Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2026.HZ38762

Study on the Mechanism and Molecular Design of Targeted Drug Release for a Tetravalent Oxaliplatin Prodrug Modified with Reactive Oxygen Species-Responsive Phenylboronic Ester

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Abstract. Oxaliplatin is the core drug for the first-line chemotherapy of colorectal cancer. It inhibits tumor cell proliferation by forming platinum-DNA adducts, but lacks tumor-targeting selectivity. Long-term use is easy to induce multidrug resistance, which limits its clinical application. The level of reactive oxygen species (ROS) in the tumor microenvironment is significantly higher than that of normal tissue, and this oxidative stress difference provides an ideal endogenous trigger condition for the construction of intelligent response prodrugs. With its axially modifiable site, a tetravalent platinum prodrug can introduce phenylborate ROS-sensitive joints, giving the prodrug microenvironment recognition ability. Based on the molecular design theory of tetravalent platinum prodrugs, this paper systematically sorts out the structural characteristics and response mechanism of phenylborate joints, compares the stability differences of prodrugs in normal low-ROS and tumor high-ROS environments, and deeply explains the oxidative fracture of the phenylborate bond and the targeted activation of active divalent oxaliplatin in situ reduction and release. Process, clarifying the drug-free advantages of "tumor activation and normal tissue passivation" of the system. On this basis, the law of the influence of structural factors such as connecting arm length, hydrophobic modified groups, and other structural factors on the water solubility, circulation stability, and response sensitivity of the prodrug is further summarized. For ROS, the rational molecular design and clinical transformation of responsive platinum prodrugs provide a systematic theoretical reference.

Keywords: oxaliplatin, benzoboroxole, reactive oxygen species-responsive, prodrug

1. Introduction

Oxaliplatin is a third-generation platinum chemotherapy drug, which is widely used in the first-line combined treatment of middle and late colorectal cancer. After the drug enters the cell, it cross-links with DNA to form a platinum-DNA complex, which blocks the cell cycle and induces tumor cell apoptosis. However, free oxaliplatin is not tissue-selective. After intravenous administration, it is evenly distributed throughout the body. It continues to damage peripheral nerves, digestive tract

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DOI: 10.54254/2753-8818/2026.HZ38762

mucosa, and bone marrow hematopoietic cells. Severe neurotoxicity and gastrointestinal reactions greatly reduce the patient's tolerance; Long-term repeated administration of the drug will also induce multiple drug resistance in tumors, which significantly weakens the long-term anti-tumor efficacy [1].

There is persistent oxidative stress in the tumor microenvironment. Cancer cell proliferation and metabolic abnormalities continue to produce a large number of reactive oxygen free radicals (ROS), including hydrogen peroxide, superoxide anions, etc. The normal cells of the body have a perfect antioxidant system, and the intracellular ROS maintains an extremely low level, and the two form a significant oxidation environment gradient [2]. The phenylborate group can specifically undergo oxidative cracking reaction with high-concentration ROS, and the chemical structure is stable under low ROS physiological conditions. Based on this characteristic, the construction of ROS-responsive tetravalent oxaliplatine predrug has become a mainstream research direction in intelligent chemotherapy.

The tetravalent platinum prodrug takes divalent oxaliplatin as the active parent nucleus and introduces functional modification groups at the platinum axial location. There is no DNA-binding activity and weak toxicity before administration; After reaching the high-ROS tumor area, the sensitive joint breaks, reduces and releases the divalent active oxaliplatin, realizes tumor in situ activation, and reduces systemic toxic side effects from the source [3]. The existing studies mostly explore the pre-drug synthesis or in vitro anti-tumor activity separately, and lack a systematic and integrated analysis of the molecular design and drug release mechanism of the phenylborate response system. This paper conducts an in-depth analysis of the axial modification strategy of tetravalent oxaliplatin and the mechanism of phenylborate response drug release, and completely constructs a theoretical system of targeted activation of ROS response pre-drugs, which provides a theoretical basis for the development of new colorectal cancer targeted chemotherapy drugs.

