A Comprehensive Review of Phosphodiesterase 4B: Functions, Structure, Disease Association, Therapeutic Applications & Potential.

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Received September 17, 2024
Accepted February 04, 2025
Electronic access February 28, 2025

Phosphodiesterase 4B (PDE4B) is an enzyme within the PDE (phosphodiesterase) family, playing a crucial function in the hydrolysis of cAMP (cyclic adenosine monophosphate), an essential molecule in cellular signaling. This review article critically examines the complex nature of PDE4B, emphasizing its functions, structure, disease association, and therapeutic potential. PDE4B is primarily located in the brain, immune cells, lung tissues, and inflammatory cells. Influences inflammatory responses, cognitive functions, and mood regulation. By modulating cAMP levels, PDE4B impacts a variety of biological pathways, making it a promising therapeutic target in various diseases. The review also examines current inhibitors like Apremilast, Crisaborole, and Roflumilast, detailing their mechanisms of action and therapeutic applications. Additionally, it highlights novel PDE4B inhibitors identified through in-silico studies, demonstrating their potential in advancing therapeutic strategies.

Introduction

Intracellular signal transduction represents a fundamental mechanism through which cells respond to environmental cues and maintain physiological homeostasis. Central to this process is cyclic adenosine monophosphate (cAMP), a ubiquitous second messenger that orchestrates the relay of extracellular signals into precise intracellular responses. As a critical molecular intermediary, cAMP bridges the gap between external stimuli—including neurotransmitters, cytokines, and growth factors—and downstream cellular processes such as gene expression, nerve cell proliferation, differentiation, and maturation[1]. Therefore, the temporal and spatial regulation of cAMP signaling is essential for maintaining cellular function and organismal physiology. The phosphodiesterase (PDE) enzyme family is the primary regulatory mechanism for controlling intracellular cAMP levels through hydrolysis[2]. Among the various PDE isoforms, PDE4B has emerged as a particularly intriguing target due to its tissue-specific expression pattern and unique regulatory characteristics[3],[4]. PDE4B displays predominant expression in the brain, immune cells, lung and airway tissues, and inflammatory cells, where it exists in five distinct isoforms[5]. This specialized distribution pattern suggests a more selective role in modulating cAMP signaling than other PDE family members. PDE4B's significance extends beyond its essential enzymatic function, as it participates in multiple signaling networks that regulate critical cellular processes. Through its involvement in the PI3K/AKT/mTOR pathway, PDE4B influences cell growth and survival mechanisms[6,7]. Similarly, its role in the cAMP/CREB signaling cascade affects gene transcription and neuronal function[8]. These diverse molecular interactions position PDE4B as a central regulator of various physiological processes, including inflammation, cognition, and mood regulation. Despite substantial research into cAMP signaling and the broader PDE enzyme family, several crucial questions regarding PDE4B's therapeutic potential remain unanswered. The current literature lacks a comprehensive understanding of how PDE4B's unique structural and functional characteristics could be leveraged for therapeutic intervention. Furthermore, while individual studies have examined specific aspects of PDE4B function, a systematic analysis of its potential as a drug target across different disease states is needed. This review aims to address these knowledge gaps through a detailed examination of three key aspects such as the structural and functional characteristics that distinguish PDE4B from other PDE isoforms, the mechanistic role of PDE4B in cAMP signaling regulation and its implications in various pathological conditions, and the current status and future prospects of PDE4B-targeted therapeutic development.

Search strategy and data sources

A systematic literature search was conducted from December 2023 to July 2024 to identify all published articles related to our manuscript from the years 1999 to 2024. The search was performed by systematically searching the search term "Phosphodiesterase 4B inhibitors in therapeutics" using three databases i.e. Google Scholar, and PubMed. The keywords used to search for articles related to our study were "Phosphodiesterase inhibitors", "hydrolysis of cAMP by PDE4 subtypes", "PDE4B structure", "PDE4B inhibitors clinical trials", "PDE4B influence on disease pathogenesis", "PDE4 inhibitors side effects", "PDE4B role cancer development", and " PDE4 subfamily selectivity". A total of 10,200 papers were initially found by systematic search, which subsequently underwent a screening process before they could be used. The basic criteria for selection are that the article must be written in English, must be an original article (i.e., not a conference proceeding or review), and must not contain any duplicates. The study includes both pre-clinical and clinical studies. 79 papers were selected after meeting the selection criteria and included in this study to discuss phosphodiesterase 4B functions, structure, disease association, and its therapeutic applications and potential.

