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TDO Target Inhibitor Research Progress Review

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Abstract

Tryptophan metabolism plays a key role in tumor immunology. Tryptophan 2,3-dioxygenase (TDO), as a key rate-limiting enzyme in this metabolic pathway, catalyzes the conversion of tryptophan into metabolites such as kynurenine, which can modulate immune cell functions and promote tumor immune evasion. Therefore, it has become a potential target for tumor immunotherapy. This article comprehensively reviews the structure and biological functions of TDO, explores its mechanisms of action in the tumor microenvironment, and summarizes its expression patterns and prognostic correlations in different types of tumors. Additionally, this review covers the mechanisms of action and research progress of TDO inhibitors, including the structural optimization and activity studies of indole derivatives, naphthotriazole diones, aminoisoxazoles, tryptanthrins, platinum (IV) complexes, and small molecule conjugates. Although most TDO inhibitors are still in the laboratory research stage, they show broad application prospects in tumor immunotherapy. Future research directions should include optimizing existing inhibitor structures, exploring new design strategies, and strengthening clinical studies to develop highly effective and low-toxicity TDO inhibitors, providing new therapeutic options for cancer patients.

Keywords

Tryptophan Metabolism, Tryptophan 2,3-Dioxygenase (TDO), Tumor Immune Evasion, TDO Inhibitors, Tumor Immunotherapy

1. Introduction

Tryptophan metabolism has extremely important biological significance in living organisms, especially in tumor immunology. As an essential amino acid, trypto-

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phan is primarily metabolized through the kynurenine pathway, the 5-hydroxytryptamine (5-HT) pathway, and the indole pathway [1]. Among these, the kynurenine pathway is the predominant metabolic route, accounting for over 95% of tryptophan metabolism. In this pathway, tryptophan 2,3-dioxygenase (TDO) is the key rate-limiting enzyme. The metabolites it catalyzes, such as kynurenine and quinolinic acid, can affect immune cell functions through various mechanisms, thus playing a significant role in tumor immunology [2].

TDO's role as a target for tumor immunotherapy is underscored by its integration into broader immunotherapy strategies. Emerging evidence suggests that blocking TDO activity can synergize with existing immune checkpoint inhibitors to augment anti-tumor immune responses. Additionally, TDO inhibitors can be combined with other metabolic reprogramming approaches to reshape the tumor microenvironment, enhancing immune cell infiltration and function. Thus, TDO not only serves as a key player in tumor immune evasion but also provides a promising target for the development of next-generation immunotherapies.

In the context of tumor immune tolerance, TDO plays a particularly prominent role. Under normal physiological conditions, TDO is predominantly expressed in the liver, where it regulates systemic tryptophan homeostasis. However, in certain cancers, TDO expression is significantly upregulated, resulting in local tryptophan depletion and the accumulation of metabolites such as kynurenine within the tumor microenvironment. These metabolic alterations can induce T-cell anergy and apoptosis, thereby suppressing anti-tumor immune responses and facilitating tumor immune evasion [3]. Therefore, TDO has emerged as a key player in tumor immune evasion and a promising target for tumor immunotherapy.

In summary, the tryptophan metabolic pathway and its key enzyme TDO play an important regulatory role in tumor immunology. In-depth studies on the structure and function of TDO, its mechanisms of action in the tumor microenvironment, and the development of TDO inhibitors will not only help understand the complex process of tumor immune evasion but also provide a theoretical basis and potential targets for developing new tumor immunotherapy strategies.

2. Structure and Biological Functions of TDO

2.1. Structure

TDO protein is a heme-containing homotetrameric enzyme widely found in organisms from bacteria to humans, with a highly conserved structure, indicating its important biological functions during evolution. TDO protein consists of monomers with a molecular mass of 35 - 45 kDa, which interact to form a stable tetrameric structure. This unique structural feature enables TDO to maintain similar functions and catalytic mechanisms across different species.

