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Research Progress of Multidrug Resistance Mechanism and Reverser in Tumor

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Abstract

Multidrug resistance (MDR) is a phenomenon in which tumor cells produce cross-resistance to antitumor drugs with different structures and target targets. MDR is the main reason for the failure of tumor chemotherapy. This article reviews the mechanism of tumor MDR and the progress of tumor MDR chemical reversal agents.

Keywords

Tumor, Multidrug Resistance, Mechanism, Chemical Reversal Agent

肿瘤多药耐药机制及化学逆转剂研究进展

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摘 要

肿瘤多药耐药(Multidrug Resistance, MDR)系肿瘤细胞对结构与作用靶位不同的抗肿瘤药物产生交叉耐药性的现象，MDR是肿瘤化疗失败的主要原因。本文对肿瘤MDR发生机制及肿瘤MDR化学逆转剂进展进行了综述。

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关键词

肿瘤，多药耐药，机制，化学逆转剂

1. 引言

肿瘤严重威胁人类生命和健康[1] [2] [3]，目前 90%以上肿瘤患者治疗失败都与肿瘤 MDR 有关[3]。本文对肿瘤 MDR 发生机制以及逆转肿瘤 MDR 的进展进行了综述。

2. 多药耐药机制

肿瘤细胞 MDR 形成机制是多因素参与的复杂过程，ABC 转运蛋白家族、miRNA、肿瘤干细胞(cancer stem cell, CSC)、自噬诱导、诱导异常、DNA 损伤修复、药物靶点突变及表观遗传诱导与之有关(图 1)。

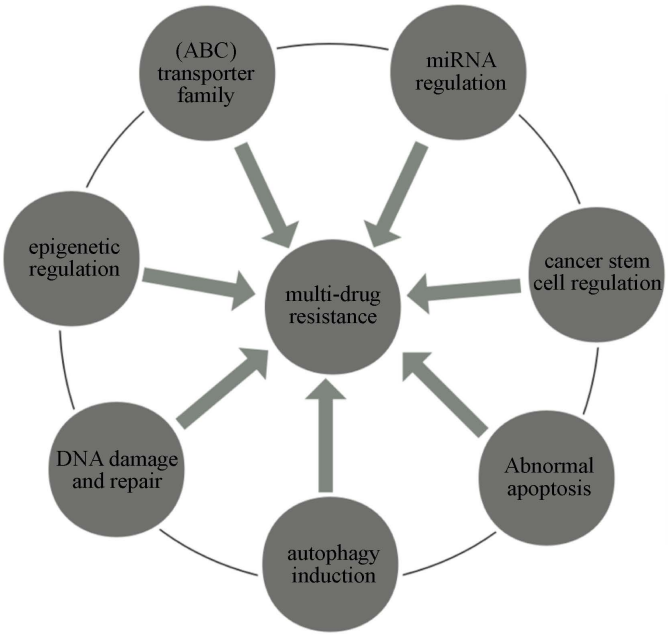


Figure 1. Potential mechanism of tumor MDR [4]
图 1. 肿瘤 MDR 潜在机制[4]

2.1. ABC 转运蛋白家族

ABC 转运蛋白能外排细胞内药物，分 ABCA 到 ABCG 亚家族[5]，共 49 种不同类型的转运蛋白[6]。如 ABCB1 促使癌细胞对米托蒽醌，沙奎那韦，表鬼臼毒素和蒽环类药物的耐药性[7] [8] [9] [10]。ABCG2 与乳腺癌、结肠癌、胃癌、小细胞肺癌和卵巢癌 MDR 关系密切[11]。ABC 转运蛋白已经成为开发新型逆转剂的靶点[12]。