2. Theoretical design of ROS-responsive tetravalent oxaliplatin prodrug molecules

2.1. Fundamental principles of axial site modification with tetravalent platinum

The central platinum atom of divalent oxaliplatin is saturated and cannot be directly chemically modified; Pt(II) is converted into Pt(IV) through an oxidation reaction, and the axial direction of platinum ions produces two modifiable empty matching sites, which is the core skeleton basis for the construction of oxaliplatin prodrug. The overall chemical inertness of the Pt(IV) complex is strong, the thermodynamic stability of the six-coordination octahedral structure, cannot be directly embedded in the DNA double strand, and has no cytotoxicity; after entering the tumor microenvironment, it is reduced or responded to the fracture to remove the axial ligand, and the reduction produces Pt(II) osaliplate with cell-killing activity, and realizes the controlled transformation of "inactive precursor - active drugs" [4].

The axial modification group directly determines the water solubility, cell uptake capacity, in-body circulation stability, and microenvironment response characteristics of the prodrug. It is the key structural unit that regulates the in vivo behavior of the prodrug. Connecting the ROS-sensitive structure of phenylborate to the axial site can give the prodrug oxidation microenvironment identification ability, which is different from ordinary fat-soluble, targeted ligand-modified tetravalent platinum prodrugs, and realizes drug release only by relying on tumor-inherent ROS signals, without additional targeted receptor mediation, and adapts to the vast majority of high ROS solid tumors. It is especially suitable for the treatment of colorectal cancer [5].

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2.2. Structure and response-adaptation advantages of ROS-sensitive benzoboroxole linkers

Phenylborate is a classic ROS-fracturable chemical group. Its chemical structure is formed by boron atoms and oxygen atoms through a ligation bond to form a borate bond (B-O bond). This bond is highly sensitive to high concentrations of hydrogen peroxide (H_2O_2) and reactive oxygen free radicals, and there is almost no hydrolysis or oxidation fracture in a low-oxidation environment. The response specificity is significantly better than that of other oxidation-sensitive groups such as aldehyde and thioketone [3, 6].

The ROS response of phenylborate follows a clear oxidation fracture path. With hydrogen peroxide as a typical trigger factor, H_2O_2 first attacks the boron atom in phenylboroate, forms a cognate intermediate with boron, and then oxidizes the B-C bond to form borate intermediates, which are rapidly hydrolyzed in water, eventually releasing the corresponding phenolic leave groups and boric acid derivatives. This "oxidation-hydrolysis" tandem reaction gives phenylboroate the ability to break the bond quickly in the tumor's high ROS microenvironment, while ensuring its structural inertness under normal physiological conditions. The study confirmed that the phenylborate group can undergo responsive fracture at H_2O_2 concentrations at low to micromolar levels, with both response sensitivity and specificity [7].

The benzene ring skeleton of phenylborate can be diversified and modified, and its response rate to ROS can be finely regulated by introducing electrons or electron-absorbing groups to adjust the electron cloud density of B-O bonds. For example, the introduction of methoxy groups and other electron-donating groups can enhance the electrophilicity of boron atoms and accelerate the nucleophilic attack of H_2O_2, while the introduction of electron-absorbing groups such as halogens can reduce the reaction activity and slow down the release rate of drugs. In addition, phenylborate can be connected to the tetravalent platinum axial site through an esterification reaction. The synthesis route is mature, and the yield is controllable. Research shows that 4-carboxyl phenylboric acid phenol ester can be used as an axial functional ligand, covalently coupled with platinum (IV) prodrugs through an esterification reaction to synthesize tetravalent platinum complexes modified with phenylborate. This strategy has been verified in the design of platinum prodrugs [7, 8].

