. CNC139的代谢产物中分离得到二酮哌嗪类halimide(**301**)，其对HCT116和A2780细胞有较强的细胞毒活性，IC_{50}分别为1 μmol/L和0.8 μmol/L[3–4]。同时Kanoh等也从焦曲霉*A. ustus* NSC-F038的代谢产物中分离得到，将其命名为phenylahistin，并发现(–)-phenylahistin(**302**)才是真正的活性成分，对P388的IC_{50}为0.35 μmol/L，而且1 μmol/L时可以将该细胞阻滞在G_2/M期[124]，良好的生物活性使其成为先导结构。之后多个课题组通过全合成出[125–126]，构效关系研究筛选出plinabulin(NPI-2358)(**303**)[5]，作为肿瘤细胞的血管分裂剂进入了Ⅱ期临床研究[127–129]。目前，plinabulin已经结束其II期临床研究，并于2015年第三季度开始在美国和中国进行其III期临床研究，用于治疗转移性的晚期非小细胞肺癌[6]。Gerwick所列的20个海洋药物中(包括7个上市药和13个临床药物)，**303**是唯一的海洋曲霉属真菌来源的药物[7]。近期，Hayashi小组对plinabulin进行结构改造得到活性更好的化合物KPU-300(**304**)(图4)，**304**对HT-29细胞的IC_{50}为7.0 nmol/L，可以有效的与微管蛋白结合(K_d = 1.3 μmol/L)，诱导微管解聚[130]。

2.2 红树林来源的曲霉天然产物

黑曲霉*A. niger* LL-LV3020代谢产生pyranonigrin A(**305**)[131]。黄柄曲霉*A. favipes*代谢产生cytochalasins Z_{16}–Z_{20}(**306**–**310**)[132]。赤散囊菌*Eurotium rubrum* QEN-0407-G2代谢产生蒽酮衍生物eurorubrin(**311**)和**312**–**314**，其中化合物**311**显示了中等强度的DPPH自由基清除活性，IC_{50}值为44.0 μmol/L[133]。苯并-γ-吡喃酮二聚体rubasperones A–C (**315**–**317**)[134]和rubasperones D–E(**318**–**321**)[135]分离自塔宾曲霉*A. tubingensis* GX1-5E。Nigerapyrones A–H(**322**–**329**)和已知物asnipyrones A和B来自黑曲霉*A. niger* MA132，其中已知化合物asnipyrones A和B的结构分别被修正为**330**和

331(图4)；化合物**323**对HepG2细胞的IC_{50}为62 μmol/L，**326**对SW1990、DMA-MB-231和A549细胞的IC_{50}分别为38、48和43 μmol/L[136]。单萜acetoxydehydroaustin B(**332**)和1,2-dihydroacetoxydehydroaustin B(**333**)(图5)来自*Aspergillus* sp. 085241B[137]。黄曲霉*A. flavus* 092008代谢产生黄曲霉毒素aflatoxin B_{2b}(**334**)，其对大肠杆菌、枯草芽孢杆菌和产气杆菌有中等的抑菌活性(MIC分别为22.5、1.7和1.1 μmol/L)，对A549、K562和L-02细胞的IC_{50}分别为8.1、2.0和4.2 μmol/L[138]。Aspergillumarins A(**335**)和B(**336**)产自曲霉*Aspergillus* sp.，在50 μg/mL时对金黄色葡萄球菌和芽孢杆菌有抑制活性[139]。

构巢曲霉*A. nidulans* MA-143代谢产生aniduquinolones A–C(**337**–**339**)、6-deoxyaflaquinolone E(**340**)、isoaflaquinolone E(**341**)、14-

