# 放射治疗用小分子增敏剂的研究进展

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**摘要** 肿瘤放射治疗作为癌症治疗的关键常用手段之一，其疗效受限于肿瘤细胞的固有辐射抵抗性和正常组织的辐射损伤。近年来，放疗用小分子增敏剂凭借其分子量小、合成可控性强以及靶向精准等独特优势，逐渐成为备受关注的研究热点。本文旨在系统综述小分子增敏剂的分类及其研究现状，重点阐述包括DNA损伤修复抑制剂、缺氧靶向剂、活性氧调节剂和表观遗传调节剂等在内的不同类型小分子增敏剂的作用机制和最新研究进展。这些小分子增敏剂通过精准干预肿瘤细胞的生物学过程，有效增强其对放疗的敏感性，进而显著提升放疗疗效。随着对肿瘤耐药机制和氧化应激的深入研究，小分子增敏剂在减少放疗相关副作用以及提高对特定肿瘤细胞选择性方面展现出广阔的应用前景，有望为肿瘤放疗领域带来新的突破。

**关键词** 放射治疗，小分子增敏剂，DNA损伤修复，缺氧靶向，活性氧调节

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## Research progress of small molecule sensitizers for radiotherapy

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**ABSTRACT** As a crucial and frequently utilized modality in cancer treatment, the efficacy of radiotherapy is often limited by both the intrinsic radioresistance of tumor cells and radiation-induced damage to healthy tissues. In recent years, small-molecule radiosensitizers for radiotherapy have become an increasingly popular research focus, owing to their distinct advantages, including low molecular weight, highly controllable synthesis, and precise targeting capabilities. This article aims to systematically review the classification and current research status of

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small-molecule radiosensitizers, with a focus on elucidating the mechanisms of action and latest research progress of different types of small-molecule radiosensitizers, including DNA damage repair inhibitors, hypoxia-targeting agents, reactive oxygen species modulators, and epigenetic regulators. These small-molecule radiosensitizers effectively enhance the radiosensitivity of tumor cells by precisely intervening in their biological processes, thereby significantly improving the efficacy of radiotherapy. With a deeper understanding of tumor resistance mechanisms and oxidative stress, small-molecule radiosensitizers show broad application prospects in reducing radiotherapy-related side effects and increasing selectivity for specific tumor cells and are expected to bring breakthroughs to the field of cancer radiotherapy.

**KEYWORDS** Radiotherapy, Small molecule sensitizers, DNA damage repair, Hypoxia targeting, Reactive oxygen species regulation

**CLC** TL13

肿瘤放射治疗(RT)作为癌症治疗的三大主要手段之一，在临床中发挥着不可替代的作用[1]。其基本原理是利用高能电离辐射(如X射线、γ射线等)与生物体系相互作用，直接作用于DNA、蛋白质等大分子，引发电离反应；同时，通过间接作用于细胞中的水分子，产生羟基自由基和水合电子等活性粒子，这些活性物种是主要的DNA损伤介质。高能辐射诱导肿瘤细胞的DNA损伤，包括单链断裂、双链断裂和碱基损伤等，进而触发细胞周期阻滞、凋亡等细胞死亡途径，最终达到抑制肿瘤生长和增殖的目的[2-4]。尽管放射治疗技术取得了显著进展，但肿瘤细胞固有的辐射抗性和正常组织的辐射损伤仍然是制约其疗效提升的关键因素[5-6]。

肿瘤细胞对辐射的抵抗性可能源于多种复杂的生物学机制[5,7-9]。肿瘤细胞往往具有增强的DNA损伤修复能力，能够快速修复辐射诱导的DNA损伤，从而在辐射作用下存活[7]。实体肿瘤内部普遍存在的缺氧微环境会降低辐射诱导的活性氧(ROS)生成，减弱辐射的细胞杀伤效果[8]。肿瘤细胞还可能通过上调抗氧化防御系统、改变细胞周期调控等方式来抵抗辐射诱导的细胞死亡[9]。另一方面，正常组织对辐射的敏感性限制了放疗剂量的提高，增加了治疗相关副作用的风险，如放射性肺炎、放射性肠炎等。这些因素共同制约了放射治疗的效果和临床应用[10-11]。

为提高放射治疗的疗效并增强其靶向性，放疗增敏剂应运而生[12-13]。其中，小分子增敏剂因其独特的优势已成为该领域的研究热点[14]。从药物开发角度来看，小分子化合物(分子量通常小于1 000 Da)具有显著的合成优势。随着计算机辅助药物设计和高通量筛选技术的发展，研究人员能够在短时间内生成和筛选大量化合物，大幅提高新药发现效率[15-18]。同时，小分子易于进行结构修饰和优化，如Liew等[19]通过对尼莫拉唑(Nimorazole，1，图1)的侧链改造，合成了水溶性和增敏效果更优的新型硝基咪唑烷基磺酰胺类化合物2和3(图1)。

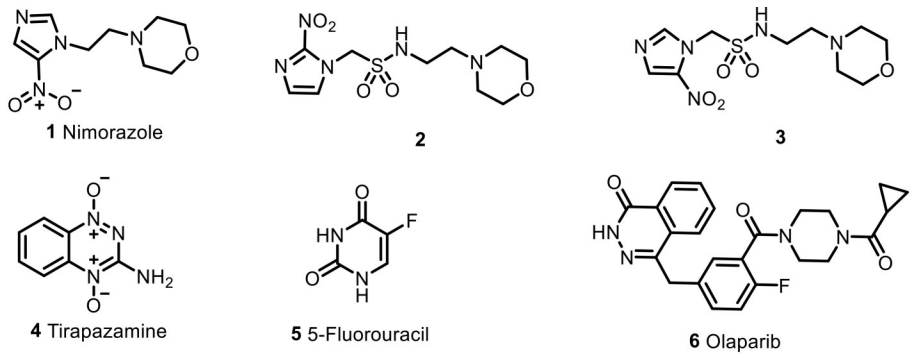


**图1** 增敏剂Nimorazole(1)、化合物2(2)、化合物3(3)、Tirapazamine(4)、5-Fluorouracil(5)和Olaparib(6)的化学结构式
**Fig.1** The chemical structures of the sensitizer Nimorazole (1), compound 2 (2), compound 3 (3), Tirapazamine (4), 5-Fluorouracil (5), and Olaparib (6)

此外，小分子药物可通过化学合成实现大规模生产，如增敏剂Tirapazamine（TPZ，4，图1）已实现公斤级制备[20]。在药物递送方面，小分子增敏剂展现出优异的生物利用度和组织渗透性[21-23]。与生物大分子相比，小分子更易穿透生物屏障到达肿瘤部位，这一特性对实体瘤治疗尤为重要。其灵活的给药方式，如氟尿嘧啶（5-Fluorouracil，5，图1）可口服或注射，便于临床应用[24]。这些优势使小分子增敏剂成为当前放射治疗研究的重要方向[25-26]。

基于此，本文综述肿瘤放射治疗领域小分子增敏剂的优势、分子分类、最新研究进展及未来发展趋势，以期为该领域的深入研究提供理论参考和实践指导。

## 1　小分子增敏剂的分类及其研究现状

小分子增敏剂的核心作用是通过特定分子机制增强肿瘤细胞对辐射的敏感性，从而提高放疗效果，这类化合物能够精准干预肿瘤细胞的生物学过程，最终使肿瘤细胞在辐射作用下更易发生不可逆的损伤和死亡[3,26]。根据作用机制的不同，小分子增敏剂可分为DNA损伤修复抑制剂、缺氧靶向剂、ROS调节剂和表观遗传调节剂（图2）。DNA损伤修复抑制剂通过阻断肿瘤细胞的DNA损伤修复通路，增强辐射诱导的DNA损伤效应[27]。缺氧靶向剂则针对肿瘤缺氧微环境，提高缺氧肿瘤细胞的辐射敏感性[28]。ROS调节剂通过增加细胞内ROS水平，放大辐射诱导的氧化应激[29]。表观遗传调节剂则通过改变染色质结构和基因表达，增强肿瘤细胞对辐射的敏感性[30]。