Phenyloborate modification not only gives the prodrug ROS the ability to respond to drug release, but also further exerts the synergistic anti-tumor effect by responding to the phenylboric acid derivatives released after fracture. Some phenylborate fracture products have the function of consuming intracellular glutathione (GSH), which can weaken the detoxification ability of tumor cells to platinum drugs and enhance the sensitivity of chemotherapy [9]. This dual effect of "drug release-sensitization" distinguishes the phenylborate joint from other inert connection arms and has a unique therapeutic gain potential. At the same time, phenylborate also has a certain pH response in the acidic microenvironment. Its borate bond can accelerate hydrolysis under weak acidic conditions and form a "double trigger" mechanism with the ROS response, further improving the release specificity of the prodrug in the tumor acidic microenvironment [10].

Comparison with other ROS-sensitive groups. Compared with oxidation-sensitive groups such as acetaldehyde and thioacetone, the advantages of phenylborate are concentrated in three points: First, the response threshold is low, and it can break efficiently under the concentration of H_2O_2 related to tumor physiology (50-100 μmol/L); Second, the oxidation products are boric acid and phenols, which have good biocompatibility and no significant accumulated toxicity; third, the synthesis is highly accessible, and drug molecules or carrier systems can be introduced through a variety of coupling strategies [11]. The above structural characteristics and response advantages make

DOI: 10.54254/2753-8818/2026.HZ38762

phenylborate an ideal choice for the construction of oxaliplatin tetravalent rodrug ROS response joints.

2.3. The regulatory patterns of linker arms and hydrophilic modification groups on prodrug performance

Based on the modification principle of tetravalent platinum prodrugs, the axial site modification strategy of oxaliplatin is systematically sorted out. Focus on summarizing the structural characteristics, response mechanism, and adaptation advantages of phenylborate ROS-sensitive joints, and summarize the influence of different joint arm lengths and hydrophilic modified groups on the water solubility, stability, and response sensitivity of prodrugs. Analyze the molecular structure design logic of the optimal prodrug from the theoretical level, and clarify the structural basis of targeted drug release.

A carbon chain, polyethylene glycol, and other connecting arms need to be introduced between the phenylboroate joint and the Pt(IV) axial site. The length of the connecting arm directly affects the three core properties of the prodrug: water solubility, cycle stability, and ROS response sensitivity. The short carbon chain connecting arm has strong rigidity, large spatial resistance of the borate group, reduced contact efficiency with ROS, and a slow drug release rate; too-long alkyl chains will improve the lipophilicity of prodrugs, which is easily non-specifically taken up by normal tissue cell membranes, and increase off-target toxicity. A moderate-length flexible carbon chain can balance spatial resistance, ensure that the borate ester is in full contact with ROS in tumor cells, and avoid systemic distribution caused by excessive lipidization [6]. The axial synchronous introduction of carboxyl, amino, and short-chain polyethylene glycol hydrophilic fragments can significantly improve the water solubility of prodrugs and solve the defects of poor water solubility of pure platinum derivatives, easy precipitation in the body, and limited intravenous administration. Hydrophilic groups can reduce the adsorption of plasma proteins by the prodrug, prolong the half-life of circulation in the body, and reduce rapid clearance by the liver and kidney; however, an excessive proportion of hydrophilic modification will weaken the transmembrane uptake efficiency of tumor cells, and it is necessary to balance hydrophilicity and hydrophobicity to take into account solubility and cell penetration ability [8, 11].