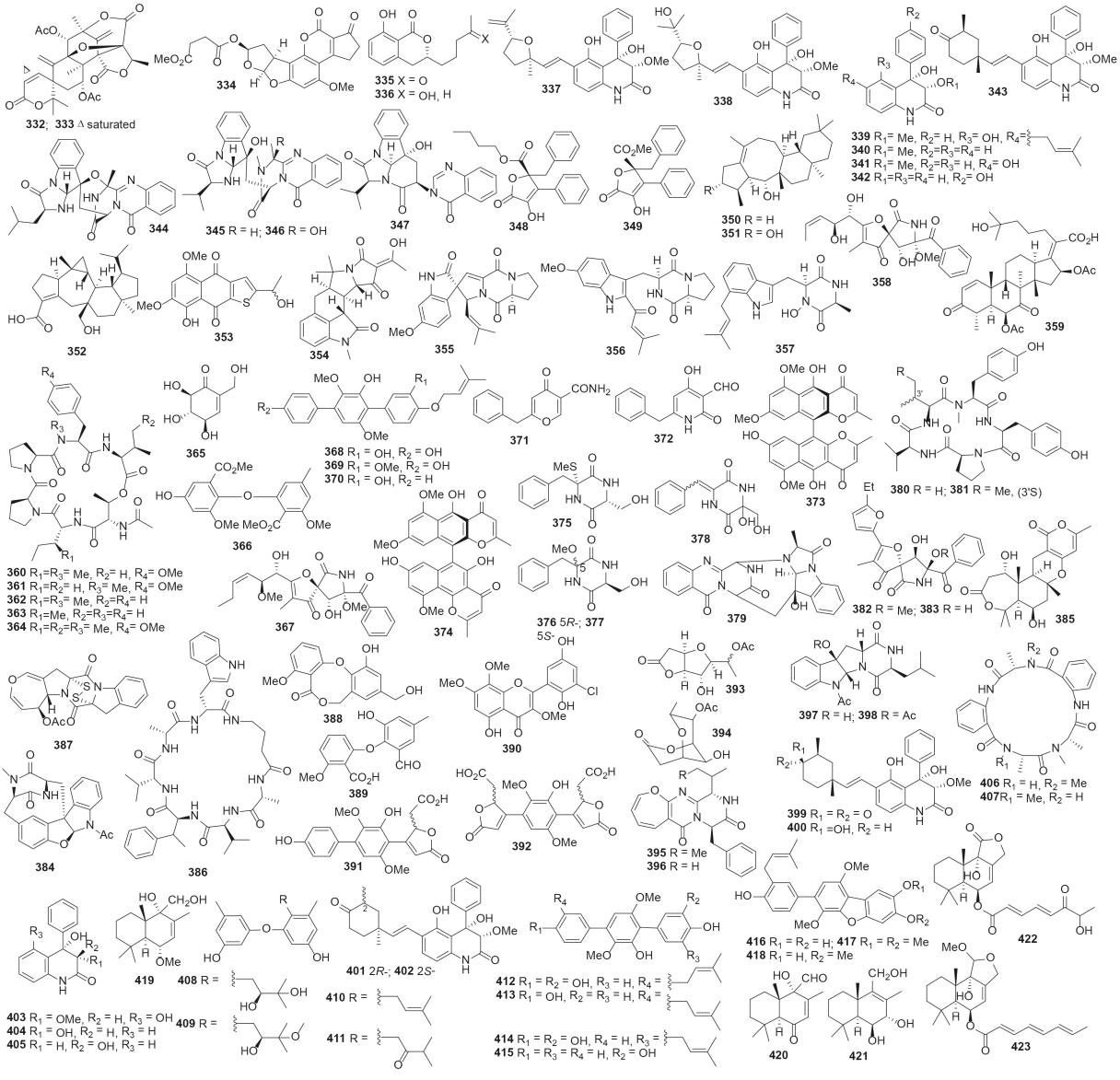

图 5. 化合物332–423的结构

Figure 5. Structures of compounds **332–423.**

hydroxyaflaquinolone F(**342**)和已知物aflaquinolone A(**343**)(图5)；化合物**338**、**339**和**343**具有抗卤虫活性，LD_{50}值分别是7.1、4.5和5.5 μmol/L[140]。喹唑啉酮生物碱aniquinazolines A–D(**344**–**347**)也产自该菌，对卤虫的LD_{50}分别为1.27、2.11、4.95 和3.42 μmol/L[141]。黄柄曲霉*A. flavipes* AIL8代谢产生flavipesins A(**348**)和B(**349**)，**348**对金黄色葡萄球菌和枯草芽孢杆菌的MIC分别为8.0 μg/mL和0.25 μg/mL[142]。二倍半萜asperterpenols A(**350**)和B(**351**)来自一株内生曲霉*Aspergillus* sp. 085242，二者对乙酰胆碱酯酶的IC_{50}值分别为2.3和3.0 μmol/L[143]。曲霉菌*Aspergillus* sp. 16-5c代谢产生二倍半萜asperterpenoid A(**352**)(图5)，它对分枝杆菌*Mycobacteriumtuberculosis*蛋白酪氨酸磷酸酶的IC_{50}值为2.2 μmol/L[144]。土曲霉*A. terreus* GX7-3B代谢产生了噻吩骈萘醌衍生物**353**[145]。

2.3 其它植物来源的曲霉天然产物

吲哚单萜speradine A(**354**)产自溜曲霉*A. tamarii* M143，抑制Ca^{2+}-ATP酶的IC_{50}为8 μmol/L、抑制组蛋白去乙酰化酶的IC_{50}为100 μg/mL，抑制藤黄微球菌*Mycrococcus luteus*的MIC 16.7 μg/mL[146]。6-methoxyspirotryprostatin B(**355**)、18-oxotryprostatin A(**356**)、14-hydroxyterezine D(**357**)、14-norpseurotin A(**358**)和**359**(图5)来自萨氏曲霉*A. sydowi* PFW1-13，其中化合物**355**–**357**对A549细胞的IC_{50}分别为8.29、1.28和7.31 μmol/L，化合物**358**和**359**对大肠杆菌、枯草杆菌和溶壁微球菌的MIC分别为3.74、14.97、7.49 μmol/L和10.65、5.33、10.65 μmol/L[147]。

3 海泥、海水等来源的曲霉天然产物

3.1 海泥来源的曲霉天然产物

肉色曲霉*A. carneus*MST-MF156代谢产生aspergillicins A–E(**360**–**364**)(图5)，对捻转血矛线虫*Haemonchus contortus*具有细胞毒性(LD_{99}为25–50 μg/mL)[148]。糖苷类化合物**365**产自变异曲霉*A. varians* KMM 4630，其在10.0 μg/mL时对海胆胚胎有毒性[149]。2,3-dimethoxyosoate(**366**)产自曲霉*Aspergillus* sp. B-F-2，其对K562细胞的IC_{50}为76.5 μmol/L，在100 μmol/L时可以诱导细胞凋亡、使细胞停滞在S期[150]。烟曲霉*A. fumigates* 030402d代谢产生11-*O*-methylpseurotin A(**367**)，对Hof1 缺失的酵母菌*Saccharomyces cerevisiae* 的抑菌圈直径为9 mm[151]。白曲霉*A. candidus* RF-5672代谢产生terprenin(**368**)、3-methoxyterprenin(**369**)和4"-deoxyterpren(**370**)，其抑制CoA-A 介导的小鼠脾淋巴细胞的IC_{50}依次为1.2、2.0和5.6 ng/mL，抑制LPS介导的小鼠脾淋巴细胞的IC_{50}分别为4.5、8.0、15.6 ng/mL[152]。炭黑曲霉*A. carbonarius* WZ-4-11代谢产生carbonarones A (**371**)和B(**372**)[153]及化合物**373**–**374**[154]，其中**371**和**372**对K562细胞的IC_{50}值分别为56.0和27.8 μg/mL[153]，**373**和**374**对结核分歧杆菌*Mycobacterium tuberculosis* H37Rv的MIC依次为43.0和25.1 μmol/L[154]。烟曲霉*A. fumigates* Fres代谢产生胶霉素**375**[155]和二酮哌嗪**376**–**378**[156]。变色曲霉*A. versicolor* MST-MF495代谢产生cottoquinazoline A(**379**)和cotteslosins A(**380**)和B(**381**)[157]。氧杂螺内酰胺azaspirofurans A(**382**)和B(**383**)来自萨氏曲霉*A. sydowi* D2-6，**382**对A549的IC_{50} 10 μmol/L[158]。二酮哌嗪azonazine(**384**)来自胰岛曲霉*A. insulicola* 088708a，有抗炎作用，其对NF-κB的IC_{50}为8.37 μmol/L[159]。杂萜asperdemin(**385**)来自变色曲霉*A. versicolor*，有溶血作用，EC_{50} 1.15 mmol/L[160]。环肽unguisin E(**386**)和deoxyapoaranotin(**387**)分别来自曲霉*Aspergillus* sp. AF119[161]和变色曲霉*A. versicolor* KMD 901[162]，*Aspergillus* sp. AF119还代谢产生barceloneic lactones B(**388**)和C(**389**)和5'-hydroxychlorflavonin(**390**)[163]以及terphyl acid(**391**)、terphyl diacid(**392**)[164](图5)。

Protulactones A、B(**393**、**394**)[165]及protuboxepins A、B(**395**、**396**)、protubonines A、B(**397**、**398**)(图5)来自*Aspergillus* sp. SF-5044[166]，该菌还代谢产生aflaquinolones A–G(**399**–**405**)[167]。*A. versicolor* ZLN-60产生环戊肽versicotides A(**406**)、B(**407**)[168]和异戊二烯化的二苯醚衍生物diorcinols B–E(**408**–**411**)[169]，其中化合物**410**对Hela和K562细胞的IC_{50}值分别为31.5和48.9 μmol/L、**411**对Hela细胞的IC_{50}值为36.5 μmol/L[169]。台中曲霉*A. taichungensis* ZHN-7-07代谢产生prenylterphenyllins A–C(**412**–**414**)、4''-dehydro-3-hydroxyterphenyllin(**415**)及prenylcandidusins A–C(**416**–**418**)，其中化合物**412**对HL-60和A549细胞的IC_{50}分别为1.5和8.3 μmol/L、**415**和**417**对P388细胞的IC_{50}分别为2.7和1.6 μmol/L[170]。补身烷倍半萜**419**–**423**(图5)来自一株焦曲霉*A. ustus*，化合物**422**抑制P388的IC_{50}为8.7 μmol/L[171]。Prenylcyclotryprostatin B(**424**)、20-hydroxycyclotryprostatin B(**425**)、9-hydroxyfumitremorgin C(**426**)、6-hydroxytryprostatin B(**427**)和spirogliotoxin (**428**)(图6)来自烟曲霉*A. fumigates* YK-7，化合物**424**和**426**对U937细胞的IC_{50}分别为25.3 μmol/L和18.2 μmol/L[172]。土曲霉*A. terreus* A8-4代谢产生7''-hydroxybutyrolactone III(**429**)和terretriones A–C(**430**–**432**)[173]；三肽presclerotiotide F(**433**)来自胰岛曲霉*A. insulicola* 088708aZA[174]；萘烷衍生物decumbenone C(**434**)来自硫色曲霉*A. sulphureus* KMM 4640，对人体黑色素瘤SK-MEL-5的细胞毒活性IC_{50}为0.9 μmol/L[175]。二酮哌嗪brevianamides S–V(**435**–**438**)来自变色曲霉*A. versicolor* MF030，化合物**435**具有选择性地抑制结核分支杆菌*Mycobacterium bovis*减毒株BCG的活性(MIC为6.25 μg/mL)，可能发展为抗结核杆菌先导药物[176]。焦曲霉*A. ustus* 094102代谢产生倍半萜ustusols A–C(**439**–**441**)和ustusolates A–E(**442**–**446**)以及香豆素ustusoranes A–F(**447**–**452**)，其中**446**和**451**对HL-60的IC_{50}值分别为9.00 μmol/L和0.13 μmol/L，**444**对A549细胞的IC_{50}为10.5 μmol/L[177]。外消旋的螺环生物碱effusin A(**453**)和dihydrocryptoechinulin D(**454**)(图6)分离自赭曲霉*A. effuses* H1-1[178–179]，其中**454**对P388和HL-60细胞的IC_{50}分别为1.83 μmol/L和4.80 μmol/L、在100 μmol/L时可以选择性的抑制拓扑异构酶I的活性[178]。