The human TDO protein monomer consists of 409 amino acids and is organized into 15 α-helices, which can be divided into three main regions: the N-terminal region (α1 - α3), the large domain (α4 - α9, α13, α14), and the small domain (α10 - α12, α15) (**Figure 1**). The N-terminal region, located at the protein's N-

terminus, primarily functions as a structural connection and stabilizer, providing the basic framework for the overall protein conformation. The large domain, which is the core region of TDO, contains the heme-binding pocket responsible for substrate tryptophan binding and catalytic reactions. This highly conserved region is the key site for TDO's enzymatic activity. The small domain, although relatively smaller in size, plays a crucial role in the formation and stability of the tetramer, as well as influencing the overall enzyme conformation and function [4].

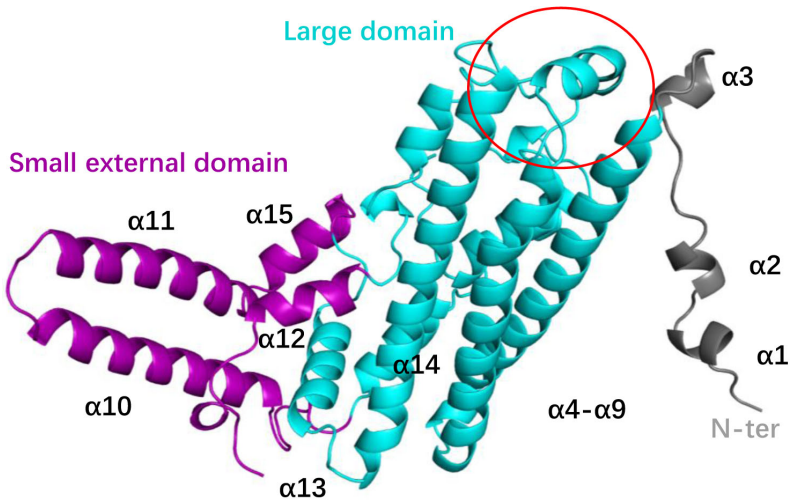


Figure 1. Human TDO domains. (the red circle marks heme binding site) (PDB code: 5TIA).

In the tetrameric structure, TDO protein exists as a homotetramer, with four monomers associated through three mutually perpendicular biaxial axes. The interaction force between adjacent monomers is strong, forming two C-shaped dimers that are perpendicularly clamped together, creating a tightly packed tetrameric structure. This unique tetrameric conformation not only enhances protein stability but also provides a synergistic platform for enzyme activity.

The main small molecule binding site of TDO is the heme-binding pocket, located in the large domain. This pocket is formed by four long helices and three short helices. Heme, as the prosthetic group of TDO, provides the active center for the catalytic reaction. Substrate tryptophan enters the enzyme's active site by binding to heme, where it undergoes an oxidation reaction. In addition to the heme-binding pocket, the surface of the TDO protein may also contain other potential small molecule binding sites, which may be involved in regulating enzyme activity, stability, or interactions with other proteins. However, their specific locations and functions require further investigation.

2.2. Biological Functions of TDO and Its Mechanisms of Action in the Tumor Microenvironment

Tryptophan 2,3-dioxygenase (TDO), as a key rate-limiting enzyme, is widely in-

volved in tryptophan metabolism and the regulation of various physiological and pathological processes. TDO activity can be induced by multiple factors, including elevated tryptophan levels, activation of glucocorticoids, and the action of inflammatory cytokines [5].

In mammals, TDO is highly expressed in the liver and can also be induced in other tissues such as the placenta, testes, and brain, serving as one of the core enzymes for maintaining systemic tryptophan homeostasis. TDO catalyzes the conversion of tryptophan into metabolites such as kynurenine, kynurenic acid, and quinolinic acid, regulating systemic tryptophan levels [6] (**Figure 2**).