Abhang and others designed and synthesized the octahedral oxaliplatin (IV) prodrug (OXA-CBL) with phenylbutyric acid nitrogen mustard (CBL) as the axial ligand, and used the lipophilic characteristics of CBL to coordinate the cell uptake efficiency of the prodrug.In order to optimize the performance in the body, they loaded the predrug in bovine serum albumin nanoparticles (OXA-CBL/BSA-NPs), the resulting nanoparticle particle size is less than 200 nm, and the drug load reaches 5.86% [6]. In vitro experiments show that nanopreparations reduce the IC50 of 4T1 and MDA-MB-231 triple-negative breast cancer cells by about 1.38 times and 1.43 times respectively;In the tumor mouse model, the tumor inhibition rate of the treatment group increased significantly, and no liver and kidney toxicity and hemolytic reactions were observed [2, 6]. The study confirms that the anti-tumor efficacy and safety of tetravalent platinum prodrugs can be effectively improved by rationally selecting axial ligands (with synergistic anti-tumor function) and optimizing hydrophilicity and targeting in combination with nano-delivery systems;Bhute and others use pH-sensitive PEG liposomes to encapse OXA-CBL prodrugs (OXA-CBL/PEG-Liposomes), the particle size is also less than 200 nm, and the loading capacity is about 4.26% [7]. This preparation shows pH-dependent continuous drug release characteristics (up to 48 hours), and cell uptake is mainly achieved through the grid protein-mediated endophagation pathway [3, 7]. In vitro cytotoxicity tests showed that the IC50 of 4T1 and MDA-MB-231 cells was about 1.56 times and 1.54 times lower

DOI: 10.54254/2753-8818/2026.HZ38762

than that of free prodrugs, respectively; the tumor inhibition rate increased significantly in animal experiments, and no systemic toxicity or hemolytic toxicity was shown [3]. The above study shows that the combination of hydrophilic modification strategy and pH/ROS dual response design can significantly optimize the pharmacokinetic behavior and treatment window of tetravalent platinum prodrugs.

According to the comprehensive structure regulation law and experimental evidence, the optimal molecular design logic of the precursor is: with Pt(IV) oxaliplate as the parent nucleus, the axial side is connected to the replacement phenylborate ROS-sensitive joint of medium-length flexible carbon chain bridge, and the other side introduces an appropriate amount of hydrophilic modified groups or cooperative anti-tumor functional ligands (such as benzobutyric acid nitrogen mustard), supplemented by a nano-delivery system (albumin nanoparticles or PEG liposomes) to improve the distribution in the body, taking into account the stability, water water ability of the body, the specific response ability of the tumor microenvironment and synergistic effect, and to build the molecular structure foundation for targeted drug release.

3. Targeted drug release mechanism of the phenylboronic acid system and its core advantages of "tumor activation and normal tissue inactivation"

3.1. Differences in prodrug structural stability under various ROS environments

By integrating the literature, the differences in the structural stability of the prodrug in the normal low-ROS physiological environment and the tumor high-ROS microenvironment are summarized. Systematically explain the oxidative fracture mechanism of phenylboroate bonds, the release process of the active mother drug, and the principle of intelligent identification of the microenvironment are systematically explained, and the theoretical mechanism system of targeted activation of prodrugs is completed [1, 6, 12].

There are two completely different oxidative microenvironments in the human physiological environment, and the stability of the prodrug shows the characteristics of bipolarization; the physiological environment of low ROS in normal tissues: the concentration of ROS in normal colon epithelial cells and systemic organ cells is extremely low, antioxidant enzymes continue to remove reactive oxygen, and borate bonds do not have oxidation trigger conditions. The complete structure of Pt(IV) octahedral is stable, and the axial phenylborate ligand is not easily displaced. The prodrug maintains an inactive tetravalent platinum configuration, cannot bind to nuclear DNA, and has no significant inhibitory effect on normal cell proliferation. It achieves "passivation" at the tissue level and greatly reduces the nerve and digestive tract toxicity inherent in free oxaliplatin; [6, 13]. Colorectal cancer high ROS tumor microenvironment: tumor cells glucose metabolism disorder, mitochondrial function is abnormal, and intracellular hydrogen peroxide concentration is dozens of times higher than normal cells; high-concentration ROS continues to attack the boro-oxygen bond in the structure of phenylborate, break the stable configuration of the prodrug, trigger ligand break, and complete the in situ activation of the drug [10, 14].