曲霉*A. westerdijkiae* DFFSCS013代谢生物碱circumdatins K(**455**)和L(**456**)、5-chlorosclerotiamide (**457**)、10-*epi*-sclerotiamide(**458**)和aspergilliamide B(**459**)(图6)，其中化合物**457**和**458**对K562细胞的IC_{50}值分别是44和53 μmol/L[180]。三聚的sydowiols A–C(**460**–**462**)产自一株萨氏曲霉*A. sydowii* MF357，化合物**460**和**462**对结核分枝杆菌*M. tuberculosis*蛋白酪氨酸磷酸酶PtpA的IC_{50}值分别为14 μg/mL和24 μg/mL。此外，化合物**462**对金黄色葡萄球菌的MIC值为12.5 μg/mL[181]。棘孢曲霉*A. aculeatus*代谢产生新苯醌aculeatusquinones A–D(**463**–**466**)，其中**464**和**466**对HL-60、K562和A549细胞的IC_{50}值在5.4–76.1 μmol/L之间[182]。杂色曲霉*A. versicolor* HDN08-60代谢产生吲哚二酮哌嗪versicamides A–H(**467**–**474**)；其中**474**对Hela、HCT-116、HL-60和K562细胞的IC_{50}分别为19.4、17.7、8.7和22.4 μmol/L，**474**也可抑制多种酪氨酸激酶的活性，10 μmol/L对KDR、RET和EGFR激酶的抑制率为23%到35%，对c-Kit的抑制率为60%[183]。米曲霉*A. oryzae*代谢产生吲哚生物碱speradines B–E(**475**–**478**)，**475**和**478**对Hela细胞的IC_{50}均为0.20 mmol/L[184]；吲哚生物碱speradines F–H(**479**–**481**)和circumdatin G(**482**)分别来自米曲霉*A. oryzae*[185]和褐黄曲霉*A. ochraceus*[186]。灰绿曲霉*A. glaucus* HB1-19代谢产生aspergentisyls A、B(**483**、**484**)和aspergiodiquinone(**485**)(图6)，**483**和**484**具有DPPH自由基清除活性，IC_{50}值分别为9.3 μmol/L和17.6 μmol/L[187]。蒽醌类衍生物aspergiolide A(**486**)产自同一株菌，对A549、HL-60、BEL-7402有细胞毒活性[188]。

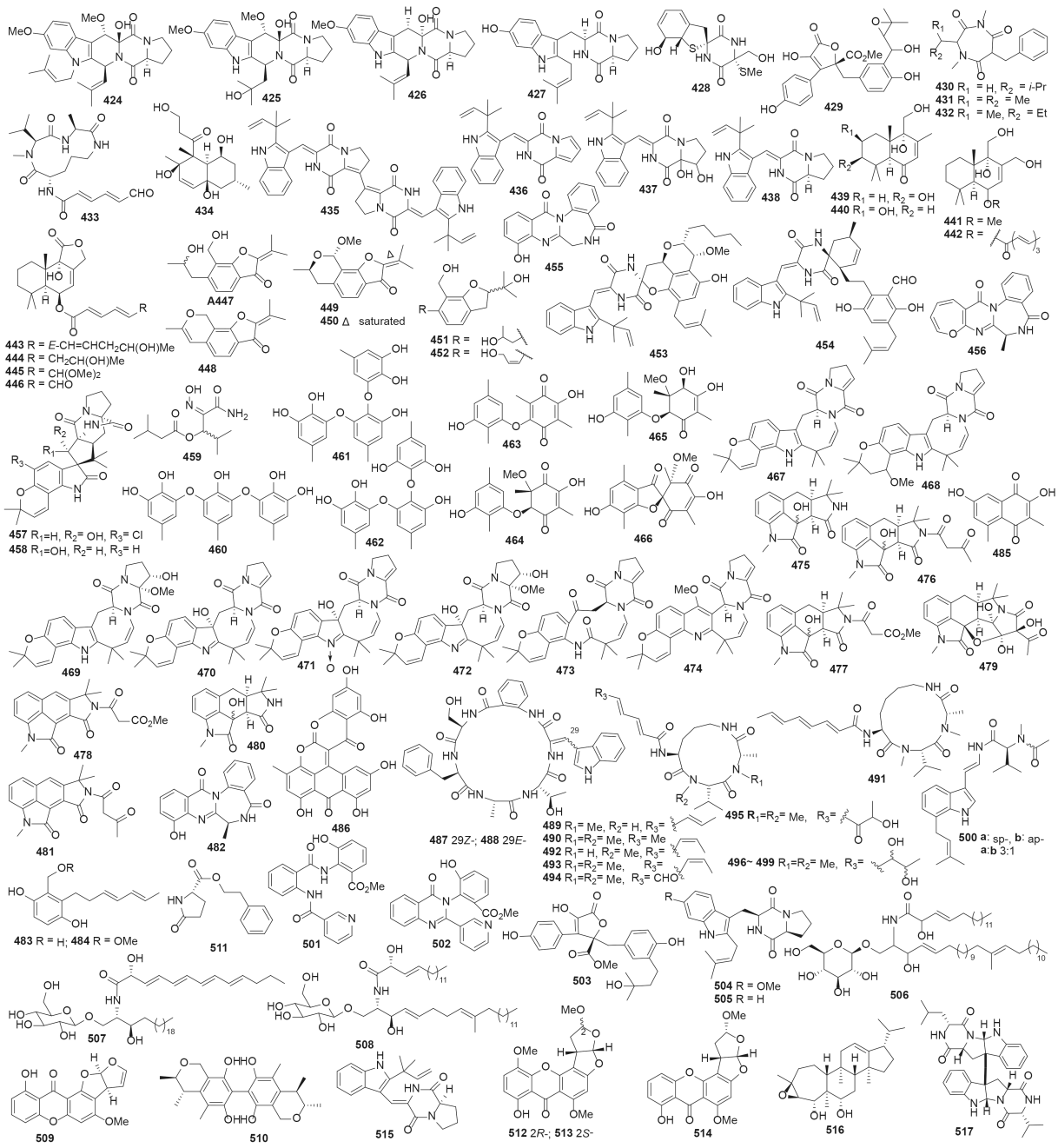

图 6. 化合物424–517的结构

Figure 6. Structures of compounds **424–517**.