2.2. miRNA 调控

miRNA 是一类小非编码 RNA，它通过调节 ABC 转运蛋白，凋亡蛋白，DNA 损伤修复，自噬和药物代谢酶等(图 2)产生肿瘤 MDR [13] [14]。

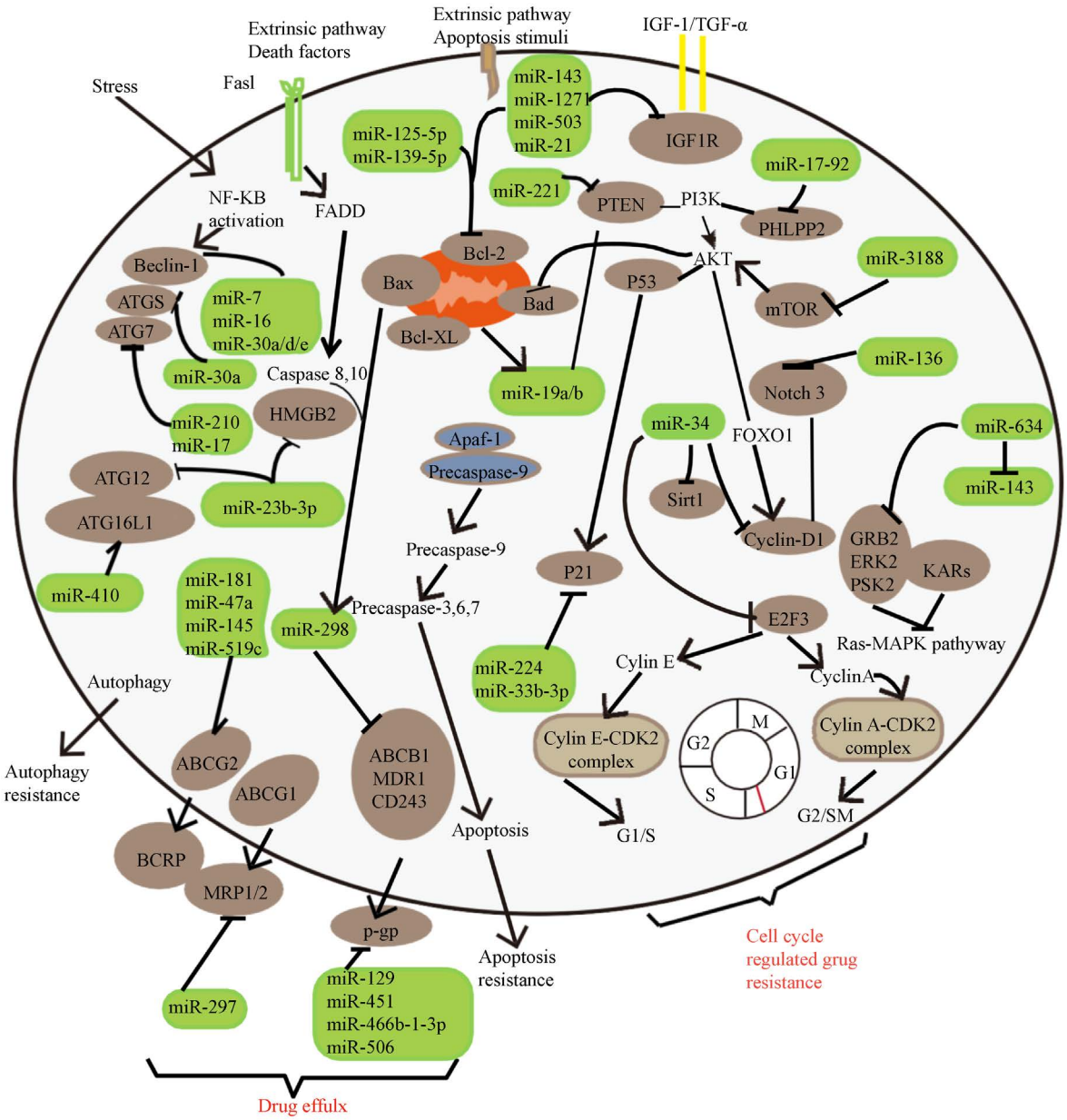


Figure 2. miRNA regulates MDR pathway in tumor cells [15]
图 2. miRNA 调控肿瘤细胞 MDR 路径[15]

2.3. 肿瘤干细胞(CSC)调控

CSC 具有自我更新和分化特性，多处于细胞 G0 期，具有很高的端粒酶活性及 DNA 复制修复能力，是造成肿瘤耐药的最根本原因[16]。通过高表达 ABC 转运蛋白和抗凋亡基因而逃避化疗及放疗，导致肿瘤复发和转移[17]。

2.4. 自噬诱导

自噬是一个高度保守的细胞降解和循环过程[18]。自噬通过降解药物分子发挥其细胞保护作用，帮助癌细胞逃避凋亡[19]。

2.5. 凋亡异常

肿瘤细胞通过抑制细胞凋亡而引起 MDR [20]。肿瘤细胞凋亡异常有凋亡蛋白抑制因子、Caspase-8蛋白、死亡受体等表达异常[21]。

2.6. DNA 损伤和修复(DDR)

肿瘤细胞 DNA 修复可以切除抗肿瘤药物致命性的 DNA 损伤，降低基于破坏肿瘤细胞 DNA 药物的效果。最新研究表明，在 10,489 例肿瘤内，80 个核心 DDR 基因中有 13 个被显著扩增和过表达，带有 DDR 基因扩增的肿瘤可产生化疗耐药而导致整体生存率下降[22]。