小分子增敏剂在不同类型肿瘤中的应用效果各异，显示出针对特定肿瘤的独特优势。例如，DNA损伤修复抑制剂在卵巢癌和乳腺癌中的应用效果尤为显著，聚腺苷二磷酸核糖聚合酶（Poly（ADP-ribose）polymerase，PARP）抑制剂如奥拉帕尼和尼拉帕尼通过阻断DNA修复通路，显著增强了放疗的敏感性，并在临床试验中表现出良好的协同效应[31-32]。缺氧靶向剂（如Tirapazamine和Evofosfamide）在肺癌和胰腺癌的研究中显示出提升放疗效果的潜力，特别是在缺氧微环境下的肿瘤细胞中，能够显著增强辐射诱导的细胞杀伤作用[28,33]。ROS调节剂（如Motexafin gadolinium和二甲双胍）在非小细胞肺癌和结直肠癌中的应用，通过增加细胞内ROS水平，显著提高了放疗的疗效[34-35]。表观遗传调节剂（如Vorinostat和Decitabine）在胶质母细胞瘤和乳腺癌中的应用，通过改变染色质结构和基因表达，增强了肿瘤细胞对辐射的敏感性[36-37]。这些研究表明，小分子增敏剂在不同肿瘤的放射治疗中具有广泛的前景。

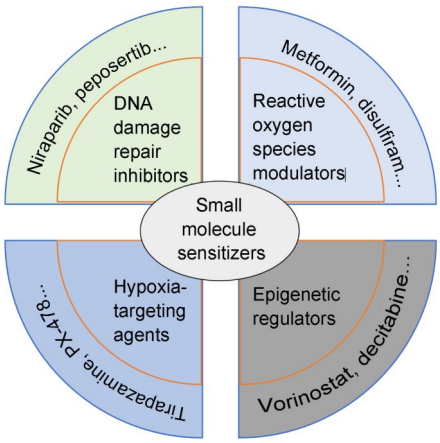


**图2**　小分子增敏剂的分类
**Fig.2**　Classification of small molecule sensitizers

### 1.1　DNA损伤修复抑制剂

辐射通过诱导DNA单链断裂（SSB）和双链断裂（DSB）杀伤肿瘤细胞，但肿瘤细胞可通过激活非同源末端连接（NHEJ）、同源重组修复（HRR）等通路修复损伤[3,7]。DNA损伤修复抑制剂通过靶向DNA修复关键酶：如PARP、共济失调毛细血管扩张突变蛋白/共济失调毛细血管扩张及Rad3相关蛋白（Ataxia telangiectasia mutated/ataxia telangiectasia and Rad3-related，ATM/ATR）、DNA依赖性蛋白激酶（DNA-dependent protein kinase，DNA-PK），阻断修复进程，增强辐射诱导的基因组不稳定性，使损伤累积并触发细胞凋亡[38-39]。

#### 1.1.1　PARP抑制剂

奥拉帕尼（Olaparib，6，图1）作为全球首个获批的PARP抑制剂，通过靶向抑制PARP-1/2的酶活性，阻断SSB的碱基切除修复（BER）通路，诱导“合成致死”效应，显著增强肿瘤细胞对放疗的敏感性[40-41]。在临床转化方面，多项研究以及临床试验证实，Olaparib可穿透血脑屏障并富集于复发性胶质母细胞瘤的肿瘤核心及浸润边缘区域，与放疗剂替莫唑胺（TMZ）联用展现出协同效应[42-43]。一项针对70岁以上新诊断胶质母细胞瘤患者的研究成功确立了Olaparib（200 mg，每日两次）联合40 Gy分次放疗的II期推荐剂量。研究结果显示，在接受

Olaparib和TMZ联合治疗的36例可评估患者中，39%在6个月随访期内未出现病情进展，这表明Olaparib在增加放疗效果方面具有潜力，特别是当与TMZ联合使用时。同时，Olaparib的安全性良好，在需要偶尔调整剂量的情况下也能被耐受[44]。

尼拉帕尼（Niraparib，7，图3）是一种高效的选择性PARP-1/2抑制剂，近年来，在强化放疗效果方面显示出良好的潜力[32,45-47]。研究指出，Niraparib通过抑制DNA损伤修复机制，增强肿瘤细胞对放疗的敏感性，尤其是在新诊断的O6-甲基鸟苷转移酶（MGMT）未甲基化的胶质母细胞瘤（Glioblastoma，GBM）患者中取得了积极的临床数据[45-46]。在一项Phase 0/2的临床研究中，使用Niraparib联合放疗显著提升了GBM内药物的药物浓度与PARP抑制效果，显示出较好的放疗增敏效果，患者的中位生存期达20.3个月[45]，另外在GBM肿瘤组织中Niraparib不仅达到了生物活性相关的浓度，还在73%的患者中观察到了明显的PAR抑制效果。此外，Niraparib在头颈部鳞状细胞癌模型中也显示了增强放疗效果的潜力，Wang等[32]的研究结果表明，Niraparib通过延迟DNA损伤修复提高了细胞的放射敏感性，同时还降低了放疗后未修复的DNA双链断裂，增强了放疗的相对生物有效性。

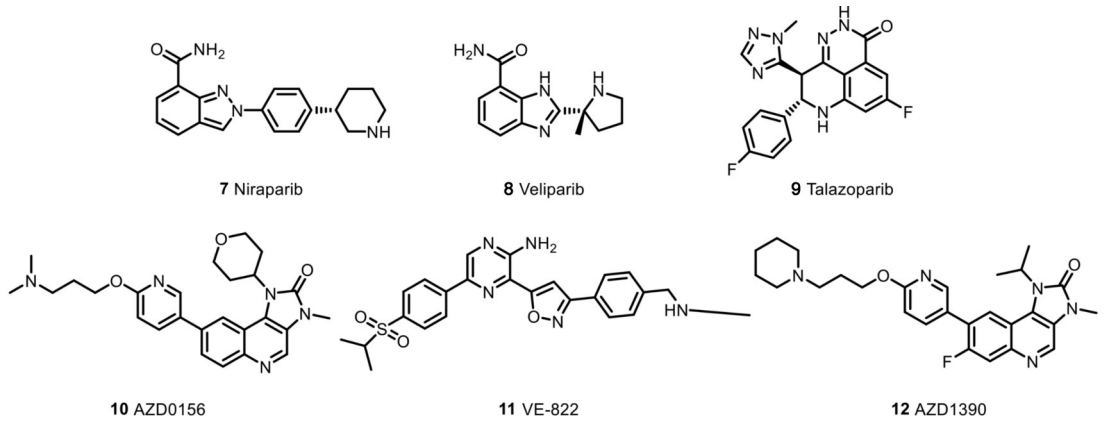


**图3** 增敏剂Niraparib（7）、Veliparib（8）、Talazoparib（9）、AZD0156（10）、VE-822（11）和AZD1390（12）的化学结构式
**Fig.3** The chemical structures of the sensitizer Niraparib (7), Veliparib (8), Talazoparib (9), AZD0156 (10), VE-822 (11), and AZD1390 (12)

Veliparib（8，图3）作为PARP抑制剂，基于抑制PARP酶活性，干扰碱基切除修复（BER）途径，导致放疗诱导的DNA单链断裂无法修复并转化为致死性双链断裂显著增强放疗的抗肿瘤效果，尤其在MGMT未甲基化的GBM和髓母细胞瘤中展现出重要潜力[48-51]。Jue等[48]在对MGMT未甲基化的GBM患者研究中，发现Veliparib联合放疗可显著抑制克隆形成能力，并诱导细胞凋亡（33.8% *vs.* 单放疗14.0%）。在颅内异种移植模型中，Jue等[48]发现，联合治疗使小鼠中位生存期延长至83 d，较单纯放疗（73 d）和Veliparib单药（64 d）显著改善，同时通过TUNEL染色证实肿瘤细胞凋亡率得到提升，增殖细胞核抗原Ki67增殖指数下降。在髓母细胞瘤模型中，Buck等[49]发现Veliparib通过延缓DNA损伤修复（彗星实验显示修复延迟超过2 h）和增加γH2AX焦点积累，增强放疗的细胞毒性，联合治疗使肿瘤细胞集落形成能力降低，并在小鼠模型中显著延长生存期。

Talazoparib（9，图3）作为新一代PARP抑制剂，阻断PARP介导的单链断裂修复功能，并通过“PARP捕获”效应将酶分子固定在损伤位点，从而放大放疗诱导的DNA双链断裂的细胞毒性，在多种肿瘤模型中展现出显著的放射增敏效应[52-55]。DuRoss等[52]在4T1乳腺癌模型中证实，Talazoparib联合放疗显著增强肿瘤细胞凋亡，活体实验显示，其通过混合胶束递送系统可提高药物生物利用度，且未增加急慢性毒性，验证了放疗增敏策略的可行性。Venneker等[53]在放化疗抵抗的软骨肉瘤研究中，发现Talazoparib与放疗的协同作用独立于IDH突变状态，可能源于部分细胞存在非经典DNA修复缺陷（如PARylation能力低下或RAD51介导的同源重组修复延迟），这种特性使得Talazoparib能克服传统生物标志物限制，拓展适用人群。Jonuscheit等[54]通过对比黑色素瘤与正常成纤维细胞发现，Talazoparib联合放疗在肿瘤细胞中产生超加性效应，存活分数显著降低，同时诱导更强的