菌核曲霉*A. sclerotiorum* PT06-1在高盐寡营养条件下产生环六肽sclerotides A、B(**487**、**488**)[189]，在高盐富营养条件下则产生环三肽sclerotiotides A–K(**489**–**499**)[190]和indole-3-ethenamide(**500**)[191]；其中化合物**487**和**488**均显示中等强度的抗白色念珠菌活性、MIC值分别为7.0 μmol/L和3.5 μmol/L，化合物**488**对HL-60细胞和铜绿假单胞菌有抑制作用、IC_{50}和MIC值分别为56.1和35.3 μmol/L；化合物**489**、**490**、**494**和**497**对白色念珠菌有选择性抑制作用，MIC分别为7.5、3.8、

30.0和6.7 μmol/L，化合物**500**对A549和HL-60细胞的IC_{50}分别为3.0和27.0 μmol/L。土曲霉*A. terreus* PT06-2在盐胁迫条件下代谢产生terremides A、B(**501–502**)和terrelactone A(**503**)，其中**501**对金黄色葡萄球菌的MIC为63.9 μmol/L、**502**对产气肠杆菌的MIC为33.5 μmol/L[192]。烟曲霉*A. fumigates* BM939代谢产生对映异构的tryprostatins A(**504**)和B(**505**)(图6)，浓度分别为50 μg/mL和12.5 μg/mL时，两者均能将tsFT-210的细胞周期阻滞于G_2/M期[193]。

3.2 海水来源的曲霉天然产物

Asperiamide A(**506**)产自曲霉*Asperillus* sp. MF-34[194]，asperiamides B(**507**)和C(**508**)则来自黑曲霉*A. niger* MF-16[195]。曲霉*Aspergillus*sp. MF-93代谢产生asperxanthone(**509**)和asperbiphenyl(**510**)(图6)，均可阻断烟草花叶病毒TMV的复制，0.2 mg/mL浓度下的抑制率分别为62.9%和35.5%[196]。杂色曲霉*A. versicolor* ZBY-3的新霉素耐药菌株u2n2h3-3代谢产生5-oxo-L-prolinate(**511**)，其对Hela细胞的IC_{50}值为49.0 μg/mL[197]。柄曲菌素类oxisterigmatocystins A–C(**512–514**)[198]和二酮哌嗪brevianamide W(**515**)[199]来自变色曲霉*A. versicolor* CXCTD-06-6a，其中**515**在13.9 μmol/L时对DPPH的清除率为55%。

3.3 未知来源的曲霉天然产物

二倍半萜aspergilloxide(**516**)和二聚二酮哌嗪**517**(图6)分别来自曲霉*Aspergillus* sp. CNM-713[200]和黑曲霉*A. niger*[201]。

4 结论和展望

从1992年Shinggu等首次报道海洋曲霉来源的新天然产物fumiquinazolines A–C[2](Numata *et al.* 1992)到2014年8月，已发现海洋曲霉来源的新天然产物512个。海洋曲霉天然产物的结构类型多样，包括聚酮、生物碱、萜类、甾体、脂肪酸、肽类及其卤代物和糖苷等；且36%的化合物表现出抗癌(肿瘤细胞毒)、抑菌、抗氧化(自由基清除)和抗寄生虫等生物活性，是发现活性新天然产物和药物先导物的重要资源。

(1) 从海洋曲霉菌的样品来源看，产生新化合物最多的曲霉菌来源或栖息地依次是海泥(149个)、海绵(100个)、其它动物(77个)和海藻(75个)，分别占29%、20%、15%和15%(图7-A)。

(2) 从化合物类型看，化合物最多的类型依次是含氮(265个)、聚酮(153个)和萜甾(96个)，分别占化合物总数的52%、30%和19%(图7-B)。进一步分析其来源，聚酮类化合物产生菌的主要栖息地是海泥和海绵，分别为26%和22%；萜甾化合

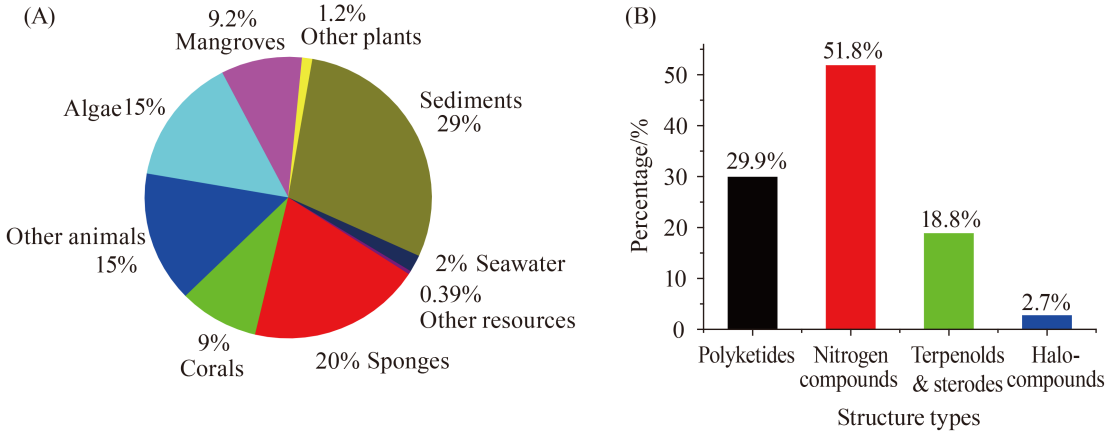

图 7. 海洋曲霉天然产物的来源(A)与结构分类(B)

Figure 7. Origin categories (A) and the main structure types (B) of marine-derived *Aspergillus* fungal NPs.

物产生菌的主要栖息地是海绵和海藻，分别为38%和25%；含氮化合物产生菌的主要栖息地是海泥，为35% (图8-A)。进一步结合来源分析，珊瑚、海藻和海泥来源的曲霉主要代谢产生含氮化合物，分别为48%、51%和63%；红树林来源的曲霉主要代谢产生聚酮化合物，约为64%；而海绵来源的曲霉天然产物的结构类型相对均衡，聚酮、含氮化合物及萜甾分别为33%、27%和36% (图8-B)。

(3) 约36%的海洋曲霉天然产物(184个)表现出细胞毒、抗菌、自由基清除和抗寄生虫等多种生物活性(图9-A和表 1)，而肿瘤细胞毒(94个)和抗菌(51个)是其主要的活性，分别占活性化合物总数的51%和28%。含氮物、聚酮和萜甾是活性化合物的三大类型，分别占活性化合物总数的57%、29%和20% (图9-B)；卤代物、含氮物、萜甾、聚酮和肽类出现活性化合物的比例分别为各类化合物总数的50%、40%、41%、38%和35%