2.7. 表观遗传诱导

表观遗传是指细胞内除遗传信息以外的其他可遗传物质的改变，与肿瘤 MDR 的恶性表型密切[23]。

3. 化学逆转剂

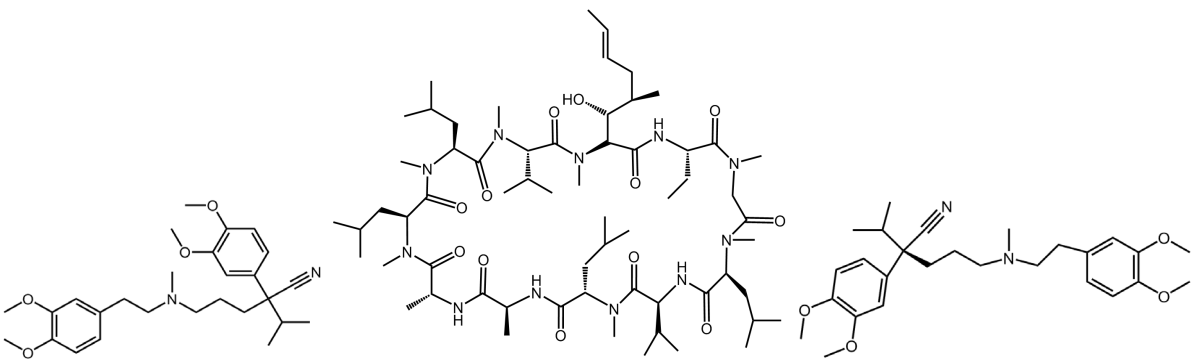
3.1. 临床研究中逆转肿瘤 MDR 药物

3.1.1. 靶向 ABCB1 耐药逆转剂

靶向 ABCB1/p-gp/MDR1 耐药逆转剂(图 3)经历了三代发展(表 1)，目前已经研发至第四代。由于毒副作用大，至今没有应用于临床。

Table 1. Targeted ABCB1 resistance reversal agents
表 1. 靶向 ABCB1 耐药逆转剂

分类	代表化合物	问题
第一代[24]	维拉帕米(Verapamil)和环孢素 A	治疗效果差、所需剂量高、易产生心脏毒副作用
第二代[25] [26]	右旋维拉帕米(dexverapamil)、哌啶类衍生物 VX-710、环孢素 A 的同系物 PSC833	选择性差，抑制 CYP450 介导的抗癌药物代谢，干扰正常细胞代谢，仍存在毒副作用
第三代[27] [28]	环丙基二苯并环庚烷类物质[Zosuquidar (LY335979)，Laniquidar (R101933)]、新型氨基哌啶类逆转剂 S9788	在一定程度上克服了前两代的不足之处，但仍然存在药代动力学异常、对正常细胞毒性大等问题