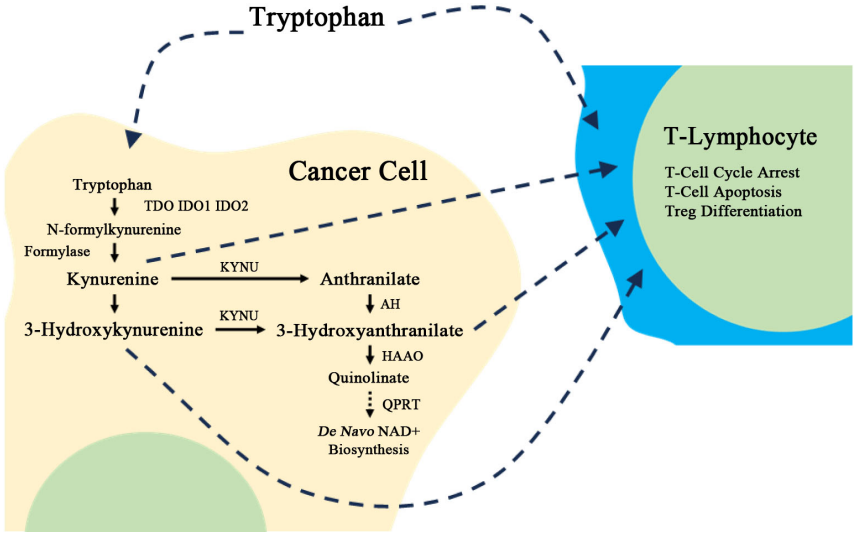


Figure 2. Role of TDO in tryptophan metabolism and T-Cell regulation.

In the nervous system, the functions of TDO are particularly significant. Metabolites generated from tryptophan metabolism can cross the blood-brain barrier and affect the synthesis of neurotransmitters and the activity of nerve cells. Studies have shown that TDO plays important roles in neurodevelopment, neuroprotection, and neurodegenerative diseases. For example, abnormal expression of TDO in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease may be associated with neuroinflammation and neuronal damage [7].

In the immune system, TDO indirectly affects the activity and function of immune cells by regulating tryptophan metabolism. Its metabolite kynurenine can activate the AHR receptor, modulating the differentiation and function of immune cells and thereby influencing the intensity and direction of immune responses. Moreover, TDO expression is regulated by various cytokines; for example, IL-6 and TNF-α can induce TDO expression, regulating tryptophan metabolism and affecting the progression of inflammatory responses [8].

In the tumor microenvironment, the role of TDO has attracted widespread attention. High expression of TDO in tumor cells leads to local tryptophan depletion, thereby suppressing T-cell proliferation and activity and promoting tumor immune evasion. This mechanism makes TDO a potential target for tumor im-

munotherapy. By inhibiting TDO activity, the tryptophan levels in the tumor microenvironment can be restored, enhancing the anti-tumor activity of T cells and thus providing a new strategy for cancer treatment. For example, studies have shown that TDO inhibitors can enhance the efficacy of immune checkpoint inhibitors by regulating tryptophan metabolism [9] [10].

2.3. Expression Patterns of TDO in Different Types of Tumors and Their Correlations with Prognosis

Studies have shown that TDO is upregulated in various cancers, including breast cancer, hepatocellular carcinoma [11], lung cancer [12] and colorectal cancer. In these tumors, high TDO expression is closely related to tumor invasiveness and poor prognosis in patients.

In breast cancer, high TDO expression is closely associated with tumor invasiveness and poor prognosis. Studies have shown that TDO expression levels are positively correlated with tumor malignancy and grade, particularly in estrogen receptor-negative and triple-negative breast cancers. Furthermore, elevated TDO expression is linked to poor prognosis in breast cancer patients, highlighting its critical role in regulating the immune microenvironment and tryptophan metabolism in this malignancy.

In hepatocellular carcinoma, TDO promotes the proliferation of hepatocellular carcinoma cells through the autocrine IL-6 signaling pathway. Additionally, high TDO expression is negatively correlated with the survival rate of patients with hepatocellular carcinoma, indicating its important role in the occurrence and development of this cancer. In other tumors such as lung cancer and colorectal cancer, high TDO expression is also associated with tumor invasiveness and poor prognosis in patients. These findings suggest that TDO not only plays an important role in the occurrence and development of tumors but also provides a potential biomarker for predicting tumor prognosis and guiding individualized treatments.