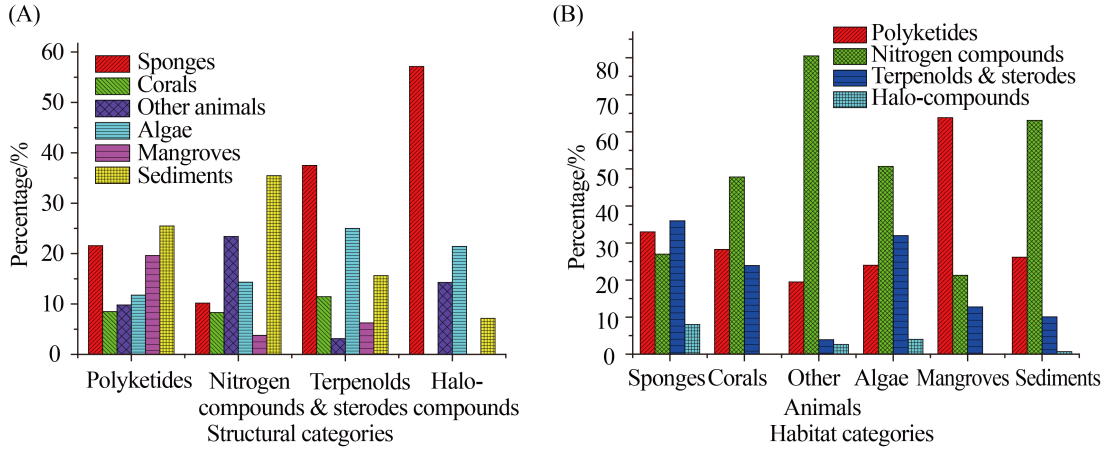

图 8. 主要结构类型化合物产生菌的栖息地(A)与不同样品来源的曲霉天然产物的结构类群(B)

Figure 8. Habitat categories on the main structures of producing strains (A) and structural categories (B) of NPs from marine-derived *Aspergillus* fungi.

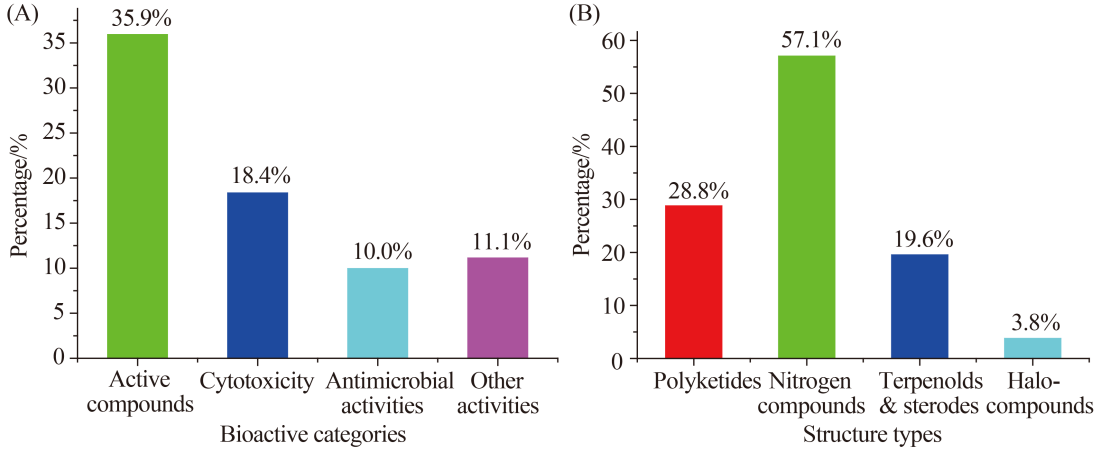

图 9. 海洋曲霉天然产物的活性分类(A)与活性化合物中各结构类型的比例(B)

Figure 9. Bioactive categories of NPs (A) and ratios of the bioactive NPs from structural types (B) of the marine-derived *Aspergillus* fungal origins.

(图10-A)；而海泥和海绵来源的曲霉最容易产生肿瘤细胞毒活性的化合物，其概率分别为21%和19% (图10-B)。

(4) 我国、其它亚洲国家和欧美国家在海洋天然产物的发展上占据了重要地位，分别贡献287、108和103个新化合物，尤其是我国海洋天然产物化学家贡献了57%的海洋曲霉来源的新天然产物(图11-A)。本文共引用了95篇(占引用文献总数的53%)我国海洋天然产物化学家发表的文章，是主要的贡献者，标志我国海洋天然产物的研究具有一定的国际影响力。但其发表在有机化学类或天然产物化学类的主流杂志如*Org. Lett.*、*J. Org. Chem.*、*Tetrahedron*和*J. Nat. Prod.*分别仅有6、1、2和11篇，仅占其文章的6.3%、1.1%、2.1%和11.6%，且未见其在*J. Am. Chem. Soc.*和*Angew. Chem., Int. Ed.*等化学综合类高水平杂志上发表文章(图11-B)，也未见有药进入临床研究。由此可见，我国曲霉菌海洋天然产物的研究，应该注重质和国家需求，而非单纯的量或发表文章。

综上，海洋曲霉可以产生结构新颖，活性多样的天然产物，具有极大的开发潜能，但是到目前为止仅有1个来源于海洋曲霉的药物，如何最大限度利用海洋曲霉这类珍贵的微生物资源来开发药物，是值得科研工作者思考和解决的问题。一

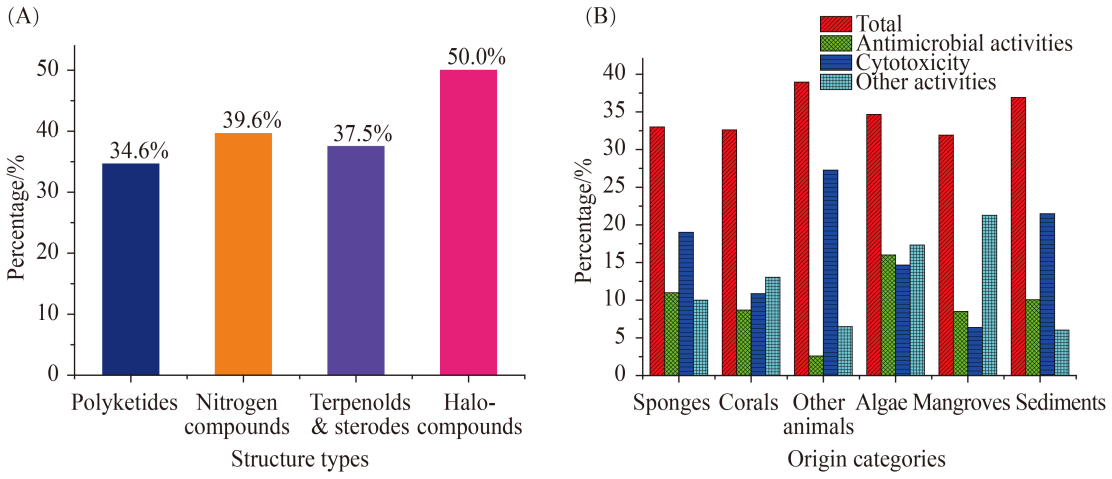

图 10. 不同结构类型化合物的活性率(A)与产生菌来源化合物的活性率(B)

Figure 10. Ratios of active NPs from the structural types (A) and the sources of the *Aspergillus* fungi (B).