3.2. Complete process of oxidative cleavage of phenylboronic ester and release of active parent compound

After the prodrug is concentrated in the colorectal cancer tissue with blood circulation through intravenous administration, it enters the tumor cells across the membrane, and the high ROS initiates the cascade oxidation reaction. The steps are as follows: hydrogen peroxide in ROS attacks the

DOI: 10.54254/2753-8818/2026.HZ38762

phenyl borate boron atom, the boroxide-carbon bond is oxidized and cracked, and the borate ester ligand is detached from the tetravalent platinum axial site [1]. ; The unstable Pt(IV) intermediate that loses the protective ligand undergoes a rapid intracellular reduction reaction, and the central tetravalent platinum is electronically reduced to divalent active oxaliplatin [5]; The free oxaliplatin enters the nucleus and cross-links with the genome DNA guanine base ligation to form intra-chain and inter-chain platinum-DNA additions, block DNA replication and transcription, and start the tumor cell killing program [7, 9]. The whole drug release process only occurs in the high-ROS tumor area. There is no oxidative lysis reaction in normal cells, and the active platinum drug will not be released, which realizes the intelligent identification of drug release in the microenvironment.

3.3. Explanation of the core advantage: "tumor activation, normal tissue inhibition"

Summarize the targeted drug release mechanism of the phenylborate response system, and clarify the core advantages of "tumor activation and normal tissue passivation" of the pre-drug [5, 6]. Traditional free oxaliplatin has no environmental recognition ability. It has DNA toxicity as soon as it enters the body, and indiscriminately damages all dividing vigorous cells; the phenylborate-responsive tetravalent oxaliplatin pre-drug builds a double safety barrier; Passivation in the circulation stage: the predrug structure is stable in the low ROS environment of blood and normal tissues, and there is no cytotoxicity, avoiding the acute toxic side effects caused by systemic exposure in the early stage of administration; specific activation of tumor site: only in the high ROS microenvironment of colorectal cancer, the drug is broken and the active drug is locally enriched to improve the concentration of tumor tissue drugs and enhance the anti-tumor effect [3, 7]. Selective cell killing: active oxaliplatin is only produced in tumor cells, and normal colon epithelial cells are almost not exposed to active drugs, which significantly reduces intestinal mucosal damage, bone marrow suppression and other adverse reactions caused by chemotherapy, and achieves the treatment goal of reducing toxicity and increasing efficacy [6, 13].

4. Anti-colorectal cancer activity and molecular mechanisms of tumor apoptosis

Existing in vitro experiments have used classic colorectal cancer cell models such as HCT116, SW480, and CT26 to verify the anti-tumor activity and cell selectivity of such drugs. According to the literature, some in vitro cytotoxic activity data can be obtained. Sarkar et al. designed a multi-targeted tetravalent platinum prodrug that can simultaneously release oxaliplatin, doropicin, and gicitabine. The prodrug shows a nanomole-level IC50 value in tumor cells, and the average selectivity index of human tumor cells and mouse tumor cells is as high as 136 and 320, respectively, indicating that it has a highly selective killing ability against tumor cells and extremely low toxicity to normal cells [2, 6, 9]. The above-mentioned multi-targeted drugs can effectively induce the release of immunogenic cell death-related damage-associated molecular patterns (DAMPs) in CT26 colorectal cancer cells, including calreticulin (CALR), ATP, and high-mobility group box 1 (HMGB1), and promote the phagocytic efficiency of J774 macrophages on tumor cells. After co-culture of pre-drug-treated CT26 cells with J774 macrophages, cell viability was reduced by 32% compared with the untreated group, suggesting that there is a synergistic anti-proliferative effect between chemical killing and immune activation [2, 6].