Functions of PDE4B

PDE4B in Inflammation

A complicated biological process known as inflammation is triggered by trauma, infection, or other types of tissue damage. This response triggers the activation of multiple cellular and molecular mechanisms, notably the release of chemical mediators such as chemokines and cytokines[9]. These mediators are crucial in attracting immune cells, including neutrophils and macrophages, to the inflammation site, where they work to eliminate the inciting factors and facilitate tissue repair. The generation of ROS is also a result of these immune cells becoming activated. Figure 1 showcases PDE4B in lung cells, emphasizing its function in the cAMP signaling pathway. Upon activation by G -protein-coupled receptor (GPCR), the alpha units leave to bind to adenyl cyclase, which converts ATP to cAMP. PDE4B then hydrolyses cAMP to 5'-AMP, thus regulating its intracellular levels. This regulation affects various downstream pathways, like Protein Kinase A (PKA) and Exchange Protein directly Activated by cAMP (EPAC). PKA, as well as ERK 1/2, lead to the activation of CREB, which promotes anti-inflammatory cytokine synthesis, whereas RAP is included in the inhibition of pro-inflammatory cytokine synthesis[10] PDE4B is an essential regulator of immune cell production of pro-inflammatory cytokines. Recent research has demonstrated that lipopolysaccharide (LPS)-induced activation of nuclear factor kappa-B (NF-B), a significant transcription factor in the response to inflammation, can be effectively inhibited by PDE4B knockdown5. This inhibition results in a marked reduction of subsequent inflammatory responses across various cell types. Furthermore, deleting PDE4B impairs LPS-induced ROS generation, highlighting its vital role in the inflammatory pathway[11]. The regulatory capacity of PDE4B in these processes highlights its possibility as a therapeutic target for managing inflammatory illnesses. Research has indicated that targeting PDE4B can modulate inflammation effectively, providing a promising avenue for developing anti-inflammatory therapies[12, 10].

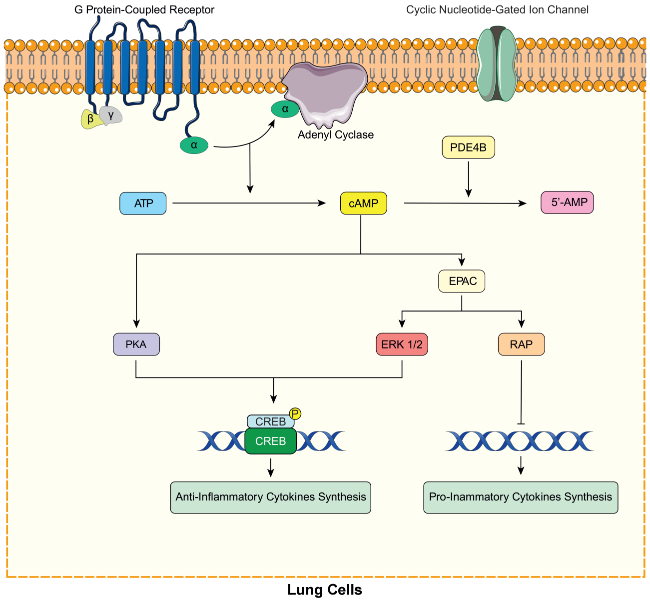

Fig. 1 Representation of PDE 4B in Inflammation in Lung Cells

Structural and Functional Overview

General Structure of Phosphodiesterase

The PDE superfamily comprises eleven gene families, each playing a crucial role in intracellular signaling[13, 14]. Due to their involvement in these signaling pathways, PDEs are promising pharmacological targets with the potential for precise therapeutic targets. The structure of phosphodiesterase families exhibits a high degree of conservation. This structure has a catalytic domain consisting of approximately 300-350 amino acid residues in the carboxy-terminal half of the protein[13, 14]. This domain includes 14-16 α-helices and a short β-hairpin, forming a highly conserved region shared among isoforms within the same gene family.