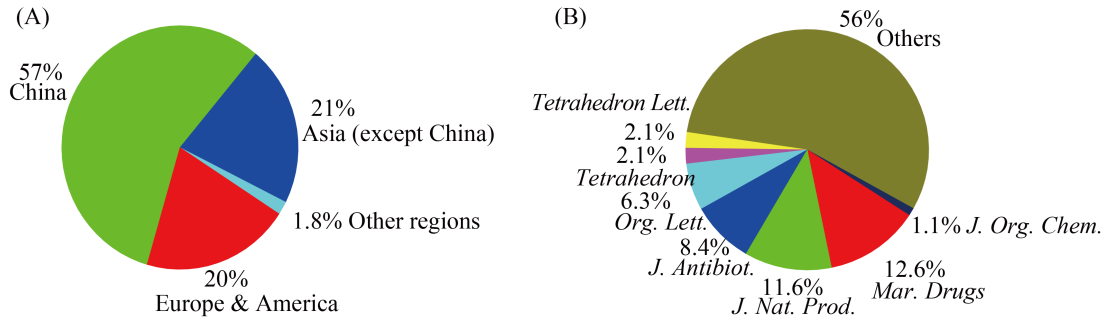

图 11. 海洋曲霉天然产物发现者国别(A)和中国学者发表论文的期刊分类(B)

Figure 11. Country categories of the discoverers (A) and publishing Journal categories of the Chinese scholars (B) on the marine-derived fungal NPs

表1. 海洋曲霉来源天然产物(1992–2014)

Table 1. Marine natural products from *Aspergillus* fungi (1992–2014)

Compounds	Producing Strains	Environments source	Bioactivity	References
1, 2	*A. cf. ochraceus* 941026	*Jaspis* of *Coriacea*, Indian-Pacific Ocean	/[a]	8
3	*A. nigere*	*Hyrtios* sp., Florida, America	Cytotoxicity	9
4	*A. niger* 94–1212	*Hyrtios proteus*, Florida, America	/	10
5–14	*A. versicolor*(Vuill)Triab	*Xestospongia exigua*, Bali Island, Indonesia	/	11–12
15–25	*A. ostianus* TUF 01F313	Unidentified sponge, Pohnpei, Micronesia	**15–17**: Antibacterial activity, **22–24**: Cytotoxicity	13–16
26–28	*A. ostianus* IBT 12704	Unidentified sponge, Pohnpei, Micronesia	/	17
29–32	*Aspergillus* sp. CNK-371	Unidentified sponge, Hawaii State	**29–31**: Cytotoxicity	18
33, 34	*A. aculeatus* CRI323-04	*Xestospongia testudinaria*, Phi Phi Island, Thailand	**33**: α-glucosidase inhibition, Antibacterial activity	19–20
35–37	*A. aculeatus* CRI322-03	Unidentified sponge, Phi Phi Island, Thailand	/	21
38, 39	*A. insuetus*	*Petrosia ficiformis*, Santa Ana Alhambra Nestorius, Spain	Inhibitor of the mammalian mitochondrial respiratory chain	22
40	*A. sclerotiorum* Huber SP080903f04	*Mycale* sp. Okinawa Island, Japan	/	23
41–54	*A. ustus* 8009	*Suberites domuncula*, The Adriatic Sea	**44, 45**: Cytotoxicity	24–25
55	*A. versicolor*	*Petrosia* sp., Jeju Island, Korea	Cytotoxicity	26
56, 57	*Aspergillus* sp. fs14	Unidentified sponge, Okinawa Island, Japan	/	27
58–61	*A. insuetus* OY-207	*Psammocinia* sp., Israel	**58**: Antibacterial activity **60**: Cytotoxicity	28
62	*A. versicolor* PF10M	*Petrosia* sp., Jeju Island, Korea	Cytotoxicity	29
63–69	*Aspergillus* sp.	*Xestospongia testudinaria*, South China Sea, China	**63–66**: Antibacterial activity **67, 69**: Cytotoxicity	30–31
70–74	*A. unguis* CRI282-03	Unidentified sponge CRI282, Thailand	**70–72**: Aromatase inhibition **70, 71**: XXO scavenging activity	32
75	*Eurotium cristatum* KUFC 7356	*Mycale* sp. State Beach, Thailand	/	33
76–89	*Aspergillus* sp.	*Tethya aurantium*, Mediterranean, Italy	**81**: Cytotoxicity **88, 89**: Antibacterial activity	34–36
90–92	*A. versicolor* MF359	*Hymeniacidon perleve*, Bohai, China	**92**: Antibacterial activity	37
93–99	*A. niger*	*Axinella damicornis*, Elba, Italy	**93–95**: Cytotoxicity	38
100	*Aspergillus niger* FT–0554	Unidentified sponge, Palau	Inhibit *Ascarissuum*	39
101, 102	*A. terreus* HKI0499	*Sinularia kavarattiensis*, Amanda Pam, India	/	40
103–107	*Aspergillus* sp.	*Dichotella gemmacea*, Weizhou Island, China	**103**: Antibacterial activity **106**: Cytotoxicity, fouling resistance	41–42
108–112	*A. sydowii* PSU-F154	*Annella* sp., Surat Thani, Thailand	/	43
113–121	*A. versicolor* LCJ-5-4	*Cladiella* sp., South China Sea, China	**116**: DPPH radical scavenging activity **121**: Antibacterial activity	44–45
124, 125	*A. fumigates*	*Zoanthus* sp., Kagoshima, Japan	/	49

(待续)

(续表1-1)

126–128	*A. fumigatus* KMM 4631	*Sinularia* sp., Ostrov Kunashir Island	**126**: Planta growth Promotion	50–51
129	*A. sydowii* SCSIO 00305	*Verrucella umbraculum*, Sanya, China	/	52
130, 131	*Aspergillus* sp.	*Zoanthus* sp., Kagoshima, Japan	Cytotoxicity	53–54
132–134	*A. terreus* SCSGAF0162	*Echinogorgia aurantiaca*, Sanya, China	**132**: Cytotoxicity, Antivirus	55
135–138	*Aspergillus* sp. XS-20090066	*Dichotella gemmacea*, Xisha Islands, South China Sea	/	56
139–141	*A. elegans*ZJ-2008010	*Sarcophyton* sp., Weizhou Island, China	**139**: Antibacterial activity	57
142	*Aspergillus* sp. SCSGAF 0076	*Melitodes squamata*, Sanya, China	/	58
143, 144	*Eurotium rubrum* SH-823	*Sarcophyton* sp., South China Sea, China	Anti-α-glycosides	59
145, 146	*A. versicolor*	*Dichotella gemmacea*, South China Sea, China	Antibacterial activity, Anti-brine shrimp activity	60
147, 148	*A. flavipes*	*Anthopleura xanthogrammica*, Qingdao, China	Cytotoxicity	61
149–156	*A. fumigatus* OUPS-T106B-5	*Pseudolabrus japonicus*, Tanabe Bay, Japan	Cytotoxicity	2, 64–65
157–159	*A. fumigatus* OUPS-T106B-5	*Pseudolabrus japonicus*, Tanabe Bay, Japan	**158, 159**: Cytotoxicity	66
160–161	*A. terreus* OUCMDZ-1925	*Chelon haematocheilus*, Yellow River estuary, China	DPPH radical scavenging; Cytotoxicity; Anti-virus	67
162–167	*Aspergillus* sp. MF275	*Mytilus edulis*, Toyama Bay, Japan	**162**: Ubiquitin-activating enzyme (E1) inhibitor	68–69
168–190	*Aspergillus* sp. MF297-2	*Mytilus edulis*, Japan	**170**, **175**: Cytotoxicity	70–75
191	*A. fumigatus* OUPS-N138	*Toxopneustes pileolus*, Japan	/	76
192–197	*A. versicolor* OUPS-N136	*Anthocidaris crassispana*, Tanabe Bay, Wakayama, Japan	**193–195**: Cytotoxicity	77
198–200	*Aspergillus* sp. HDf2	*Anthocidaris crassispina*, Hainan, China	/	78
201–203	*A. clavatus* C2WU	*Xenograpsus testudinatus*, Taiwan, China	**201–202**: Cytotoxicity	79–80
204–210	*A. fumigatus*	*S. japonicus*, Lingshan Island, Qingdao, China	**207–210**: Cytotoxicity	81
211–212	*A. fumigatus* WFZ-25	*S. japonicus*, Jiaozhou Bay, China	/	82
213–220	*A. niger* F97S11	*Aplidium* sp., Fiji	/	83
221	*Aspergillus* sp. MF297	*Mytilus edulis*, Toyama Bay, Japan	Cytotoxicity	84
222–224	*A. flavus* OUCMDZ-2205	*Penaeus vannamei*, Lianyungang sea area, China	**222**: Antibacterial activity **222–223**: Cytotoxicity	85
225	*A. flavipes* Z-4	*Ligia oceanica*, Oceania	/	86
226–227	*Aspergillus* sp. 05F16	Unidentified marine alga, Indonesia	/	87
228	*A. insulicola*	Unidentified marine alga, Bahamas	/	88
229–232	*A. versicolor* CNC 327	*Penicillus capitatus*, Caribbean	**229**: Cytotoxicity	89
233	*Aspergillu* sp.	*Sargassum* sp., Philippines	**233**: Antibacterial activity	90
234	*A. parasiticus* MFA153	*Carpopeltis cornea*, Korea	/	91
235	*A. terreus* MFA 460	*Halymenia acuminata*, Korea	UV-A absorbing activity	92
236	*Aspergillus* sp. MFA 212	*Lomentaria catenata*, Ulsan, Korea	UV-A absorbing activity; DPPH radical scavenging	93
237–238	*A. sydowii*	*Acanthophora spicifera*, Bay of Bengal India	/	94