G2/M期阻滞，这种选择性增敏作用源于肿瘤细胞基线PARP1/2高表达及修复压力下的PARP2代偿性上调。有关Talazoparib的I期临床试验证实了Talazoparib与放疗联用治疗复发性妇科肿瘤安全可行，其通过增强放疗敏感性使局部控制率提升至72%[55]。

### 1.1.2 ATM/ATR抑制剂

AZD0156（10，图3）是一种高效的ATM激酶抑制剂，通过靶向DNA损伤修复（DDR）通路显著增强肿瘤细胞对放疗的敏感性，并可以协调调控细胞周期、激活抗肿瘤免疫增强放疗效果[56]。研究表明，AZD0156在多种肿瘤模型中均表现出显著的放疗增敏效果。在黑色素瘤细胞中，Scheper等[57]发现，AZD0156与放疗联合使用可协同诱导G2/M期阻滞，显著降低克隆形成能力，同时选择性保护正常组织成纤维细胞，展现出良好的治疗作用。此外，在头颈鳞状细胞癌（MOC2）和黑色素瘤（B78）模型中，Jin等[58]发现AZD0156与放疗联合不仅通过抑制ATM通路增强DNA损伤效应，还能激活STING依赖的I型干扰素反应，上调肿瘤细胞MHC-I，促进$CD8^+$T细胞浸润，从而增强抗肿瘤免疫应答。在乳腺癌MCF-7细胞中，Yilmaz等[59]发现AZD0156联合2~10 Gy放疗可诱导G0/G1期阻滞，显著降低克隆形成存活率，而对正常肺成纤维细胞WI-38的影响较小，进一步证实了其作为增敏剂对放疗的增敏作用。

VE-822（11，图3）是一种高效的ATR激酶抑制剂，通过靶向DDR通路显著增强肿瘤细胞对放疗的敏感性[60]。Thidil Puliyappadamba等[61]的研究表明，VE-822在GBM中表现出显著的放疗增敏效果。其作用机制主要依赖于稳定5'-3'核酸外切酶EXO1，阻断辐射诱导的EXO1降解，导致DNA过度切除和同源重组（HR）修复抑制。在体外实验中，VE-822处理显著增强了GBM细胞系对电离辐射（IR）的敏感性。更重要的是，VE-822能够穿透血脑屏障，在体内实验中与放疗联合使用可抑制颅内肿瘤的DNA修复，延缓肿瘤生长并显著延长荷瘤小鼠的生存期。在胰腺导管腺癌（PDAC）模型中，Fokas等[60]发现VE-822通过抑制Chk1磷酸化、增加持续性DNA损伤（γH2AX和53BP1 foci）和减少Rad51 foci形成，显著增强了癌细胞对放疗和吉西他滨的敏感性，同时不影响正常细胞的存活。

AZD1390（12，图3）作为一种新型ATM/ATR抑制剂，通过靶向抑制DDR通路中的关键激酶，显著增强放疗对多种实体肿瘤的疗效，其作用机制与穿透血脑屏障的特性使其在GBM和中枢神经系统（CNS）肿瘤治疗中具有独特优势[62−65]。在GBM患者中开展的I/II期临床试验显示，AZD1390在肿瘤组织内达到药理学有效浓度，并显著抑制放疗诱导的pRAD50磷酸化（较对照组降低98%以上），临床耐受性良好，48/49例患者进入治疗性放疗联合阶段，在治疗期间复发性GBM患者中位总生存期（OS）达15.4个月，具有显著临床获益[62−63]。在Tew等[65]对乳腺癌CM的PDX模型的研究中，AZD1390联合放疗使$HER2^+$（CM14）和三阴性（CM16）亚型肿瘤生长抑制率分别达80%和77%，脑内原位移植模型生存期延长78%（222 d *vs.* 对照组123 d），机制研究发现，AZD1390通过促进致突变性非同源末端连接（NHEJ）加剧基因组不稳定性，且其疗效与TP53突变状态无关，突破了传统ATM抑制剂依赖p53缺陷的限制。

M3541（13，图4）作为一种新型高选择性ATP竞争性ATM抑制剂，在亚纳物质的量浓度下即可有效抑制ATM自磷酸化（Ser1981）及其下游靶点（如CHK2、KAP1和p53）的活化，显著延缓DSB修复，导致γH2AX焦点持续积累，这种修复缺陷迫使携带未修复DNA的癌细胞进入异常有丝分裂，阻断放疗诱导的DNA损伤信号传导，成为增强放疗疗效的潜在增敏剂[66−67]。在体外实验中，M3541与放疗联用显著降低多种癌细胞系的克隆形成能力，诱导G2/M期阻滞及多倍体化，最终通过染色体结构异常导致细胞死亡。动物模型中，M3541联合分次放疗（如30×2 Gy临床等效方案）在头颈部（FaDu）、肺（NCI-H1975）及结直肠（Capan-1）移植瘤中实现完全且持久的肿瘤消退，且未加重正常组织毒性（如放射性皮炎）。尽管I期临床试验显示，M3541（50~300 mg）与姑息放疗联用安全性良好，但其剂量-反应关系不明确及药代动力学不理想，说明需要进一步的研究与开发[68]。

### 1.1.3 DNA-PK抑制剂

M3814（Peposertib，14，图4）作为新型DNA-PK抑制剂，通过靶向抑制非同源末端连接（NHEJ）这一关键DSB修复通路，显著增强放疗的抗肿瘤效应[69]。Bendell等[70]研究显示，M3814通过阻断DNA-PK催化活性，延长放疗诱导的DSB损伤的持续存在，从而增强肿瘤细胞对电离辐射的敏感性。而Chauhan等[71]则发现，在胰腺神经内分泌肿瘤（QGP-1）异种移植模型中，M3814联合分次放疗

(4×2 Gy)可显著抑制肿瘤生长，联合组较单纯放疗组肿瘤体积减少更显著，且肿瘤血管生成明显受抑，而单药M3814无独立抗肿瘤活性，证实其作为放疗增敏剂的协同作用机制。此外，Zenke等[69]M3814口服给药于两种人类癌症的异种移植模型中，采用临床确立的6周分次放疗方案，显著增强了离子辐射的抗肿瘤活性，并在无毒性剂量下实现了肿瘤的完全消退。

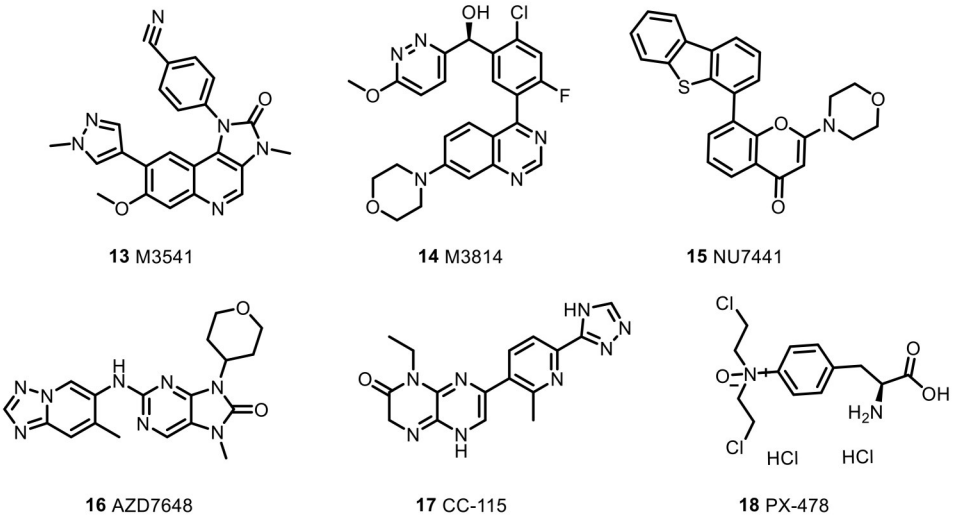


**图4** 增敏剂M3541(13)、M3814(14)、NU7441(15)、AZD7648(16)、CC-115(17)和PX-478(18)的化学结构式
**Fig.4** The chemical structures of the sensitizers M3541 (13), M3814 (14), NU7441 (15), AZD7648 (16), CC-115 (17), and PX-478 (18)