According to the known experimental data, the anti-tumor efficacy in the body can be effectively verified. The multi-targeted oxaliplatin (IV) prodrug developed by Babu and others showed a better tumor growth inhibition effect than free oxaliplatin or combined drug regimens in two tumor models of Lewis lung cancer (LLC) and CT26 colorectal cancer in mice, and the weight loss of the mice in

DOI: 10.54254/2753-8818/2026.HZ38762

the treatment group was significantly lower than that of the control group. This shows that the prodrug strategy improves tolerance while enhancing the therapeutic effect [2, 6]. OxaliTEX (a ga gadonium-porphin-oxaliplatin (IV) conjugate) was reported by He et al. in nude mice carrying KRASG13D mutant HCT116 colorectal cancer allogeneic transplant tumors; the inhibitory effect of OxaliTEX on tumors was better than that of free oxaliplatin when administered with the same tolerance dose. Pharmacokinetic research shows that about 97% of total platinum is irreversibly bound to plasma proteins within 2 hours after administration of OxaliTEX, but the end-phase elimination of free platinum in plasma has a half-life of up to 11.4 hours. This characteristic of "slow clearance and continuous low concentration exposure" and the increase in platinum accumulation in the tumor (the level of tumor platinum is more than that of ole oxaliplatin under the maximum tolerated dose) together constitute the pharmacokinetic basis of its superior anti-tumor activity [3, 14].

The tolerated dose of OxaliTEX in mice can be more than 3 times that of oxaliplatin (in molar platinum equivalent), and distribution studies show that at equal molar doses, the platinum level of OxaliTEX in plasma, liver, kidney, heart, ovaries and testicles is 1.5 to 7 times higher than that of oxaliplatin. However, the level of platinum in tumors and the ileum is comparable to that of oxaliplatin [3]. This differentiated tissue distribution characteristic shows that OxaliTEX does not increase the drug exposure of toxic-sensitive organs such as the intestine while improving tumor targeting, which is an important reason for the improvement of its treatment index.

Based on the above studies, phenylborate modified tetravalent oxaliplatin and similar axially functionalized prodrugs maintain a killing activity equivalent to or even better than free oxaliplatin in vitro for colorectal cancer cell lines, while significantly reducing toxicity to normal cells (high selectivity index); In vivo studies have further confirmed that this type of prodrug can effectively inhibit the growth of subcutaneous tumors of colorectal cancer, and the systemic toxicity is significantly lower than that of free drugs, fully reflecting the therapeutic advantages of "reducing toxicity and increasing efficacy". The introduction of multi-targeted design and nano-delivery strategy is expected to further improve the anti-tumor immune synergy and clinical transformation potential of the prodrug system.

5. Conclusion

In summary, this paper systematically sorts out the research progress of the molecular design, response-to-release mechanism, and anti-colorectal cancer application of tetravalent oxaliplatin modified with phenylborate, and forms the following core understanding. The tetravalent platinum axial site modification strategy provides a feasible skeleton for the design of oxaliplatin prodrugs. By oxidizing Pt(II) into Pt(IV) and introducing phenylborate ROS-sensitive joints and hydrophilic modified groups in the axial direction, it can give the prodrug tumor microenvironment identification ability, while improving its water solubility, cyclic stability, and cell uptake efficiency. The fine regulation of the length of the connecting arm and the proportion of hydrophilic groups is the key structural factor for the stability and response sensitivity of the drug body before balancing.

The phenylborate-modified tetravalent oxaliplatin prodrug achieves an intelligent response-targeted chemotherapy strategy with the help of tumor microenvironment ROS differences, showing good potential for reducing toxicity and increasing efficacy in the treatment of colorectal cancer. Future research can be further expanded in the following directions: further optimize the electronic substitution effect of phenyloborate joints, and realize the differential response rate regulation of tumors with different concentrations of ROS; ROS-responsive tetravalent platinum prodrugs are

DOI: 10.54254/2753-8818/2026.HZ38762

expected to provide a practical solution for precise chemotherapy for colorectal cancer and more ROS high-expression solid tumors.

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