维拉帕米
Verapamil

环孢素 A
Cyclosporin A

右旋维拉帕米
dexverapamil

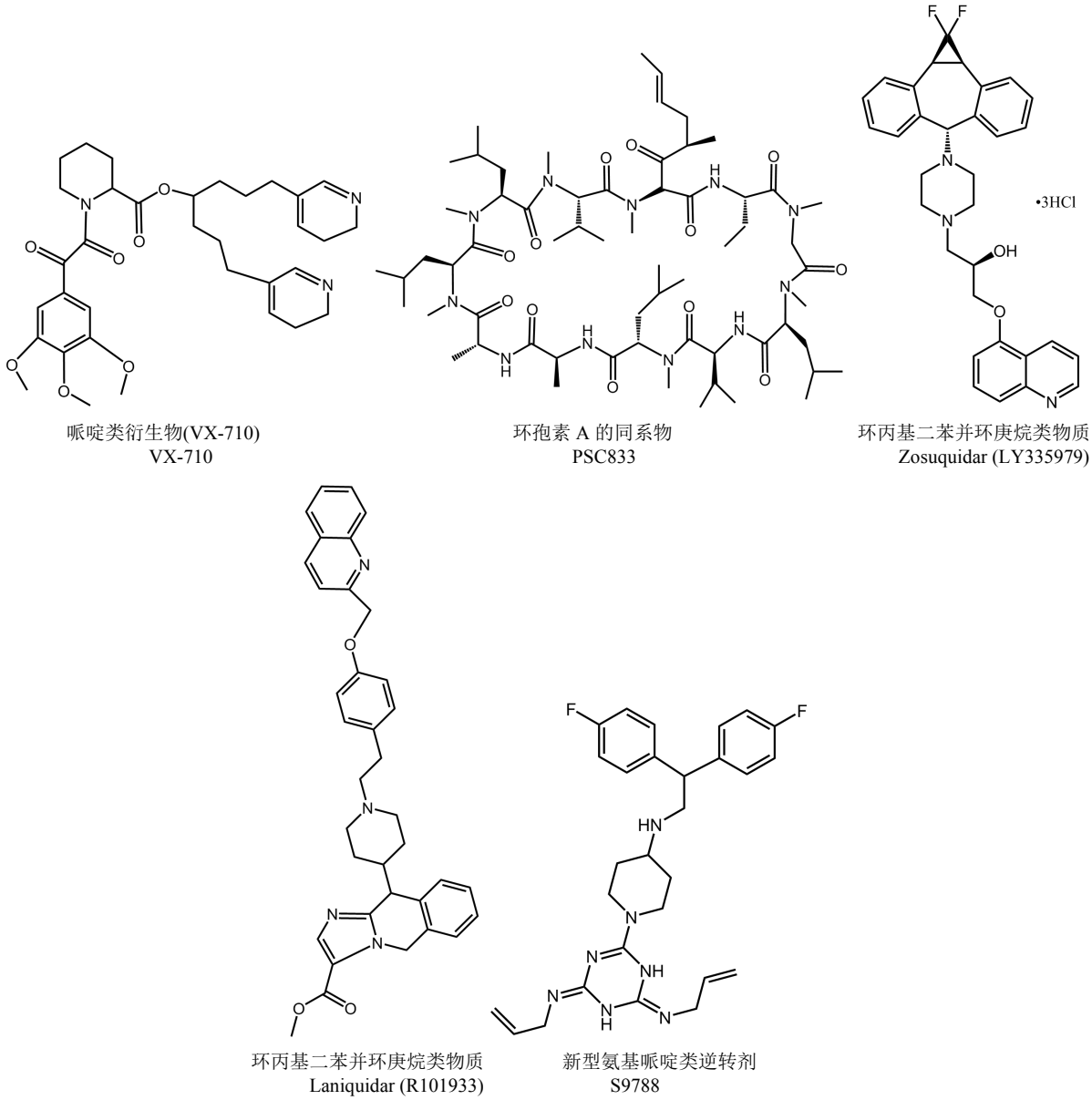


Figure 3. Targeting ABCB1 resistance reversal agent
图 3. 靶向 ABCB1 耐药逆转剂

3.1.2 谷胱甘肽转移酶(GST)/谷胱甘肽(GSH)抑制剂

GST/GSH 过度表达而产生 MDR [29]。抑制 GSH 的药物有丁硫氨酸亚碘胺(BSO)、依地尼酸(EA)、硝基咪哇类等。BSO 是谷氨酰半胱氨酸合成酶的特异性抑制剂，它通过降低细胞内 GSH 的浓度，增加肿瘤细胞对抗癌药物的敏感性逆转 MDR。EA 可以抑制 GST 的活性，在 GST 的催化作用下，EA 与 GSH 结合形成的 EA-GSH 复合物比 EA 更强作用[29] [30]。小分子化合物 APR-246 (图 4)具有调节细胞内 GSH 水平的作用，毒副作用小，是潜在的 MDR 逆转剂，正在进行临床试验[31]。

3.1.3. 拓扑异构酶(Topo)抑制剂

Topo 是细胞凋亡过程中关键的核内酶。临床用药初期，TopoI 抑制剂(伊立替康、拓扑替康等)抗肿瘤敏感性较高，但易产生耐药性。TopoII 抑制剂 XR11576 (图 5)可逆转 TopoI/ABCB1/MRP 导致的 MDR

[32]，目前在 I 期临床研究中。TopoI 和 TopoII 抑制剂联合使用可产生一加一大于二的协同作用，达到逆转 MDR 的效果，国内外已进入临床实验[33] [34] [35]。

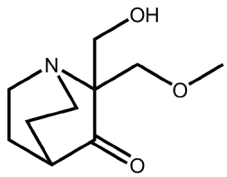


Figure 4. APR-246 structural formula
图 4. APR-246 结构式

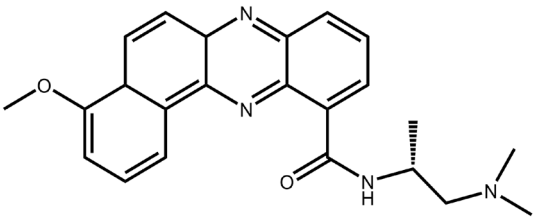


Figure 5. XR11576
图 5. XR11576

3.1.4. 酪氨酸激酶抑制剂(TKIs)