NU7441(15,图4)近年来在放疗增敏领域展现出显著潜力[72-74]。在Yang等[72]的研究中，NU7441不仅降低了HepG2细胞的DNA-PKcs(S2056)的蛋白表达，还增加了γH2AX焦点的数量，并诱导细胞周期停滞在G2/M期，这些结果说明NU7441通过抑制DNA修复和细胞周期检查点，显著增强了肝癌细胞的放疗敏感性。在肺癌治疗中，Menon等[73]将NU7441应用于多功能双药载纳米颗粒(MDNP)中，这种纳米颗粒能够有效减少肺部肿瘤，同时降低系统毒性，与化疗药物吉西他滨联合使用，以实现局部化放疗的协同增效。在Ohuchi等[74]对口腔鳞状细胞癌的研究中，NU7441能够消除6 Gy X射线照射后HSC2和HSC2-R细胞的集落形成能力，并显著增强放疗诱导的细胞凋亡，其机制是NU7441通过抑制DNA-PKcs的磷酸化，阻断了NHEJ修复途径，从而克服了癌细胞的放疗抵抗。

AZD7648(16,图4)是一种高效、高选择性的DNA依赖性蛋白激酶(DNA-PK)抑制剂，通过抑制DNA-PK靶蛋白(如DNA-PKcs Ser2056、γH2AX和RPA32)的磷酸化，阻碍放疗后DNA损伤修复，导致基因组不稳定性和细胞死亡通过阻断非同源末端连接(NHEJ)修复通路，显著增强放疗对肿瘤细胞的杀伤效果[75-79]。Nakamura等[75]研究显示，AZD7648与放疗联合应用在多种免疫健全小鼠模型(如MC38、CT26)中诱导高达75%的肿瘤完全消退，该组合治疗不仅直接增敏放疗，还重塑肿瘤微环境：降低$CD8^+$ T细胞的PD-1表达，减少耗竭表型(PD-1+Lag-3+细胞)，同时增强NK细胞的颗粒酶B活性，并显著上调I型干扰素(IFN)信号通路，增强小鼠对肿瘤的免疫调节。Fok等[76]发现，ZD7648与DNA损伤类药物(如多柔比星)或PARP抑制剂(如奥拉帕尼)联用也显示协同效应，尤其在ATM缺陷模型中可诱导深度肿瘤消退，凸显其在联合治疗中的广谱潜力。但是Baker[77]和Hong[78]等发现，AZD7648在增强放疗对肿瘤控制的同时，亦会增敏正常组织(如肠道隐窝、口腔黏膜)的放射损伤，导致体重下降、皮炎等毒性，其增敏比(SER)与肿瘤相近(2.0~2.5)，说明临床需优化剂量与照射范围以平衡疗效与安全性。

CC-115(17,图4)是一种同时靶向哺乳动物雷帕霉素靶蛋白(mTOR)激酶和DNA-PK的双重抑制剂，其通过抑制DNA-PK介导的非同源末端连接(NHEJ)修复通路，显著增强放疗对DNA双链断裂(DSB)的杀伤效果[80-83]。Bürkel等[80]在转移性黑色素瘤细胞研究中，发现CC-115联合放疗可导致细

胞凋亡和坏死率显著上升，在9种黑色素瘤细胞系中，7种出现放疗增敏效应，且半数以上呈现超叠加协同作用，而健康成纤维细胞未受影响，说明CC-115具有选择性增敏特性。Klieber等[81]在头颈部鳞状细胞癌（HNSCC）的研究中，发现CC-115联合放疗可诱导G2/M期阻滞并增加细胞死亡，但其效果弱于选择性DNA-PK抑制剂AZD7648，CC-115联合IR使HNSCC细胞死亡率提升2倍，而AZD7648联合IR则达到6倍。但是CC-115对HPV阳性HNSCC的协同效应更为显著，可能与mTOR通路抑制增强HPV相关癌细胞的放射敏感性有关。

### 1.2 缺氧靶向剂

实体瘤内部因异常血管结构和快速增殖常形成缺氧区域，而缺氧细胞对辐射的敏感性仅为常氧细胞的三分之一[84]。缺氧靶向剂通过模拟氧效应或靶向缺氧诱导因子（HIF-1α）信号通路，增强缺氧细胞的辐射敏感性[85-86]。

Tirapazamine（TPZ，4，图1）作为一种缺氧靶向剂，通过选择性杀伤肿瘤缺氧细胞增强放疗疗效。TPZ在低氧环境下被还原为活性自由基，诱导DNA损伤并抑制缺氧细胞的修复能力，从而克服放疗对缺氧细胞的抵抗性[28,87]。Lunt等[88]的研究显示，在KHT小鼠模型中，TPZ联合放疗显著降低了原发肿瘤的缺氧分数，进一步分析表明，TPZ通过靶向中等氧张力区域的放疗抵抗细胞，将局部控制率从20%提升至50%，并显著减少转移灶形成，这一结果说明TPZ可能通过抑制缺氧细胞介导的转移途径发挥抗肿瘤作用。然而，在头颈部鳞癌的III期临床试验中，TPZ联合顺铂及放疗未显著改善患者总生存期（2年OS率：TPZ/CIS组66.2% *vs.* 顺铂组65.7%），说明TPZ的疗效可能与肿瘤缺氧状态的选择性相关[89]。为进一步优化TPZ的靶向性和疗效，Sun等[90]开发了TPZ负载的外泌体纳米平台（MT），该平台在低剂量放疗（2 Gy）下通过放疗介导的氧耗加剧肿瘤缺氧，促进TPZ激活，显著抑制肿瘤生长，疗效优于传统高剂量放疗（6 Gy）。

PX-478（18，图4）通过抑制HIF-1α蛋白表达，阻断其介导的糖代谢、血管生成和细胞存活信号通路，从而克服肿瘤细胞的放疗抵抗[91-92]。Palayoor等[93]在体外实验中发现，PX-478显著降低前列腺癌细胞（PC3和DU145）的HIF-1α水平，并在常氧和缺氧条件下增强放疗敏感性（增强因子分别为1.4和1.56），同时诱导DNA损伤标志物γH2AX的持续表达。Frame等[94]发现，PX-478在放疗复发性前列腺癌模型中通过抑制HIF-1α/PLOD2信号轴，减少肿瘤细胞的侵袭、迁移和外渗，进而增加放疗的效果。Schwartz等[91]在胰腺癌模型中，发现PX-478联合分次放疗显著抑制肿瘤生长，并通过血管成像生物标志物早期评估治疗反应。Panahi等[95]发现，PX-478在CAR-T细胞治疗中可以通过增强T细胞功能，增强放疗的效果。

SN30000（19，图5）作为缺氧靶向小分子增敏剂，通过生物还原代谢生成细胞毒性代谢物，靶向杀伤放疗抵抗的缺氧细胞，而放疗则主要清除富氧增殖细胞，两者联合形成治疗协同效应[96-98]。Mao等[96]开发的混合连续体/代理模型（SABM）动态揭示了SN30000协同放疗的机制：模型显示，SN30000穿透肿瘤球体后，在中心缺氧区（<0.15 μmol/L $O_2$）激活，通过代谢产生DNA氧化损伤，选择性标记缺氧细胞死亡；而放疗主要杀伤外周富氧细胞（$OER_{\alpha max}$=2.63）。当联合应用时，SN30000清除放疗后因再氧合存活的缺氧细胞，同时抑制其通过慢性缺氧途径坏死，使肿瘤球体再生延迟显著延长。模型预测与实验数据高度吻合，联合治疗使克隆原细胞杀伤率得到显著提升，较单药呈超倍增效应。Chitneni等[97]通过$^{18}$F-EF5 PET证实，SN30000治疗后24 h肿瘤缺氧区域标准化摄取值（$SUV_{mean}$）显著下降，且联合15 Gy放疗使H460移植瘤完全缓解率达71%，这种疗效的空间异质性可通过SABM可视化：放疗后外周细胞快速溶解导致中心再氧合，而SN30000通过持续清除新生缺氧细胞阻断该逃逸途径。

Evofosfamide（TH-302，20，图5）作为新型缺氧靶向小分子增敏剂，通过生物还原激活机制精准杀伤放疗抵抗的缺氧细胞，与放疗形成空间协同效应，显著提升抗肿瘤效果[99-101]。Peeters等[99]的研究显示，TH-302在横纹肌肉瘤和H460非小细胞肺癌模型中单药即可延长肿瘤生长延迟时间，联合单次8 Gy放疗后协同效应进一步增强，且在更高放疗剂量（12 Gy）下呈现协同作用，TH-302显著降低肿瘤缺氧分数。Yaromina等[100]基于$^{18}$F-HX4 PET示踪TH-302分布，提出逆向剂量描绘技术：对TH-302低摄取区（LDUV）实施放疗剂量提升（15 Gy到18.5 Gy），结果显示，LDUV剂量聚焦较均匀放疗或高摄取区（HDUV）剂量提升显著延长肿瘤控制时间，且平均剂量降低3.5 Gy，实现“精准