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(续表1-2)

239	*Aspergillus* sp. MFB024	*Sargassum horneri*, Korea	Antibacterial activity	95
240–248	*A. niger* EN-13	*Colpomenia sinuosa*, Qingdao, China	**242**: Antibacterial activity; DPPH radical scavenging **243**: Antibacterial activity	96–100
249–251	*A. flavus* c-f-3	*Enteromorpha tubulosa*, Putian, China	**251**: Cytotoxicity	101–102
252–255	*A. ochraceus* EN-31	*Sargassum kjellmanianum*, Daliancoastline, China	**252**: DPPH radical scavenging	103–104
256–259	*A. oryzaer* cf-2	*Heterosiphonia japonica*, Yantai, China	**258**: Antibacterial activity	105–106
260–261	*Aspergillus* sp. SpD081030G1f1	*Sargassum* sp., Ishigaki Island, Japan	DPPH radical scavenging	107
262–263	*A. flavus*	*Codium fragile*,Yeosu, Korea	Antibacterial activity	108
264–265	*A. flavus* cf-5	*Corallina officinalis*, Yantai, China	/	109
266–277	*A. carneus* KMM4638	*Laminaria sachalinensis*, Kunachir Island	/	110–111
278–282	*A. wentii* EN-48	*Sargassum* sp., Unknown place	**278–282**: Cytotoxicity **282**: DPPH radical scavenging	112–113
283	*A. versicolor*	*Halimeda opuntia*, Egyptian Red Sea (5–8 m)	Antibacterial activity	114
284–291	*A. ustus* cf42	*Codium fragile*, Zhoushan Island, China	**287**: Antibacterial activity	115
292–293	*A. versicolor*pt20	*Sargassum thunbergii*, Pingtan Island, China	/	116
294–295	*A. versicolor* dl29	*Codium fragile*, Dalian, China	**294**: Anti-brine shrimp activity, Antibacterial activity **295**: Inhibition of *H. akashiwo*	117–118
296	*A. versicolor* EN-7	*Sargassum thunbergii*, Qingdao, China	/	119
297	*E. herbariorum* HT-2	*Enteromorpha prolifera*, Qingdao, China	Cytotoxicity, Antibacterial activity	120
298	*A. ochraceus* Jcma1F17	*Coelarthrum* sp., Paracel Islands, China	Cytotoxicity, Anti- H3N2 and EV71 activity	121
299	*Aspergillus* sp. BM-05 and BM-05ML	*Sargassum* sp., Helgoland, North Sea, Germany	Cytotoxicity	122
300	*A. pseudodeflectus*	*Sargassum fusiform*, Miura Peninsula, Japan	Cytotoxicity	123
301	*Aspergillus* sp. CNC139 *A. ustus* NSC-F038	*Halimeda copiosa*, Philippines	Cytotoxicity	3, 4
305	*A. niger* LL-LV3020	Mangrove wood, Hong Kong, China	/	131
306–310	*A. favipes*	Mangrove Plant *Acanthus ilicifolius*, Dongzhai Gang, China		132
311–314	*Eurotium rubrum* QEN-0407-G2	Marine mangrove plant *Hibiscus tiliaceus*, Hainan Island, China	**311**: DPPH radical scavenging	133
315–321	*A. tubingensis* GX1-5E	Radix of *Pongamia pinnata*, South China Sea, Guangxi	/	134–135
322–331	*A. niger* MA132	Mangrove, Hainan, China	**323**, **326**: Cytotoxicity	136
332–333	*Aspergillus* sp. 085241B	Mangrove, Shankou, Guangxi, China	/	137
334	*A. flavus* 092008	Mangrove plant, Hainan, China	Cytotoxicity, Antibacterial activity	138
335–336	*Aspergillus* sp.	*Bruguiera gymnorrhiza*, South China Sea, China	/	139
337–347	*A. nidulans* MA-143	*Rhizophora stylosa*, Unknown place	**338–339**, **343, 344–347**: Anti-brine shrimp activity	140–141
348–349	*A. flavipes* AIL8	*Acanthus ilicifolius*, Daya Bay, Shenzhen, China	Antibacterial activity	142
350–351	*Aspergillus* sp. 085242	Mangrove plant, Guangxi, China	Acetylcholinesterase inhibition	143

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(续表1-3)

