**RECENT ADVANCEMENTS ON MEDICINAL ACTIVITY OF INDOLE DRUGS**

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**ABSTRACT**

Indole is one of the most significant scaffolds for drug discovery. The majority of significant synthetic medicine compounds contain indole scaffolds, which have paved the path for the development of reliable targets. Derivatives of indoles have a distinctive capacity to attach to enzymes reversibly while resembling the structure of peptides. 2-arylindoles tend to be the most promising lead among the molecules in the indole class for potential therapeutic development. The 2-arylindole derivatives possess antimicrobial, antituberculosis, anticancer, antioxidant, anti-inflammatory, anti-diabetic, antiviral, and antiproliferative activity. This provides incredible possibilities for finding novel medications with various mechanisms of action. Novartis developed the medication panobinostat (LBH589), a non-selective histone deacetylate inhibitor, to treat acute myeloid leukaemia and multiple myeloma. The approval of panobinostat in the third line of treatment in combination with bortezomib and dexamethasone was based on its efficaciousness when used in combinatorial regimens. Novartis markets panobinostat under the Farydak brand.

**Keywords:**Indole, panobinostat, acute myeloid leukaemia, multiple myeloma

1. **INTRODUCTION**

A significant quantity of heterocyclic compounds are used in drugs solely due to their distinctive chemical and biological characteristics, which are essential for an array of physiological processes.One of the most promising and pharmacologically active of these is indole. Indole's chemical reactivity has made it accessible to modification, resulting in a wide range of new lead compounds that have been effectively employed as innovative therapeutic candidates to treat various pharmacological conditions.Among the indole-based compounds used are amedalin, an antidepressant, reserpine, an antihypertensive, and vincristine, an anticancer drug[1].

**PANOBINOSTAT: A NON-SELECTIVE HISTONE DEACETYLATE INHIBITOR**

1. **Drug Chemistry**

Panobinostat is a member of a recently discovered class of drugs known as deacetylase (DAC) inhibitors. Panobinostat is a strong oral nonselective pan-histone deacetylase inhibitor (HDAC). It has been approved by the FDA to treat multiple myeloma in conjunction with dexamethasone and bortezomib. Panobinostat (chemical name: 2-hydroxypropanoic acid, compound with 2-(E)-N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3- yl)ethyl]amino]methyl]phenyl]-2-propenamide [1 : 1][2].



**Figure 1: Structure of Panobinostat**

In all four HDAC classes (Histone Deacetylases), preclinical activity has been demonstrated. It causes apoptosis in multiple myeloma cells that are resistant to traditional treatments at low doses. In myeloma cell lines, it also causes caspase activation and poly-(ADP-ribose) polymerase (PARP) breakage, and it suppresses cell growth[3].

1. **Mechanism of Action**

Since histones were the first identified targets of DACs, panobinostat inhibits a wide variety of DACs, commonly referred to as histone DACs (HDAC).It is understood that DACs control the acetylation of over 1,750 proteins involved in several biological processes, such as chromatin remodelling, gene transcription, cell cycle progression, protein degradation, and cytoskeletal reorganisation, in addition to DNA replication and repair[4].Unfavourable findings have been connected to the overexpression of DACs in multiple myeloma [5]. All class I (HDACs 1, 2, 3, and 8), class II (HDACs 4, 5, 6, 7, 9, and 10) and class IV (HDAC 11) HDACs are inhibited by panobinostat, with half maximum inhibitory doses for each class I, II, and IV HDAC in the nanomolar range. When compared to vorinostat, another pan-DAC inhibitor that was studied for the treatment of multiple myeloma, panobinostat's potency was ten times higher for all HDACs. It is now one of the most potent pan-DAC inhibitors in clinical research [6]. It is believed that panobinostat largely exerts its anticancer effects by inhibiting protein metabolism and altering gene expression through epigenetic modifications. By inhibiting signal transducer and activator of transcription 3, Akt, and hypoxia-inducible factor 1α, class I HDACs can alter gene expression and assist reactivate epigenetically silenced tumour suppressor genes. Class I HDACs target histones and transcription factors like p53 [7, 8].

Additionally, it has been demonstrated that panobinostat and PI bortezomib work in concert. The way in which panobinostat affects protein breakdown helps to explain this synergy. High levels of protein turnover make multiple myeloma cells susceptible to PIs, which impede the metabolism and excretion of proteins made inside the cell and, as a result, trigger a proapoptotic signal. On the other hand, if the proteasome is unable to break down these proteins fast enough, the proteins can form aggregates called aggresomes, which are then carried by microtubules to an autophagosome where lysosomes break them down. The transportation of these protein aggregates for breakdown depends on the interaction of HDAC6 with tubulin and the motor protein dynein.Hyperacetylated microtubules and ineffective aggresome-mediated breakdown result from HDAC6 inhibition. When bortezomib and panobinostat are administered together, the proteasome and aggresome pathways are simultaneously inhibited, which leads in synergistic cytotoxicity. Bortezomib inhibits the proteasome's ability to degrade protein and stimulates the creation of aggresomes[9].

Furthermore, panobinostat in conjunction with bortezomib plus dexamethasone or the IMiDlenalidomide plus dexamethasone facilitated deregulation of other genes that were not affected by doublet treatment alone, according to in vitro and in vivo models of multiple myeloma[10].