3. Mechanisms of Action of TDO Inhibitors

TDO, a heme-containing monooxygenase, plays a crucial role in tryptophan metabolism. Its active site features a complex and highly conserved structure centered around a heme group. The iron atom within the heme can coordinate with the nitrogen atom of tryptophan's indole ring to form a stable complex. Additionally, key residues in the active site, such as His55 and Thr254, interact with tryptophan's indole ring and amino group via hydrogen bonds, further stabilizing substrate binding. Other residues, including Phe140, Leu147, and Met335, primarily engage in hydrophobic interactions or van der Waals forces with the indole ring, providing the necessary spatial environment for substrate binding and catalysis [13] [14].

In recent years, significant progress has been made in the research of TDO inhibitors. TDO inhibitors primarily interact with key residues in the active site

through various non-covalent interactions, competitively occupying the binding site of tryptophan and thereby blocking the catalytic reaction. Hydrogen bonding is one of the key mechanisms for inhibitor binding. For example, the amino group of the inhibitor can form hydrogen bonds with the heme propionic acid chain or His55, significantly enhancing the binding affinity of the inhibitor. Additionally, hydrophobic interactions also play an important role in inhibitor binding. Hydrophobic groups in the inhibitor can form tight hydrophobic stacks with hydrophobic residues in the active site (such as Phe140, Leu147, and Met335), further enhancing binding stability. Meanwhile, the indole ring or similar structure in the inhibitor can interact with the heme group and surrounding residues (such as His55, Phe140, and Leu147) through van der Waals forces. This interaction helps precisely position the inhibitor in the active site, thereby improving its inhibitory potency [14] [15].

In summary, the structural characteristics of the TDO active site provide important target information for inhibitor design. The synergistic action of hydrogen bonds, hydrophobic interactions, and van der Waals forces is key to achieving efficient inhibition. Future research will further elucidate the binding modes between TDO and inhibitors to provide a theoretical basis for developing highly selective and potent TDO inhibitors.

4. Research Progress on TDO Inhibitors

In recent years, medicinal chemists have made significant progress in the research of TDO inhibitors, developing a series of small molecule inhibitors with high activity. Based on different core structures, these inhibitors can be classified into indole derivatives, naphthotriazole diones, aminoisoxazoles, tryptanthrins, platinum (IV) complexes, and small molecule conjugates. This section summarizes the research progress of these TDO small molecule inhibitors.

4.1. Indole Derivatives

In 1995, Salter *et al.* [16] first reported a series of 3-(2-(pyridyl)ethenyl)indole derivatives as TDO inhibitors (**Figure 3**). Among them, compound 1 (680C91) exhibited good inhibitory activity with an IC_{50} value of 0.28 μM, becoming the lead structure of this class of compounds.

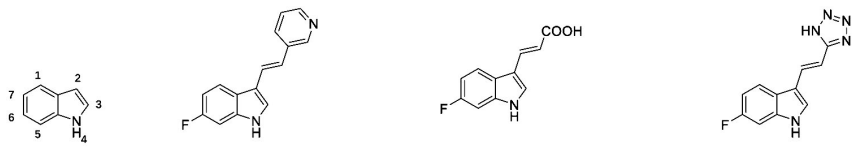


Figure 3. Indole derivatives inhibitors of TDO protein.

In 2011, Dolusic *et al.* [17] further expanded the research on these derivatives based on compound 1. They replaced the indole ring, increased the side chain on

the indole ring, modified the ethylene chain, and changed the aromatic side chain, significantly enhancing TDO inhibitory activity. Structure-activity relationship (SAR) studies indicated that the indole ring, as the core structure, is crucial for TDO inhibitory activity. For example, introducing a fluorine atom at position 5 or 6 of the indole ring can significantly enhance inhibitory activity, while introducing groups like hydroxymethyl may reduce the dissociation degree of the molecule, thereby enhancing its biological activity. Additionally, modifying the ethylene chain and aromatic side chain, such as replacing the pyridine-3-yl side chain and introducing hydrogen bond acceptors or negatively charged groups at specific positions on the benzene ring, can further optimize the compound's activity and water solubility.