增效减毒”。Spiegelberg等[101]在食管癌(OE19/OE21)模型中证实TH-302与放疗联用不加重正常组织毒性，TH-302联合10 Gy放疗使肿瘤生长延迟显著优于单药，且未增加肠道急性损伤(隐窝存活率、黏膜面积及血浆瓜氨酸水平无差异)或肺部远期纤维化风险(CT密度变化与单放组一致)。

NLCQ-1(21,图5)作为新型缺氧靶向小分子增敏剂，通过弱DNA嵌入及生物还原激活机制选择性杀伤放疗抵抗的缺氧细胞，显著增强放疗疗效[102-104]。Papadopoulou等[102-103]在头颈鳞癌(WSU-HN-31)模型中研究显示，NLCQ-1单药可诱导10 d肿瘤生长延迟，联合放疗后协同效应显著：单次10 Gy放疗联合NLCQ-1使肿瘤生长延迟从7 d提升至36.5 d，且分次放疗(4次2 Gy)联用后延迟时间从3.5 d增至15.5 d。Papadopoulou等[103]将NLCQ-1与TPZ作了比较，NLCQ-1在低氧条件下对V79细胞的放射增敏比(SER)达2.27~2.56(20 μmol/L)，其C1.6值(7.2 μmol/L)显著优于替拉扎明(TPZ，16.9 μmol/L)，治疗指数(ThI)高达145。体内实验显示，NLCQ-1(10 mg/kg)联合20 Gy放疗在EMT6肿瘤中实现1.52倍增敏，放疗前45~60 min给药可产生超1个数量级的细胞杀伤协同效应。此外，在自发转移性KHT肉瘤模型中，NLCQ-1联合25 Gy放疗使肺转移发生率从95%降至33%，转移负荷中位评分从4降至0，其疗效优于RB6145和TPZ。

AQ4N(Banoxantrone,22,图5)是一种前药，在缺氧条件下被还原为活性代谢物AQ4，后者通过嵌入DNA并抑制拓扑异构酶II，导致DNA损伤和细胞死亡，从而选择性杀伤缺氧肿瘤细胞显著增强放疗效果[105-107]。Patterson等[105]在MAC26肿瘤的研究中发现AQ4N与放疗联合使用时，其增敏效果具有药物剂量和放疗剂量依赖性，且在放疗前后16 h内给药均能产生相似的增敏效果。此外，AQ4N还被应用于纳米药物递送系统，与其他放疗增敏剂(如伏立诺他)联合使用，以克服肿瘤的放疗抵抗[106]。

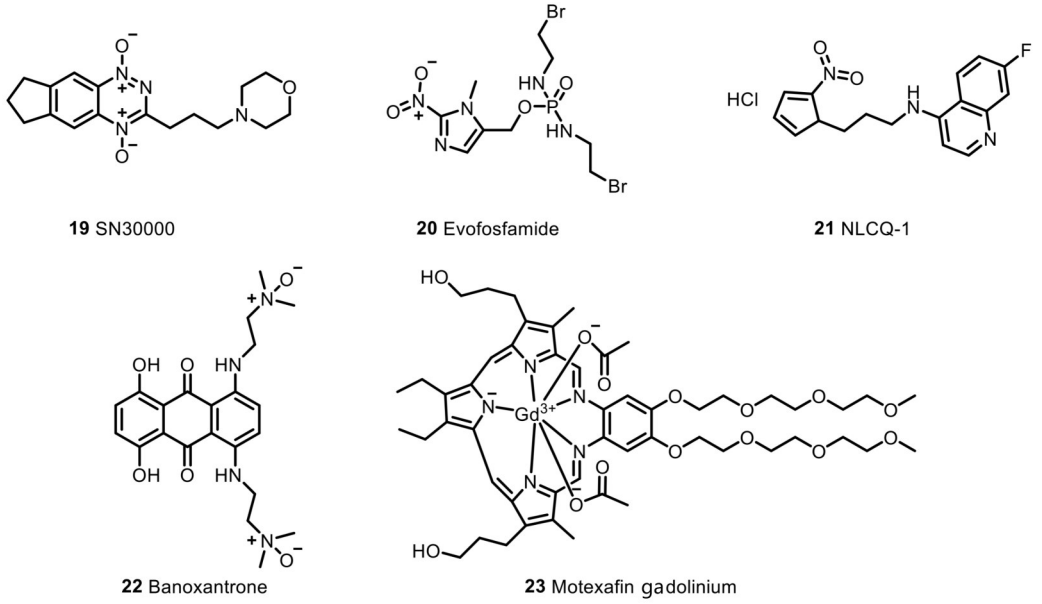


**图5** 增敏剂SN30000(19)、Evofosfamide(20)、NLCQ-1(21)、Banoxantrone(22)和Motexafin gadolinium(23)的化学结构式
**Fig.5** The chemical structures of sensitizers SN30000 (19), Evofosfamide (20), NLCQ-1 (21), Banoxantrone (22), and Motexafin gadolinium (23)

### 1.3 ROS调节剂

ROS调节剂通过调控细胞内的氧化还原平衡来增强辐射效果。辐射诱导的ROS是造成细胞损伤的重要介质，ROS调节剂通过增加细胞内ROS水平或抑制抗氧化防御系统，放大辐射诱导的氧化应激，从而加剧肿瘤细胞的损伤和死亡[29,108]。

Motexafin gadolinium(MGd,23,图5)作为一种ROS调节剂选择性蓄积于肿瘤细胞，通过增强肿瘤细胞内的氧化应激水平，破坏肿瘤细胞的氧化还原平衡，显著提高放疗疗效和诱导细胞凋亡[34]。在非小细胞肺癌(NSCLC)脑转移患者的III期临床试验中，MGd联合全脑放疗(30 Gy)显著延长了神经进展时间(TNP)，尤其在北美地区患者中效果更

为显著[109]。MGd联合放疗在多形性胶质母细胞瘤（GBM）治疗中也显示出潜力[110-111]。在一项I期临床研究中，中位生存期达17.6个月，较历史对照组的11.8个月显著延长，其间MGd的安全性良好，主要不良反应为可逆性转氨酶升高和轻度皮肤反应[111]。McHaffie等[112]发现，MGd的疗效与放疗的及时性密切相关，在脑转移诊断后3周内启动放疗的患者中，MGd的增敏效果更为显著。此外，MGd联合立体定向放射外科（SRS）治疗脑转移瘤的神经毒性发生率低（4.4%），未增加放疗相关并发症。

二甲双胍（Metformin，24，图6）作为ROS调节剂，通过激活AMPK信号通路并抑制PI3K/Akt/mTOR通路，降低肿瘤细胞的抗氧化能力，增加放疗诱导的ROS积累，从而增强DNA损伤和细胞凋亡[29,113-114]。Fernandes等[35]发现，在结直肠癌模型中，二甲双胍联合放疗显著降低细胞存活率，并在体内实验中显示出与增敏剂5-氟尿嘧啶相当的肿瘤抑制效果（557 mm³ *vs*. 398 mm³）。此外，二甲双胍联合放疗在头颈鳞癌（HNSCC）和局部晚期宫颈癌的临床研究中显示出良好的耐受性和潜在疗效，能够减少肿瘤缺氧体积（宫颈癌缺氧分数平均降低10.2%），并改善患者无病生存期（2年DFS：67% *vs*. 33%）[115-116]。

BSO（Buthionine sulfoximine，25，图6）通过抑制γ-谷氨酰半胱氨酸合成酶（γ-GCS），显著降低细胞内GSH水平，导致谷胱甘肽过氧化物酶4（GPX4）失活，进而抑制细胞对ROS的清除能力，破坏肿瘤细胞的抗氧化防御系统，增加放疗诱导的氧化损伤，从而增强放疗疗效[117-118]。在胶质瘤模型中，Lippitz等[119]发现，BSO联合$^{125}$I间质放疗显著延长小鼠中位生存期，显示出其作为放疗增敏剂的潜力。在三阴性乳腺癌（TNBC）治疗中，Zeng等[118]将BSO与铁死亡诱导剂联合使用，通过抑制GPX4活性和触发Fenton反应，协同增强放疗的抗肿瘤效果，显著抑制肿瘤生长和转移。在神经内分泌肿瘤中，Delbart等[120]BSO联合$^{177}$Lu-DOTATATE治疗通过降低GSH水平，增强放疗的氧化损伤效应，显著抑制肿瘤代谢活性，且未增加肝肾或骨髓毒性。