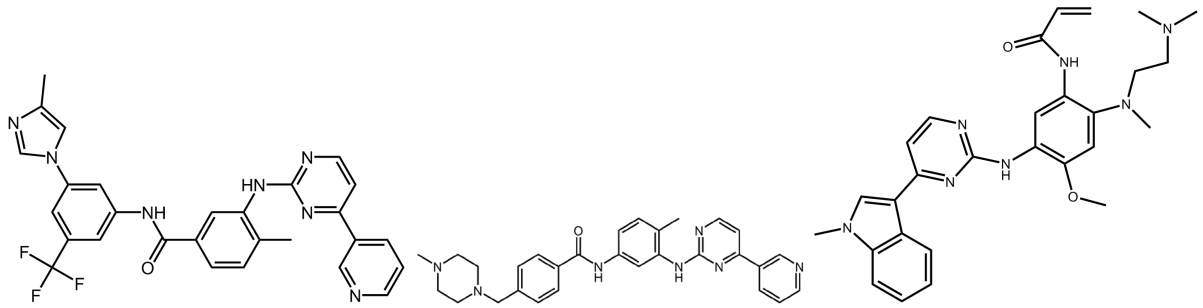
TKIs (图 6)抑制 ABC 转运蛋白活性，逆转肿瘤细胞对一些传统化疗药物的 MDR。如伊马替尼(Imatinib)可逆转 ABCB1 过度表达的表皮癌细胞系(KB-G2)对长春新碱、紫杉醇、依托泊苷的耐药性[29] [36]，尼洛替尼(Nilotinib)逆转 ABCC1 介导的肿瘤多药耐药，但会改变传统抗癌药物的血药动力学，不宜用于临床。厄洛替尼联合曲妥珠单抗表现出较好的耐受性和增强抗肿瘤活性，联合化疗治疗 MDR 患者值得进一步临床研究[37]。

达沙替尼(Dasatinib)属第二代酪氨酸激酶抑制剂，用于已经治疗，包括甲磺酸伊马替耐药或不能耐受的慢性骨髓性白血病所有病期的成人患者，不良反应大部分轻度到中度[38]。

奥西替尼(Oxitinib)是第三代不可逆的口服 EGFR-TKI，可以有效和选择性地抑制 EGFR 敏感突变和 EGFR T790M 耐药突变，MET 扩增是 EGFR-TKI 产生 MDR 原因之一，临床前研究和初步临床资料表明，联合使用 MET 抑制剂和 EGFR-TKI 是治疗 EGFR-TKIs 获得性耐药的有效方法[39]。

3.1.5. 其它

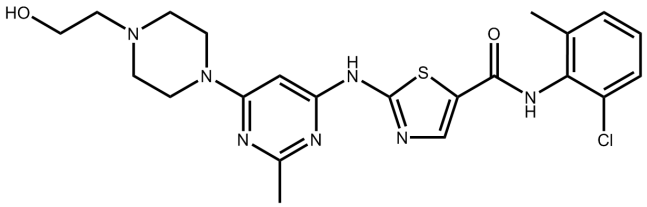
蛋白激酶 C(PKC)可以改变药物在 MDR 细胞中的蓄积，部分 MDR 肿瘤细胞中 PKC 活性增加。



尼洛替尼
Nilotinib

伊马替尼
Imatinib

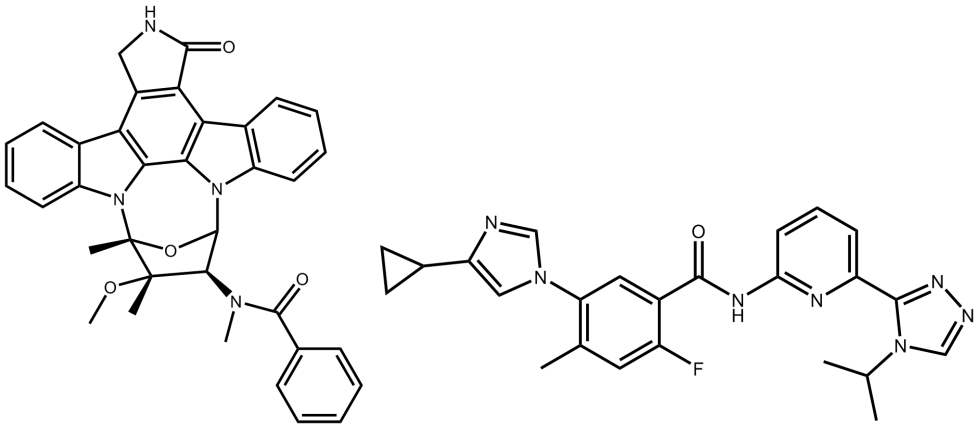
奥西替尼
Oxitinib



达沙替尼
Dasatinib

Figure 6. TKIs inhibitors
图 6. TKIs 抑制剂

CGP41251 (图 7)是高度选择性的 PKC 抑制剂，具有抗肿瘤及有效逆转 MDR 的作用，使 MDR 细胞对阿霉素和长春新碱的敏感性增加。然而，由于它逆转 MDR 的同时也产生较大的毒性作用，限制了临床应用[40]。GS-4997 (图 7)是一种凋亡信号调节激酶 1 (ASK1)抑制剂，处于 III 期临床试验中，研究发现 GS-4997 可以抑制肿瘤 MDR 细胞中 ABCB1 和 ABCG2 的表达，提示 GS-4997 有希望发展 MDR 逆转剂[41]。