After testing and screening for water solubility, lipophilicity, and other aspects, several small molecules with good enzyme inhibitory activity were identified, among which compounds 2 and 3 had inhibitory activities of IC_{50} = 3 μM and 0.62 μM, respectively. Particularly, compound 3, with a fluorine atom introduced at position 6 of the indole ring and a tetrazole group on the pyridine ring, exhibited good TDO inhibitory activity, high selectivity, and excellent oral bioavailability, making it a candidate for further preclinical evaluation. Subsequent experiments showed that compound 3 significantly inhibited cancer and was identified as an effective TDO inhibitor, named LM10.

4.2. Naphthotriazole Dione Derivatives

In 2015, Wu *et al.* [18] reported a series of naphthotriazole dione derivatives as TDO inhibitors (**Figure 4**). The research team first constructed a ligand-binding model of human TDO (hTDO) through homology modeling and used this model to perform virtual screening on a selected chemical database, identifying compound 4 as a potential TDO inhibitor. Subsequent structure-activity relationship (SAR) studies revealed that the naphthotriazole dione core structure is crucial for TDO inhibitory activity. By introducing different substituents on this core structure, such as hydrophobic groups on the benzene ring and rigid tertiary amides at the para and meta positions of the N-benzyl group, the inhibitory effect on TDO can be significantly improved, thereby enhancing biological activity.

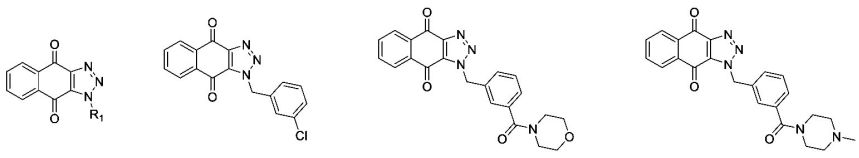


Figure 4. Naphthazarinone derivatives inhibitors of TDO protein.

After a series of structural modifications and activity tests, several small molecules with good enzyme inhibitory activity were obtained, among which com-

pounds 5 and 6 showed particularly prominent TDO inhibitory activity. Especially compound 6, with an IC_{50} value of 30 nM, was 24 times more potent than the initial compound 4 (IC_{50} = 711 nM). Compound 6 not only exhibited excellent TDO inhibitory activity but also had 21 times higher selectivity for TDO than IDO, showing good selectivity. Structural analysis indicated that compound 6 formed additional hydrogen bonds with the conserved Arg144 residue in the TDO active site through the introduction of an N-methylpiperazine amide group on the naphthotriazole dione core structure. This structural feature is considered a key factor in enhancing its activity. Therefore, compound 6 was selected as a candidate for further preclinical evaluation and is expected to be an effective TDO inhibitor for the treatment of cancer and other TDO-related diseases.

4.3. Aminoisoxazole Derivatives

In 2018, Pei *et al.* [19] reported a series of aminoisoxazole derivatives as TDO inhibitors (**Figure 5**). Researchers discovered aminoisoxazole derivatives as effective TDO inhibitors through high-throughput screening (HTS), with compound 7 (cellular EC_{50} of 85 nM) being the most effective hit compound. Using compound 7 as the lead, the research team enhanced TDO inhibitory activity by replacing the amino group on the isoxazole ring and optimizing the side chain on the isoxazole ring.

7
TDO IC_{50} = 0.14 μM

8
TDO IC_{50} = 0.029 μM

9
TDO IC_{50} =0.028 μM

10
TDO IC_{50} = 0.34 μM

Figure 5. Aminoisoxazole derivatives inhibitors of TDO protein.

Structure-activity relationship studies indicated that the isoxazole ring, as the core structure, is crucial for efficient TDO inhibition. The presence of an amino group on the isoxazole ring is essential for TDO inhibitory activity, while replacing it with other substituents may lead to significant activity loss. Additionally, modifying the benzene ring, such as introducing specific substituents or replacing it with other hydrophilic heterocycles, can further adjust the compound's activity and stability. These findings laid a solid foundation for designing TDO inhibitors with high inhibitory activity, good stability, and bioavailability.