双硫仑（Disulfiram，26，图6）作为ROS调节型小分子增敏剂，通过抑制醛脱氢酶（ALDH）及超氧化物歧化酶（SOD）阻断ROS清除，同时与铜离子螯合生成Cu（DSF）-2复合物，诱导线粒体氧化应激并催化Fenton反应，显著放大放疗诱导的DNA损伤，多机制协同增强放疗疗效，其作用已在多种实体瘤模型中验证[121-123]。临床前研究显示，Ying等[121]在胰腺癌模型的研究中，发现双硫仑单药即可增加放疗后DNA双链断裂，联合4 Gy放疗使克隆原细胞存活分数（SF）降低，并增强G2/M期阻滞及凋亡。Lian等[122]在骨肉瘤的研究中，发现双硫仑还可以通过激活p53/p21-CDKN2C轴促进细胞周期阻滞，并上调促凋亡蛋白BAX/Caspase-3，使放疗后肿瘤体积缩小50%。针对胶质母细胞瘤的I/II期试验证实，双硫仑（375 mg/d）联合放疗及替莫唑胺的1 a无进展生存率达57%，总生存率69%，且携带IDH1/BRAF/NF1突变患者1年生存率达100%（*vs*. 野生型42%）[123]。

ML385（27，图6）作为新型ROS调节剂型小分子增敏剂，通过阻断NRF2介导的抗氧化防御系统：放疗激活NRF2并促使其核转位，上调SLC7A11、GPX4等抗氧化基因表达，清除ROS并抑制脂质过氧化，导致肿瘤放疗抵抗，显著增强肿瘤放疗敏感性[124-125]。Yan等[124]在食管鳞癌（ESCC）模型中研究显示，ML385使NRF2核表达降低，下调SLC7A11/GPX4轴，导致谷胱甘肽（GSH）合成减少、ROS及脂质过氧化水平累积，进而触发铁死亡，ML385联合放疗使克隆形成抑制率提升，平均致死剂量（$D_0$）从3.42 Gy降至2.67 Gy，并通过诱导G2/M期阻滞和凋亡增强疗效，体内实验显示，联合治疗组肿瘤体积缩小70%。Qin等[125]在三阴性乳腺癌的研究中，发现ML385通过抑制放疗诱导的NRF2活化，阻碍DNA损伤修复，同时显著增加放疗后ROS水平，特异性杀伤癌症干细胞（CSCs），ML385使TNBC干细胞（$ESA^+$/$CD44^+$/$CD24^-$亚群）对放疗敏感性提升3倍，并延迟DNA双链断裂修复（γ-H2AX焦点残留率增加40%）。同时，ML385联合放疗可使肿瘤球形成数减少80%，且抑制Keap1-NRF2相互作用可逆转放疗抵抗。

JQ-1（28，图6）通过ROS动态调节以及抑制溴结构域蛋白BRD4，显著增强肿瘤放疗敏感性。其核心机制在于靶向抑制BRD4介导的抗氧化基因转录，导致ROS清除能力下降并放大放疗诱导的氧化应激[126-128]。Ren等[126]在口腔鳞癌（OSCC）模型的研究中，发现JQ-1联合5 Gy放疗使细胞凋亡率提升2倍，促凋亡蛋白Bax及cleaved caspase-3表达上调，并通过下调PD-L1逆转肿瘤免疫逃逸，其

机制是JQ1阻断了BRD4的乙酰化识别功能，使放疗后ROS蓄积增加，触发线粒体凋亡通路。Ni等[127]在宫颈癌模型中，发现JQ-1可以通过抑制BRD4-RAD51AP1轴阻碍DNA同源重组修复，使放疗诱导的DNA双链断裂修复效率降低，同时增强ROS介导的次级损伤效应，JQ-1联合放疗使宫颈癌移植瘤体积缩小70%，且高表达BRD4患者预后较差。

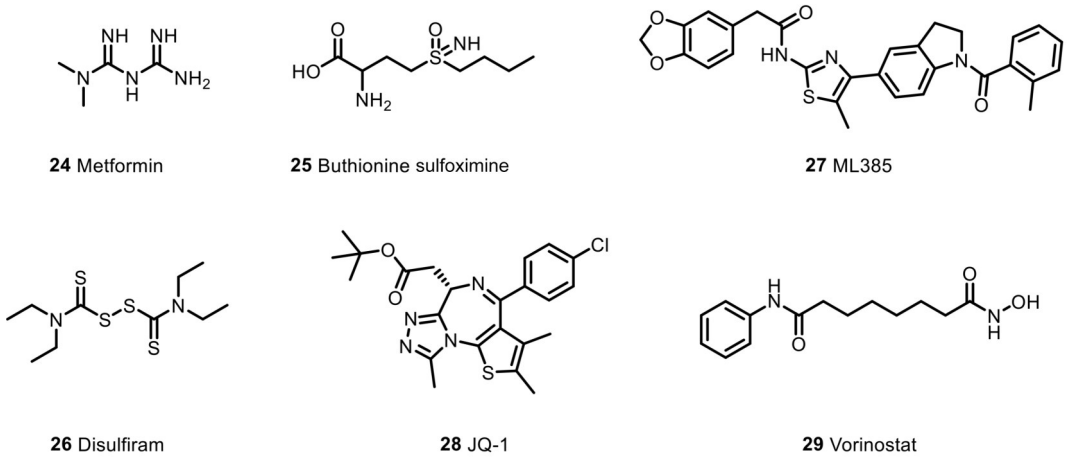


**图6** 增敏剂Metformin(24)、Buthionine sulfoximine(25)、Disulfiram(26)、ML385(27)、JQ-1(28)和Vorinostat(29)的化学结构式

**Fig.6** The chemical structures of the sensitizers Metformin (24), Buthionine sulfoximine (25), Disulfiram (26), ML385 (27), JQ-1 (28), and Vorinostat (29)

### 1.4 表观遗传调节剂

表观遗传改变可影响DNA损伤应答相关基因的表达[30,129]。表观遗传调节剂通过抑制组蛋白去乙酰化酶(HDAC)或DNA甲基转移酶(DNMT)，改变染色质结构，使DNA更易受辐射损伤，增强肿瘤细胞对辐射的响应[30]。

#### 1.4.1 HDAC抑制剂

Vorinostat(29，图6)通过抑制HDAC活性，增加组蛋白乙酰化水平，抑制DNA损伤修复相关基因的表达，显著增强放疗的抗肿瘤效果[36]。Baschnagel等[130]在乳腺癌脑转移模型的研究显示，Vorinostat联合放疗显著增加γH2AX焦点数量(DSB标志物)，并诱导有丝分裂灾难，使肿瘤细胞放射敏感性提高(剂量增强因子为1.57)。Wen等[131]在胶质母细胞瘤的研究中，发现Vorinostat与替莫唑胺和放疗联合使用显示出协同抗肿瘤活性，且耐受性良好。此外，在非转移性胰腺癌的I期临床试验中，Vorinostat(400 mg/d)联合卡培他滨和放疗(30 Gy/10次)显示出良好的安全性，并延长了患者的中位生存期(1.1年)[132]。

Panobinostat(30，图7)是FDA批准的一种组蛋白脱乙酰酶抑制剂，通过增加组蛋白乙酰化水平和增强DNA损伤修复抑制，显著提高放疗的抗肿瘤效果[133-134]。在肝细胞癌中，Choi等[135]发现，Panobinostat联合质子放疗比联合X射线放疗更显著地抑制细胞克隆形成，并通过下调抗凋亡蛋白Mcl-1表达进一步增强放疗敏感性。在复发性高级别胶质瘤的I期临床试验中，Panobinostat(30 mg)联合分次立体定向再放疗(FSRT)显示出良好的耐受性，6个月无进展生存率(PFS6)达83%，中位总生存期为16.1个月[136]。此外，在不可手术的III期非小细胞肺癌(NSCLC)患者中，Panobinostat(45 mg，每周两次)联合姑息性放疗显示出66%的疾病控制率和9个月的中位生存期，且毒性可控[137]。Liu等[138]发现Panobinostat还通过上调自然杀伤细胞(NK细胞)配体(如MICA/MICB和RAE-1/H60)的表达，增强NK细胞介导的细胞毒性，从而在放疗联合HDAC抑制的治疗中发挥免疫调节作用。