1. **Pharmacokinetics and Metabolism**

20 mg of panobinostat administered orally undergo rapid absorption, reaching the highest possible plasma concentration in one to two hours[11, 12].Panobinostat's median maximum plasma levels when taken orally ranged from 5.5 to 21.2 ng/ml. When panobinostat was taken orally, its absolute bioavailability was 21%. Food consumption had no discernible impact on the bioavailability or rate of absorption of the drug. With a half-life of thirty-one hours, panobinostat is eliminated almost equally by all patients in the form of urine and faeces[13, 14]. CYP and non-CYP enzymes primarily catalyse the hydrolysis, acidosis, and glucuronidation processes that break down panobinostat. Panobinostat exposure may be greatly increased by CYP3A4 inhibitors, necessitating careful monitoring for medication interactions or possibly lowering panobinostat dosage. Conversely, CYP34 inducers are to be shunned wherever feasible as they have the potential to drastically lower panobinostat exposure. Additionally, panobinostat may inhibit CYPY2D6, thus it's best to stay away from related substrates. QT prolongation has been observed with panobinostat administration, particularly when given intravenously. As a result, concurrent use of medications that lengthen QT should be avoided. Previous research on the administration of panobinostat in patients with haematological or renal impairment has demonstrated that hepatic impairment is linked to decreased drug clearance and increased plasma exposure, whilst renal function had no effect on drug clearance and tolerability[15, 16].

 Panobinostat is still a vital treatment option for patients with refractory or relapsed multiple myeloma, even in the face of notable advancements in the disease's therapeutic management. Multiple clinical trials have provided data confirming its continued effectiveness as a therapy, even for individuals who have had extensive pretreatment. When combined with other drugs, HDAC inhibitors like panobinostat have the potential to completely change the way multiple myeloma is treated by extending survival times and improving response quality while posing less toxicity to patients[17].

1. **REFERENCES**

[1] Kumar D, Sharma S, Kalra S, Singh G, Monga V, Kumar B. Medicinal perspective of indole derivatives: recent developments and structure-activity relationship studies. Current drug targets. 2020 Jul 1;21(9):864-91.

[2] Atadja P. Development of the pan-DAC inhibitor panobinostat (LBH589): successes and challenges. Cancer letters. 2009 Aug 8;280(2):233-41.

[3] Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A, Yao TP. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell. 2003 Dec 12;115(6):727-38.

[4] Choudhary C, Kumar C, Gnad F, Nielsen ML, Rehman M, Walther TC, Olsen JV, Mann M. Lysine acetylation targets protein complexes and co-regulates major cellular functions. Science. 2009 Aug 14;325(5942):834-40.

[5] Mithraprabhu S, Kalff A, Chow A, Khong T, Spencer A. Dysregulated Class I histone deacetylases are indicators of poor prognosis in multiple myeloma. Epigenetics. 2014 Nov 2;9(11):1511-20.

[6] Laubach JP, Moreau P, San-Miguel JF, Richardson PG. Panobinostat for the treatment of multiple myeloma. Clinical cancer research. 2015 Nov 1;21(21):4767-73.

[7] Atadja P. Development of the pan-DAC inhibitor panobinostat (LBH589): successes and challenges. Cancer letters. 2009 Aug 8;280(2):233-41.

[8] Kalushkova A, Fryknäs M, Lemaire M, Fristedt C, Agarwal P, Eriksson M, Deleu S, Atadja P, Österborg A, Nilsson K, Vanderkerken K. Polycomb target genes are silenced in multiple myeloma. PloS one. 2010 Jul 9;5(7):e11483.

[9] Catley L, Weisberg E, Kiziltepe T, Tai YT, Hideshima T, Neri P, Tassone P, Atadja P, Chauhan D, Munshi NC, Anderson KC. Aggresome induction by proteasome inhibitor bortezomib and α-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood. 2006 Nov 15;108(10):3441-9.

[10] Ocio EM, Vilanova D, Atadja P, Maiso P, Crusoe E, Fernández-Lázaro D, Garayoa M, San-Segundo L, Hernández-Iglesias T, de Álava E, Shao W. In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. haematologica. 2010 May;95(5):794.

[11] Clive S, Woo MM, Nydam T, Kelly L, Squier M, Kagan M. Characterizing the disposition, metabolism, and excretion of an orally active pan-deacetylase inhibitor, panobinostat, via trace radiolabeled 14 C material in advanced cancer patients. Cancer chemotherapy and pharmacology. 2012 Oct;70:513-22.

[12] Van Veggel M, Westerman E, Hamberg P. Clinical pharmacokinetics and pharmacodynamics of panobinostat. Clinical Pharmacokinetics. 2018 Jan;57(1):21-9.

[13] Srinivas NR. Clinical pharmacokinetics of panobinostat, a novel histone deacetylase (HDAC) inhibitor: review and perspectives. Xenobiotica. 2017 Apr 3;47(4):354-68.

[14] Savelieva M, Woo MM, Schran H, Mu S, Nedelman J, Capdeville R. Population pharmacokinetics of intravenous and oral panobinostat in patients with hematologic and solid tumors. European Journal of Clinical Pharmacology. 2015 Jun;71:663-72.

[15] Sharma S, Witteveen PO, Lolkema MP, Hess D, Gelderblom H, Hussain SA, Porro MG, Waldron E, Valera SZ, Mu S. A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and varying degrees of renal function. Cancer chemotherapy and pharmacology. 2015 Jan;75:87-95.

[16] Slingerland M, Hess D, Clive S, Sharma S, Sandstrom P, Loman N, Porro MG, Mu S, Waldron E, Valera SZ, Gelderblom H. A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function. Cancer chemotherapy and pharmacology. 2014 Nov;74:1089-98.

[17]Eleutherakis-Papaiakovou E, Kanellias N, Kastritis E, Gavriatopoulou M, Terpos E, Dimopoulos MA. Efficacy of panobinostat for the treatment of multiple myeloma. Journal of Oncology. Jan 13;2020.