After testing and screening for cellular activity and stability, several small molecules with good TDO inhibitory activity were obtained, among which compound 10 exhibited good TDO inhibitory activity with a cellular EC_{50} of 77 nM. Particularly, compound 10 showed significantly enhanced stability in human whole blood, with a retention rate of 91%. Therefore, compound 10 was selected as a candidate for further preclinical evaluation.

4.4. Tryptanthrin Derivatives

In 2018, Zhang *et al.* [20] systematically evaluated a series of tryptanthrin derivatives, including compound 11, for their TDO inhibitory activity (**Figure 6**). The research team optimized the expression conditions of recombinant human TDO (hTDO) and the enzyme activity detection method, establishing two new cell-based TDO activity detection models and conducting a detailed analysis of the inhibitory activity of these derivatives.

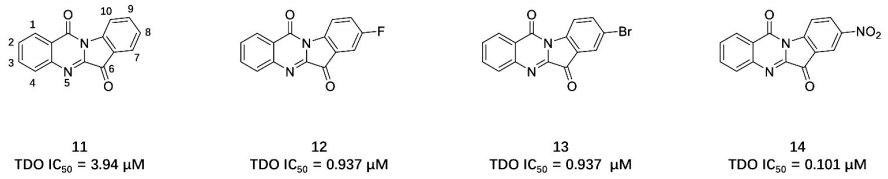


Figure 6. Tryptanthrin derivatives inhibitors of TDO protein.

In structure-activity relationship (SAR) studies, it was found that the substituents at position 8 of the tryptanthrin core structure significantly affect TDO inhibitory activity. Compounds with electron-withdrawing groups (such as -F, -Br, or -NO_2) at position 8 exhibited higher TDO inhibitory activity, while substituents at position 2 had a negative impact on activity. Molecular docking studies further revealed that compounds 12 and 13 could strongly coordinate with the heme iron (Fe) of hTDO through the oxygen atom on the tryptophan ring, thereby binding to the active site of hTDO. This coordination is the key mechanism by which tryptanthrin derivatives inhibit TDO activity.

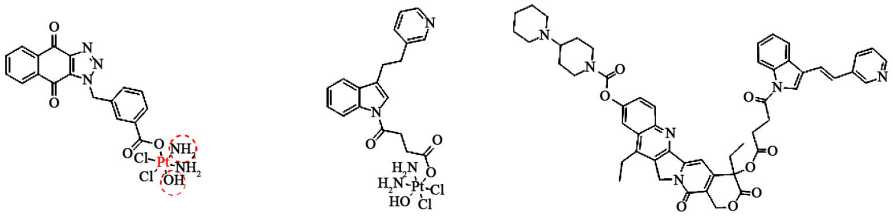
In enzyme activity and cell-based screening, compounds 12, 13, and 14 showed excellent TDO inhibitory activity with nanomolar IC_{50} values. For example, compound 14 had average IC_{50} values of 0.040 μM in U87 MG cells and 0.061 μM in HEK293-hTDO cells, demonstrating its highly efficient TDO inhibitory capacity. These results indicate that tryptanthrin derivatives have the potential to become highly effective TDO inhibitors and may play an important role in tumor immunotherapy.

In summary, tryptanthrin derivatives, with their unique structure and high inhibitory activity, have become important lead compounds for developing new TDO inhibitors. Future research will further optimize the structure of these compounds to enhance their selectivity and bioavailability and explore their application prospects in tumor immunotherapy.

4.5. Platinum (IV) Complexes and Small Molecule Conjugates

Between 2019 and 2021, Hua *et al.* [11] [21]-[23] developed a series of platinum (IV) complexes and small molecule conjugates as TDO inhibitors (**Figure 7**). These inhibitors combined platinum (IV) prodrugs with TDO inhibitors to achieve a synergistic effect between chemotherapy and immune modulation. It was found that platinum (IV) complex 15 exhibited significant TDO inhibitory activity with an IC_{50} value of 0.85 μM, effectively blocking the generation of kynurenine (Kyn) and

inhibiting the activation of AHR, thereby enhancing anti-tumor immune responses. Compound 16 had an IC_{50} value of 0.27 μM against HepG-2 cells. Additionally, compound 17, as a small molecule conjugate, showed significantly higher inhibitory activity against HepG-2 cells than single chemotherapy drugs, with an IC_{50} value of 1.82 μM, demonstrating high anti-tumor activity. Compound 16 showed significant anti-tumor activity but also exhibited moderate cytotoxicity in normal cell lines, highlighting the need for further optimization to improve the therapeutic window.