罗米地辛(Romidepsin，31，图7)作为HDAC抑制剂，通过表观遗传调控与DNA损伤修复抑制双重机制显著增强放疗疗效[139-141]。Ma等[139]在前列腺癌模型的研究中，发现Romidepsin通过抑制HDAC1/2活性，下调DNA-PK、RAD51及磷酸化ATM表达，阻断NHEJ及HR修复通路，使得DNA双链断裂修复受阻，Romidepsin(10 nmol/L)联合

2~8 Gy放疗使雄激素敏感（LNCaP）及不敏感（22Rv1）细胞的克隆存活率降低，并诱导γ-H2AX焦点数增加。Saito等[140]在黑色素瘤模型的研究中，发现Romidepsin预处理通过诱导G0/G1期阻滞（比例提升30%），使碳离子放疗对B16F10细胞的凋亡率增加2倍，且效果优于传统放疗（γ射线），因G1期细胞缺乏HR修复能力而对辐射更敏感。

Entinostat（MS-275，32，图7）作为I类及IV类HDAC选择性抑制剂，通过多维度机制增强放疗疗效[142-143]。Cassandri等[142]在横纹肌肉瘤RMS的研究中，发现Entinostat（1~1.9 μmol/L）通过抑制HDAC1/2/3活性，下调细胞周期蛋白Cyclin A/B/D1，上调p21/p27，阻断ERK及PI3K/Akt/mTOR通路，诱导G0/G1期阻滞（RH30细胞G1比例增加40%），并抑制融合阳性（FP）-RMS的N-Myc表达。联合放疗（4 Gy）后，其显著抑制DNA损伤修复：在FP-RMS细胞中，HR修复关键蛋白ATM磷酸化水平降低，并下调抗氧化基因NRF2、SOD、CAT及GPx4表达，导致ROS蓄积，使克隆形成率降低。体内实验显示，Entinostat（2.5 mg/kg）联合分次放疗（6 Gy×3）使FP-RMS移植瘤完全消退，且对放疗抵抗的RH30模型实现100%无进展生存。Kim等[143]在Lewis肺癌模型的研究中，发现Entinostat联合放疗（12 Gy分2次）使肿瘤体积缩小75%，并显著提升CD8+ T细胞浸润，减少调节性T细胞比例（转录组分析显示，其通过激活JAK/STAT3/IFN-γ通路及上调MHC-II基因，如H2-Aa、H2-Ab1），促进抗原呈递，使抗PD-1疗法疗效提升，三联方案（Entinostat+放疗+抗PD-1）进一步使IFN-γ+CD8$^+$ T细胞增加，肿瘤控制率得到提高。

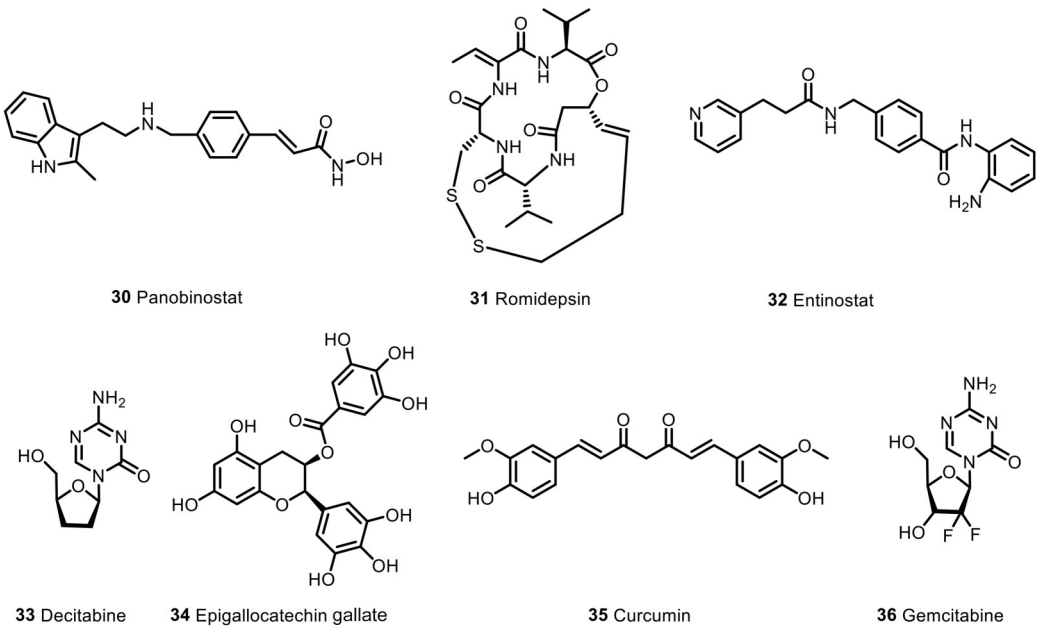


**图7** 增敏剂Panobinostat（30）、Romidepsin（31）、Entinostat（32）、Decitabine（33）、Epigallocatechin gallate（34）、Curcumin（35）和Gemcitabine（36）的化学结构式

**Fig.7** The chemical structures of the sensitizers Panobinostat (30), Romidepsin (31), Entinostat (32), Decitabine (33), Epigallocatechin gallate (34), Curcumin (35), and Gemcitabine (36)

### 1.4.2 DNMT抑制剂

地西他滨（Decitabine，33，图7）作为一种DNA甲基转移酶（DNMT）抑制剂，通过诱导DNA去甲基化和重新激活肿瘤抑制基因，降低肿瘤细胞的DNA甲基化水平，显著增强放疗的抗肿瘤效果。在Minoia等[37,144]对乳腺癌髓系肉瘤的研究中，Decitabine联合放疗（30 Gy）实现了完全代谢缓解，并在27个月内维持疾病缓解状态，显示出其作为放疗增敏剂的潜力。Son等[145]发现Decitabine通过上调I类主要组织相容性复合物（MHC）和共刺激分子的表达，显著增强肿瘤细胞对放疗的敏感性，在他们的研究中Decitabine与电离辐射（IR）联合治疗可进一步上调这些分子，并增强T细胞介导的细胞毒性及IR诱导的IFN-γ释放，从而提升抗肿瘤免疫反应。Turpin等[146]在研究年轻患者的免疫抵抗性肿瘤的过程中发现，低剂量Decitabine联合低分割放疗（8 Gy×3）和PD-1抑制剂（Pembrolizumab）显示出协同抗肿瘤活性，且耐受性良好。

表没食子儿茶素没食子酸酯（Epigallocatechin gallate，EGCG，34，图7）作为天然多酚类化合物，不仅展现出显著的抗氧化与抗炎特性，还可通过抑制DNA甲基转移酶（DNMT）的表观遗传调控机制增强放疗的肿瘤杀伤效应[147-151]。研究表明，EGCG通过抑制DNMT活性，降低肿瘤细胞基因组DNA的异常高甲基化水平，从而重新激活沉默的抑癌基因（如p16、RARβ等），逆转肿瘤细胞对放疗的耐受性。Zhang等[147]在对乳腺癌患者的治疗中，口服EGCG（400 mg/次，每日3次）联合放疗显著降低了血清血管内皮生长因子（VEGF）和肝细胞生长因子（HGF）水平，同时抑制基质金属蛋白酶MMP-9/MMP-2活性，从而削弱肿瘤侵袭与血管生成能力，进一步放大放疗的疗效。López等[148]的研究显示，EGCG联合放疗可协同阻滞口腔鳞癌细胞周期于G2/M期（增加10%~15%），并通过增强5-氟尿嘧啶（5-FU）的细胞毒性，使低剂量5-FU（25 μmol/L）联合EGCG的抑瘤效果优于高剂量单药（200 μmol/L）。但是López等[148]同时发现，EGCG的放射增敏作用具有剂量依赖性：在2.5 Gy放疗下，EGCG显著抑制癌细胞迁移，但在5 Gy时因潜在辐射保护效应而减弱，说明需优化放疗剂量以实现协同。此外，EGCG还能减轻放射性皮炎发生率，Zhu等[149]的研究显示，局部应用EGCG使乳腺癌患者3~4级皮炎发生率降至0%，症状缓解率达71%~90%。