CGP41251　　GS-4997

Figure 7. CGP41251 and GS-4997
图 7. CGP41251 和 GS-4997

3.2. 逆转肿瘤 MDR 临床前研究药物

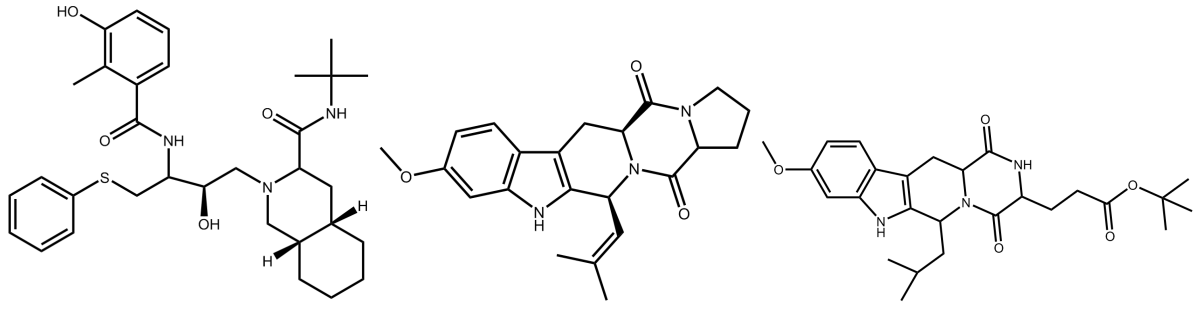
论当前逆转肿瘤 MDR 临床前研究药物结构见图 8，进展见表 2。

Table 2. Drugs that reverse tumor MDR preclinical research
表 2. 逆转肿瘤 MDR 临床前研究药物

分类	代表化合物	研究情况
ABCB1 抑制剂	NFV	降低 MDR 细胞内 ATP 含量，促进 K562/ADR 细胞凋亡，逆转 MDR，后续需进行动物和临床 MDR 研究[42]
ABCG2 抑制剂	FTC, Ko143	FTC 存在严重中枢神经系统毒性，未进行进一步临床研究；Ko143 比 FITC 毒性小，动物实验表明 Ko143 可逆转 ABCG2 介导的 MDR [43] [44]
src 家族激酶抑制剂	A-770041	抑制 Src 和 Lck 的激活和表达，逆转骨肉瘤细胞对紫杉醇和阿霉素的 MDR，其逆转机制有待进一步研究[45]

Continued

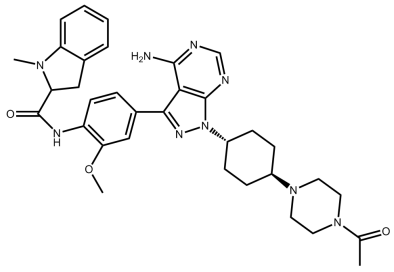
c-Met 激酶抑制剂	PHA-665752	PHA-665752 通过抑制 PI3K-Akt 信号传导， 再抑制 c-Met 活化可使骨肉瘤细胞对顺铂敏感[46]
ALK 抑制剂	NVP-TAE684	作为治疗难治愈和复发的 ALK 阳性淋巴癌的一种策略，未进行临床实验； 通过刺激 ABCB1 ATP 酶活性来抑制 ABCB1 的表达， 提示 NVP-TAE684 是 ABCB1 介导 MDR 的研究方向[47]
BCL-2 抑制剂	Venetoclax	增加了化疗药在 MDR 细胞内积累， venetoclax 是联合治疗中克服 ABCG2 介导的 MDR 的有效策略[48]
其它	Ethaselen, RAL	Ethaselen 与某些化疗药物相结合，具有致敏化合物的功效[49]； RAL 体外试验表明可增强 ER-MDR 乳腺肿瘤对紫杉醇的敏感性[50]



NFV

FTC

Ko143



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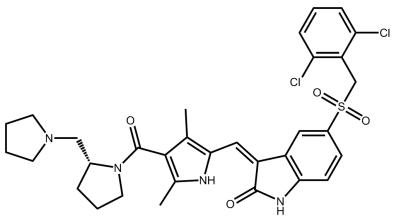

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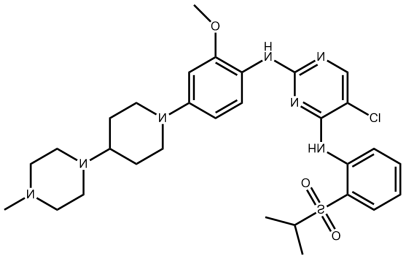
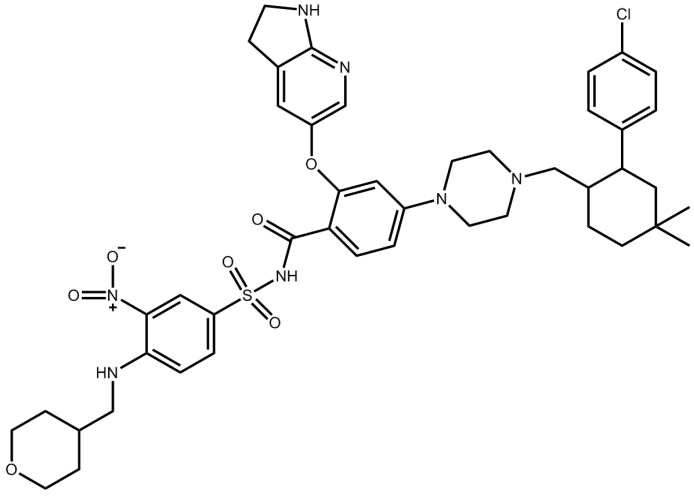