15
TDO IC_{50} = 0.85 μM

16
HepG-2 IC_{50} = 0.27 μM

17
HepG-2 IC_{50} = 1.82 μM

Figure 7. Platinum (IV) complex and small molecule conjugate inhibitors of TDO.

Structure-activity relationship studies indicated that the core structure of platinum (IV) complex inhibitors is the platinum (IV) metal center, with ligands including amine (NH_2) and hydroxyl (-OH) groups. The presence of hydroxyl groups significantly enhanced the cell uptake capacity and anti-tumor activity of the complexes, while also improving TDO inhibitory activity. Additionally, in the series of small molecule conjugates, the core structure of the TDO inhibitor was the indole ring, and the introduction of lipophilic side chains significantly enhanced inhibitory activity. These structural features suggest that platinum (IV) complexes and small molecule conjugates can significantly enhance TDO inhibitory activity and anti-tumor effects by optimizing ligands and functional groups.

5. Summary and Outlook

Tryptophan 2,3-dioxygenase (TDO) plays a key role in tumor immune evasion by catalyzing the catabolism of tryptophan, leading to tryptophan depletion and the accumulation of metabolites such as kynurenine, which suppress the activity of effector T cells and natural killer cells, activate regulatory T cells, and create an immunotolerant microenvironment. In recent years, research on TDO inhibitors has gained attention, although it started relatively late, and has made some progress.

Currently, research on TDO inhibitors primarily focuses on the development of small molecule inhibitors. Although several types of TDO inhibitors have been reported, most remain in the laboratory research stage, with only a few advancing to clinical trials. Each class of TDO inhibitors has distinct characteristics. Structurally, they feature different heterocyclic cores that bind to the TDO active site through various mechanisms. In terms of activity, indole derivatives, naphthotriazole diones, aminoisoxazoles, and tryptanthrins all demonstrate potent TDO inhibitory activity.

However, their bioavailability and stability require further optimization. Platinum (IV) complexes and small molecule conjugates, which integrate chemotherapy drugs with TDO inhibitors, achieve synergistic effects between chemotherapy and immune modulation, thereby exhibiting high anti-tumor activity. Overall, each type of inhibitor offers unique advantages in terms of activity, selectivity, bioavailability, and stability, but also presents distinct challenges. Future research must further optimize their performance to meet clinical demands, as the development of TDO inhibitors continues to face significant hurdles.

In tumor immunotherapy, the development of new TDO inhibitors is of great significance. First, TDO inhibitors can be used as monotherapy to inhibit tumor growth by modulating immune responses in the tumor microenvironment. Second, TDO inhibitors can be combined with other immunotherapeutic drugs to enhance the effects of immune checkpoint inhibitors and overcome tumor immune evasion. Additionally, TDO inhibitors can be used in combination with other treatments such as chemotherapy and radiotherapy to improve overall therapeutic effects. The research on TDO inhibitors is expected to develop in several directions: first, further optimizing the structure of existing inhibitors to enhance their selectivity and activity; second, exploring new inhibitor design strategies, such as structural modifications based on natural products and high-throughput screening; third, strengthening clinical research on TDO inhibitors to verify their efficacy and safety in different types of tumors. Moreover, with a deeper understanding of the mechanisms of action of TDO in tumors, new targets and therapeutic strategies may be discovered. Based on current research, naphthotriazole dione and tryptanthrin derivatives are the most promising due to their high potency and selectivity. The synergistic anti-tumor strategy involving platinum (IV) complexes and small molecule conjugates also shows significant potential. Future research should prioritize the development of these scaffolds and strategies, while exploring structure-based drug design and AI-assisted approaches to discover new inhibitors.

In summary, TDO inhibitors have broad application prospects in tumor immunotherapy, and continuous in-depth research will bring more treatment options and hope to cancer patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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