姜黄素（Curcumin，35，图7）是一种天然多酚类的DNMT抑制剂，通过多机制的表观遗传调控，显著增强放疗对多种肿瘤的杀伤效果[152-155]。Zhu等[152]发现姜黄素可调控鼻咽癌（NPC）中环状RNA（如has-circRNA-102115）的表达，通过“circRNA-miRNA-mRNA”网络（如hsa-miR-335-3p/MAPK1轴）抑制肿瘤干细胞特性，使放疗后$CD133^+$细胞比例从15.7%降至5.5%，并恢复MAPK1表达以增强放射敏感性（增敏比SER达0.76）。Cai等[153]在GBM的研究中，发现姜黄素通过增强中子放疗（高LET）诱导的ROS生成，促进亚G1期细胞比例增加，激活Caspase-3及PARP1裂解，显著抑制肿瘤细胞侵袭。Yang等[154]在乳腺癌干细胞的研究中，发现姜黄素联合葡萄糖纳米金颗粒（Glu-GNPs）可靶向抑制缺氧诱导因子HIF-1α和热休克蛋白HSP90的表达，减少肿瘤干细胞在低氧微环境中的自我修复能力，并显著增加放疗后ROS水平，诱导细胞凋亡，同时抑制球体形成能力。Kim等[155]在非小细胞肺癌的研究中，发现姜黄素与顺铂联用可协同抑制表皮生长因子受体（EGFR）信号通路，使放疗增敏比达1.96，并降低A549细胞迁移和侵袭能力。

吉西他滨（Gemcitabine，36，图7）作为放射增敏剂在多种实体瘤治疗中展现出显著潜力，其机制是抑制DNMT以增强放疗敏感性和延长DNA损伤修复[156-158]。Mohamed等[159]在膀胱癌的临床研究中，老年患者接受吉西他滨联合低分割放疗后，完全缓解率达到80.6%，且2年无病生存率为72.6%，显示了吉西他滨作为放射增敏剂的潜力。此外，在胰腺导管腺癌的新辅助治疗中，吉西他滨联合放疗显著提高了$R_0$切除率和淋巴结阴性状态的比例，进一步支持其在放疗中的协同作用[160]。在局部晚期胰腺癌（LAPC）的治疗中，吉西他滨联合放疗和免疫治疗显著延长了患者的中位总生存期和无进展生存期，且未显著增加严重不良事件的发生率[161]。

## 2 挑战与发展趋势

尽管小分子增敏剂在肿瘤放疗中展现出显著潜力，但其临床转化仍面临多重挑战，需系统性突破。首要问题在于肿瘤选择性不足，许多小分子增敏剂（如DNA-PK抑制剂AZD7648）对肿瘤与正常组织的增敏比相近[77-78]，导致放射性皮炎、肠黏膜炎等剂量限制性毒性。实体瘤的异质性（如缺氧区域分布不均）进一步加剧靶向难度[84]，例如替拉扎明在头颈癌临床试验中因肿瘤缺氧异质性未能显著改善生存[89]。其次，耐药性问题限制了长期疗效。肿瘤细胞可通过代偿性激活旁路修复通路（如HR修复替代PARP抑制）或表观遗传重塑逃避杀伤，长期使用PARP抑制剂可能诱导BRCA1/2突变肿瘤的HR功能恢复，削弱放疗增敏效果[31,162]。此外，药代动力学与递送障碍制约药物效力，如ATM抑制剂M3541因血脑屏障穿透能力不足或半衰期短，难以在肿瘤部位维持有效浓度[68]，而缺氧靶向剂的分布监测策略仍需优化以匹配动态微环境。

针对上述挑战，未来研究需聚焦多维度创新。在药物设计层面，开发多靶点抑制剂（如同时抑制DNA-PK和mTOR的CC-115）可克服单通路耐药性[80]，而基于生物标志物（如HR缺陷、缺氧程度）的精准分层有望实现个体化用药[97]。递送系统革新是提升选择性的关键，例如铜-TPZ脂质体通过

缺氧响应释放药物，显著提高肿瘤蓄积[163]，而外泌体负载TPZ联合低剂量放疗可通过氧耗动态增强靶向性[90]。新兴放疗技术的融合为增敏剂提供了新场景：重离子放疗的高线性能量转移(LET)特性可减少缺氧依赖性，与PARP抑制剂联用可能协同增效[164]；超高剂量率放疗(FLASH)的超高速剂量率在保护正常组织的同时，需匹配新型增敏剂以维持肿瘤杀伤[165]。此外，免疫放疗协同策略逐渐成为热点，表观遗传调节剂Entinostat通过上调MHC-II表达促进T细胞浸润[143]，而ROS调节剂Motexafin Gadolinium可通过氧化应激释放肿瘤抗原，增强免疫应答[109]。未来跨学科合作(如放射生物学、纳米医学与人工智能辅助药物筛选)将推动小分子增敏剂在肿瘤放疗中的突破性应用。

此外，近些年辐射化学机制的创新突破为小分子增敏剂的临床转化面临肿瘤选择性不足、转移灶控制乏力及耐药性演化等难题提供了变革性解决方案[166-167]。刘志博团队[168]开创的放疗驱动前药精准激活策略，通过利用电离辐射在生物介质中产生的活性粒子(如羟基自由基和水合电子等，图8(a))，实现了肿瘤微环境中的时空可控药物释放。针对转移性肿瘤这一临床痛点(90%癌症死亡与之相关)，该团队开发了基于医用β核素[$^{177}$Lu]Lu的铂(IV)前药激活系统：β射线触发铂(IV)轴向配体还原裂解，在胰腺癌转移模型中同步清除原发灶与微转移灶，使中位生存期延长[168]。为解决传统增敏剂正常组织毒性问题，团队发展了乏氧响应型激活技术——肿瘤乏氧区升高的水合电子产额可特异性还原氮氧化物前药(图8(b))，在胶质瘤模型中实现抑瘤率提升，且肝肾毒性降低[169]。此外，抗体药物精准控释系统取得关键突破：基于N-烷基-4-吡啶保护的“辐射可剪切连接子”设计放疗响应型ADC，X射线触发后原位释放毒素MMAE，在活体细胞和荷瘤小鼠中均表现出良好的活性[170]；而季铵盐裂解技术(图8(c))则通过临床剂量(2 Gy)介导卡菲佐米前药活化，使肿瘤体积缩小[171]。这些创新策略显著提升了放化疗联合的“治疗窗”，并为克服耐药性提供新路径：放疗激活的铂药(图8(d))可促进免疫原性细胞死亡，对肿瘤的抑制效果显著优于临床使用的铂药物联合放疗，却没有增加副作用[172]。

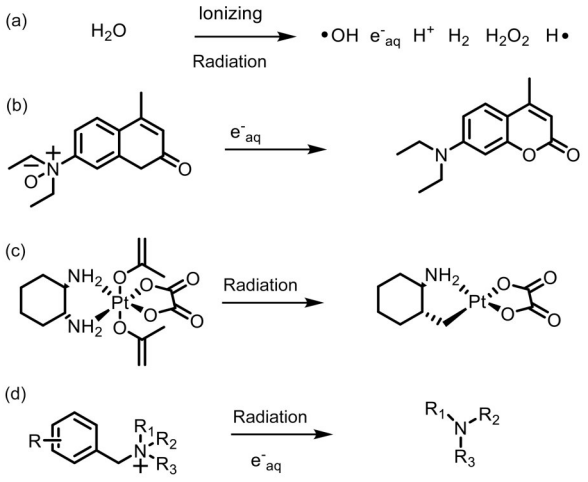


**图8** 放疗用前药策略的相关机制：(a)水在辐射下的分解；(b)N-氧化物化合物辐解产生的的荧光反应；(c)放疗触发的铂类化疗前药在肿瘤中的还原作用；(d)辐射诱导季铵基团裂解

**Fig.8** Mechanisms related to prodrug strategies for radiotherapy: (a) water decomposition under radiation; (b) fluorogenic reaction of N-oxide compounds during radiolysis; (c) radiotherapy-triggered reduction of platinum-based chemotherapeutic prodrugs in tumors; (d) radiation-induced cleavage of quaternary ammonium groups

## 3 总结

小分子增敏剂作为肿瘤放疗的重要辅助手段，通过多种机制显著增强了肿瘤细胞对辐射的敏感性，为提高放疗疗效提供了新的策略。本文综述了DNA损伤修复抑制剂、缺氧靶向剂ROS调节剂和表观遗传调节剂等小分子增敏剂的作用机制及研究进展。这些药物通过抑制DNA修复、改善缺氧微环境、增加活性氧生成或调节表观遗传修饰，显著增强了放疗的抗肿瘤效果。尽管小分子增敏剂在临床前和临床研究中展现出显著潜力，但其应用仍面临选择性不足、毒副作用和耐药性等挑战。未来研究应聚焦于多靶点药物开发、联合免疫治疗、纳米技术的应用以及利用辐射化学机制开发放疗用前药，以进一步提高放疗的疗效和安全性。通过跨学科协同创新，小分子增敏剂有望为肿瘤放疗带来新的突破，显著提高患者的治疗效果和生存质量。

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