NVP-TAE684



Venetoclax

Figure 8. The drugs that reverse tumor MDR preclinical research
图 8. 逆转肿瘤 MDR 临床前研究药物

3.3. 逆转肿瘤 MDR 先导化合物

3.3.1. 天然先导化合物

以查耳酮、7-异戊烯氧基香豆素(7-IP)和麻疯树二萜类天然产物为先导合成的化合物(图 9)具有良好的 MDR 逆转效果(表 3)。

Table 3. Lead compounds derived from natural products
表 3. 来源于天然产物的先导化合物

先导化合物	合成产物	最优逆转 MDR 产物	研究情况
查耳酮[51]	B 环上被喹喔啉单元取代衍生物	化合物 1 和 2	逆转 ABCG2 介导的米托蒽醌外排。B 环 4 位的取代是关键，在该位置，O-苄基残基是抑制 ABCG2 最有效的取代基
7-IP [52] [53]	含有 7-IP 核的丁炔基－氨基链衍生物	化合物 1e	无剂量依赖性，其逆转特性与丁炔基-氨基侧链有关，特别是端胺是逆转肿瘤 MDR 的关键特征
麻疯树二萜类[54]	通过结构修饰产生了 22 种新的衍生物	化合物 19、25、26	化合物 26 有更大的 MDR 逆转能力和更低细胞毒性，对其进一步的评价和结构修饰具有重要意义

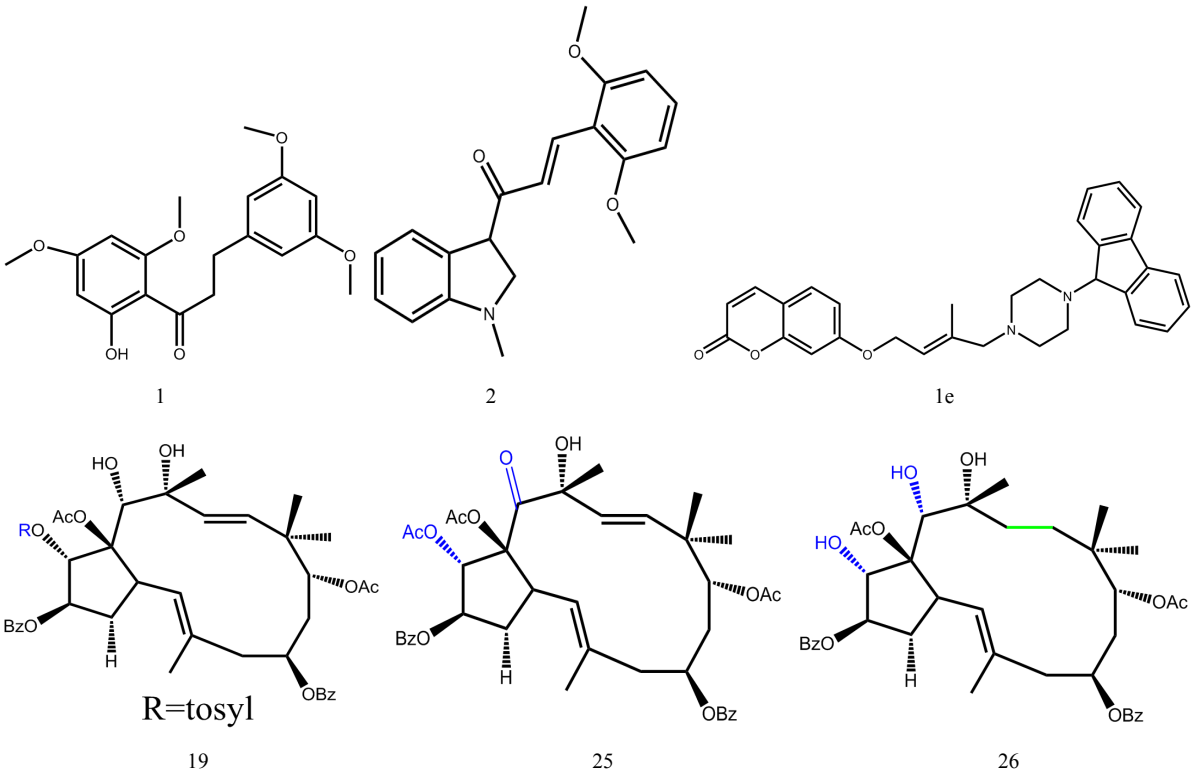


Figure 9. Compounds synthesized using natural products as the lead
图 9. 以天然产物为先导合成的化合物