352	*Aspergillus* sp. 16-5c	Mangrove plant, South China Sea, China	mPTPB inhibition	144
353	*A. terreus* GX7-3B	*Bruguiera gymnoihiza*, Guangxi, China	/	145
354	*A. tamarii* M143	Driftwood, Okinawa Island, Iapan	Ca^{2+}-ATPase inhibition, Antibacterial activity	146
355–359	*A. sydowi* PFW1-13	Driftwood, Baishamen,Hainan, China	Cytotoxicity, Antibacterial activity	147
360–364	*A. carneus* MST-MF156	Sediment, Jordan River Bridge, Tasmania, Australia	Antiparasitic activity	148
365	*A. varians* KMM 4630	Sediment, Sakhalin Island	Cytotoxicity	149
366	*Aspergillus* sp. B-F-2	Sediment, Behai Bay, China	Cytotoxicity	150
367	*A. fumigates* 030402d	Sediment (>30 m), Vanuatu	Antimicrobial activity	151
368–370	*A. candidus* RF-5672	Sediment, Shodo Island, Kagawa Prefecture, Japan	Cytotoxicity	152
371–374	*A. carbonarius* WZ-4-11	Sediment, Weizhou Island, China	**371–372**: Cytotoxicity; **373–374**: Antimicrobial activity	153–154
375–378	*A. fumigates* Fres	Sediment, Jiaozhou Bay, Qingdao, China	/	155–156
379–381	*A. versicolor* MST-MF495	Beach sand sample, Cottesloe, Western Australia	/	157
382, **383**	*A. sydowi* D2–6	Sediment, Jiaozhou Bay, Qingdao, China	**382**: Cytotoxicity	158
384	*A. insulicola* 088708a	Sediment, Hawaii	Anti-inflammation	159
385	*A. versicolor*	Sediment, Sakhalin Bay, Russian	Antihemolysis	160
386	*Aspergillus* sp. AF119	Sediment, Xiamen beach, China	/	161
387	*A. Versicolor* KMD 901	Sediment, East Sea, Korea	/	162
388–392	*Aspergillus* sp. AF119	Sediment, Xiamen beach, China	/	163–164
393–405	*Aspergillus* sp. SF-5044	Sediment, Dadaepo Beach, Busan, Korea	/	165–167
406–411	*A. versicolor* ZLN-60	Sediment, Yellow Sea	**410**, **411**: Cytotoxicity	168–169
412–418	*A. taichungensis* ZHN-7-07	Root soil of the mangrove plant *Acrostichum aureum*	**412**, **415, 417**: Cytotoxicity	170
419–423	*A. ustus*	Rhizosphere soil of the mangrove *Acrostichum aureurm*, Guangxi, China	**422**: Cytotoxicity	171
424–428	*A. fumigates* YK-7	Sediment, Yingkou, China	**424**, **426**: Cytotoxicity	172
429–432	*A. terreus* A8-4	Mangrove-associated marine sediments, Guangxi, China	/	173
433	*A. insulicola* 088708aZA	Sediment, Hawaii	/	174
434	*A. sulphureus* KMM 4640	Sediment, Unknown place	Cytotoxicity	175
435–438	*A. versicolor* MF030	Sediment, Bohai Sea, China	**435**: Antitubercular activity	176
439–452	*A. ustus* 094102	Rhizosphere soil of the mangrove plant *Bruguiera gymnorrhiza*, Wenchang, Hainan, China	**444, 446, 451**: Cytotoxicity	177
453, 454	*A. effuses* H1-1	Mangrove rhizosphere soil, Fujian, China	**454**: Cytotoxicity	178–179
455–459	*A. westerdijkiae* DFFSCS013	Sediment (–2918 m), South China Sea	**457, 458**: Cytotoxicity	180
460–462	*A. sydowii* MF357	Sediment, Bohai Sea, China	**460, 462**: Antimicrobial activity	181

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(续表1-4)

463–466	*A. aculeatus*	Sediment, Langqi Island, Fujian, China	**464, 466**: Cytotoxicity	182
467–474	*A. versicolor* HDN08-60	Sediment, South China Sea	**474**: Cytotoxicity; Inhibition of PTKs	183
475–478	*A. oryzae*	Sediment, Langqi Island, Fujian, China	**475, 478**: Cytotoxicity	184
479–481	*A. oryzae*	Sediment, Langqi Island, Fujian, China	/	185
482	*A. ochraceus*	Sediment, Sea of Japan	/	186
483–485	*A. glaucus* HB1-19	Mangrove rhizosphere soil, Fujian, China	**483, 484**: DPPH-radical scavenging	187
486	*A. glaucus* HB1-19	Mangrove rhizosphere soil, Fujian, China	Cytotoxicity	188
487–500	*A. sclerotiorum* PT06-1	Putian Sea Salt Field, Fujian, China	**487–490, 494, 497**: Antimicrobial activity **488, 500**: Cytotoxicity	189–191
501–503	*A. terreus* PT06-2	Putian Sea Salt Field, Fujian, China	**501, 502**: Antimicrobial activity	192
504, 505	*A. fumigates* BM939	Sediment (–760 m), Oi River, Japan	Cytotoxicity	193
506	*Asperillus* sp. MF-34	Sea water, Mei-Zhou Gulf, Fujian, China	/	194
507, 508	*A. niger* MF-16	Sea water, Quanzhou Gulf, Fujian, China	/	195
509, 510	*Aspergillus* sp. MF-93	Sea water, Quanzhou Gulf, Fujian, China	Antivirus	196
511	*A. versicolor* ZBY-3	Sea water (–800 m), Southeast Pacific	Antimicrobial activity; Cytotoxicity	197
512–515	*A. versicolor* CXCTD-06-6a	Sea water (–800 m), Pacific Ocean	**515**: DPPH-radical scavenging	198–199
516	*Aspergillus* sp. CNM-713	Unknown source	/	200
517	*A. niger*	Unknown source	/	201

[a] /: no bioactivity was reported.

方面要通过培养基改造、表观遗传修饰和共培养等手段，继续发现新的活性天然产物；另一方面也是最重要的，是如何开展对现有活性天然产物的成药性研究，而化合物的量依然是制约成药性研究的瓶颈因素。发酵工程、代谢工程是开展微生物活性产物规模化制备、获取足量产物的有效方法，而合成生物学为代谢工程有效而系统的分子生物学工具。由于真菌的基因组较大、酶系复杂，制约着其合成生物学的研究。近年来，曲霉次级代谢产物合成酶系及其相关基因结构、功能的研究取得了很大的进展，多个曲霉的基因组序列被公开。一些曲霉属真菌次级代谢产物的生合成机理被阐明，为曲霉属真菌活性天然产物的规模化制备和工业化生产提供了技术和理论基础。如张立新课题组发现真菌毒素verruculogen中的过氧桥键是由一个依赖α-酮戊二酸的单核非血红素酶FtmOx1催化合成的[202]。降血脂的一线药物洛伐他汀(lovastatin)最初是从曲霉中发现，目前控制洛伐他汀的生物合成酶被发现，并通过曲霉发酵实现工业化生产[203–204]；洛伐他汀的衍生物辛伐他汀(simvastatin)也是一种有效的调血脂药物，经典的合成方法是从洛伐他汀出发，经过水解(得到关键中间体monacolin J)、保护、酰化和脱保护等多步反应得到。Yi Tang等在解析洛伐他汀生物合成中酰化酶的基础上，利用全细胞培养，在大肠杆菌(*Escherichia coli*)过表达酰基转移酶lovD，实现了辛伐他汀的高效合成(转化monacolin J为simvastatin的转化率达到99%以上，且产量达到克级：4–6 g/L)[205–206]。这些研究成果为海洋曲霉属真菌药物的开发提供了重要的参考。

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New natural products from the marine-derived *Aspergillus* fungi-A review

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Abstract: Marine-derived fungi were the main source of marine microbial natural products (NPs) due to their complex genetic background, chemodiversity and high yield of NPs. According to our previous survey for marine microbial NPs from 2010 to 2013, *Aspergillus* fungi have received the most of attention among all the marine-derived fungi, which accounted for 31% NPs of the marine fungal origins. This paper reviewed the sources, chemical structures and bioactivites of all the 512 new marine NPs of *Aspergillus* fungal origins from 1992 to 2014. These marine NPs have diverse chemical structures including polyketides, fatty acids, sterols and terpenoids, alkaloids, peptides, and so on, 36% of which displayed bioactivities such as cytotoxicity, antimicrobial activity, antioxidant and insecticidal activity. Nitrogen compounds are the major secondary metabolites accounting for 52% NPs from the marine-derived *Aspergillus* fungi. Nitrogen compounds are also the class with the highest ratio of bioactive compounds, 40% of which are bioactive. Plinabulin, a dehydrodiketopiperazine derivative of halimide had been ended its phase II trial and has received its phase III study from the third quarter of 2015 for the treatment of advanced, metastatic non-small cell lung cancer.

Keywords: marine-derived fungi, *Aspergillus* sp., natural products, chemical structures, bioactivities, sources

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