3.3.2. 合成先导化合物

近年来化学合成的 LS-2-3j、479、C4、D3 和 D6 先导化合物结构见图 10，进展见表 4。

Table 4. Lead compound from chemical synthesis
表 4. 来源于化学合成的先导化合物

合成类别	先导化合物	研究情况
新型二氢茚并[1,2-b]吲哚衍生物[55]	LS-2-3j	下调 ABCB1 和 ABCG2 的 mRNA 和蛋白表达水平，增强 MDR 细胞中 DOX 和 MITX 的蓄积，逆转 MDR；可用作肿瘤 MDR 药物发现和开发的先导化合物
新型 5-氰基-6-苯基嘧啶衍生物[56]	479	逆转 ABCB1 和 ABCG2 介导的 MDR 方面表现出选择性双重活性，是设计和开发双目标 MDR 逆转剂的先导化合物。
十二种新颖的 5-氧代六氢喹啉衍生物[57]	C4、D3、D6	评估了对耐药性人子宫肉瘤细胞系(MES-SA/DX5˚)的逆转作用，发现 C4，D3 和 D6 能够同时阻断 3 种参与 MDR 的转运蛋白，在此基础上，进一步合成改造，有希望发现克服 MDR 药物

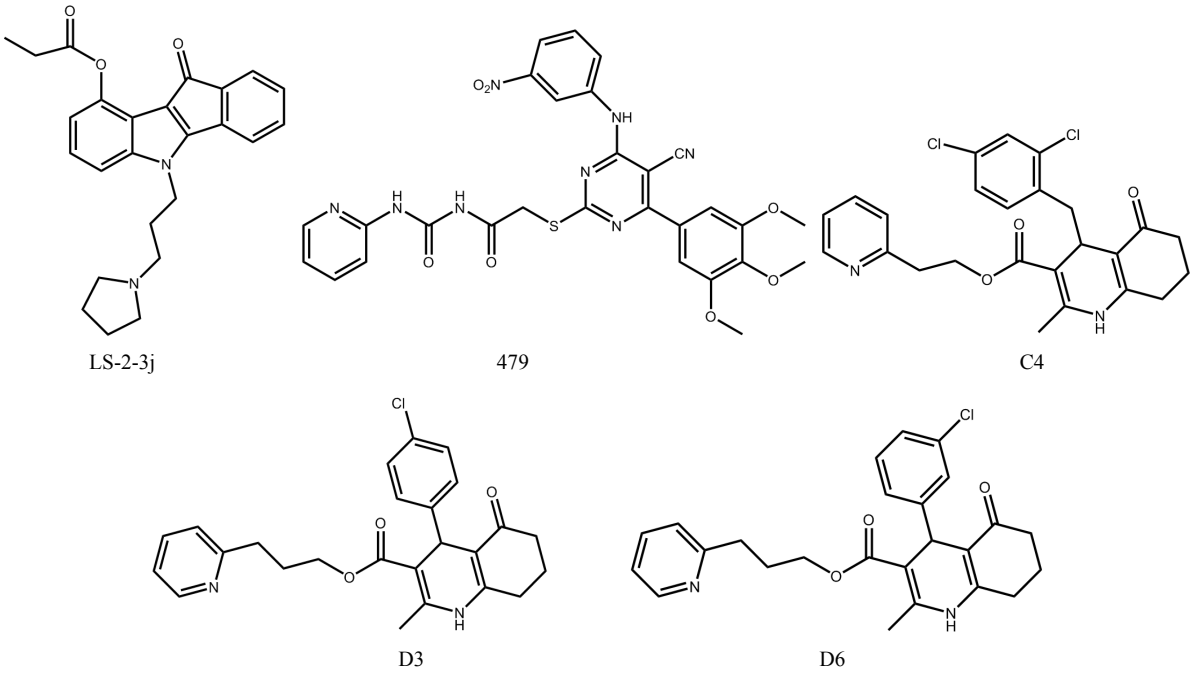


Figure 10. The lead compound of chemical synthesis
图 10. 化学合成的先导化合物

4. 结语与展望

肿瘤 MDR 是肿瘤治疗失败主要原因，明确 MDR 机制，联合用药是克服肿瘤 MDR 的有效手段。目前化学逆转剂毒副作用限制了临床应用，开发高效低毒的靶向药物是当务之急，先导化合物的发现与结构优化是主要努力方向之一，有望开发理想的 MDR 逆转剂。

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