A distinctive feature within this conserved region is a binuclear metal center essential for catalytic activity[15]. This center is encircled by helices H6 and H13 and the loop connecting helices H7 and H8, creating a highly conserved pocket.

PDE4 Family

The phosphodiesterase four enzyme family includes subtypes A, B, C, and D[17]. This family only modulates intracellular cyclic adenosine monophosphate (cAMP) levels. These enzymes are broadly expressed in the brain, keratinocytes, cardiovascular tissue, and smooth muscle.

The localization of PDE4 isoforms in various human tissues and cells, as depicted in Figure 2, highlights their crucial role

Table 1: Overview of various phosphodiesterase (PDE) families, localization in different tissues, the number of associated genes, substrate specificity (cAMP, cGMP), primary functions, and known inhibitors.

Type	Localization	Genes	Substrate Specificity	Primary Function	Inhibitors	References
PDE1	Brain, smooth muscle, heart, lung	3	cAMP / cGMP	Vascular smooth muscle contraction, dopaminergic signaling, sperm function, immune cell activation	Vinoceptine, nicardipine, nimodipine	16, 17
PDE2	Adrenal gland, lung, heart, platelets, brain, liver, corpus cavernosum	1	cAMP/ cGMP	Regulation of aldosterone secretion, calcium channel phosphorylation in the heart, neuronal cGMP regulation, endothelial cell function during inflammation	ENHA	18, 19, 20
PDE3	Heart, liver, lung, platelets, vascular smooth muscle, corpus cavernosum	2	cAMP/ cGMP	Cardiac contraction, platelet aggregation, smooth muscle contraction in the vascular system, maturation of oocytes, release of renin, insulin signaling, and cell cycle/proliferation	Cilostamide, cilostazol, milrinone	20
PDE4	Lung, mast cells, liver, kidney, brain	4	cAMP	Brain activity, vascular smooth muscle proliferation, neutrophil infiltration, activation of monocytes and macrophages, vasodilation, and cardiac contractility	Roflumilast, Crisaborole, Apremilast	20
PDE5	Corpus cavernosum, lungs, vascular smooth muscle, platelets, brain, esophagus	3	cGMP	Brain cGMP signaling, platelet aggregation, and vascular smooth muscle contraction	Sildenafil, tadalafil, vardenafil, dipyridamole, zaprinast	20, 21
PDE6	Retina	1	cAMP	Phototransduction	Dipyridamole	20
PDE7	Skeletal muscle, T-cells, heart, kidney, brain, pancreas	2	cAMP	Immune cell activation, memory	Dipyridamole	20
PDE8	Testes, thyroid, eye, liver, kidney, heart, skeletal muscle, pancreas, T-cells	3	cAMP	T-cell activation, sperm or Leydig cell function, T4 and T3 production	Zaprinast	20, 22
PDE9	Brain, kidney, liver, lung	3	cGMP	cGMP signaling in the brain	Dipyridamole, papaverine	20
PDE10	Brain, testes	1	cAMP/ cGMP	Learning and memory	Tadalafil, zaprinast	18
PDE11	Prostate, skeletal muscle, kidney, liver, testes, pituitary, salivary glands	1	cAMP/ cGMP	Sperm development and function	Dipyridamole	23

Table 2: Overview of PDE4 Family, detailing their No. Of Variants, Length, Location.

PDE 4 Subtype	No of Variants	Length	Location	References
PDE 4A	1 – 11	Long and short isoforms	Mainly in the brain, heart, testes, and fat tissue.	17, 24
PDE 4B	1 – 5	Long and super-short isoforms	high levels in the heart, skeletal muscle, immunological cells, brain, and lung.	17, 25
PDE 4C	1 – 5	Long isoforms	Mainly in the testes, seldom in the lungs, and nonexistent in the immune system and blood.	25, 26
PDE 4D	1 – 9	Long and super-short isoforms	Mostly in immune cells, skeletal muscle, and the brain.	27

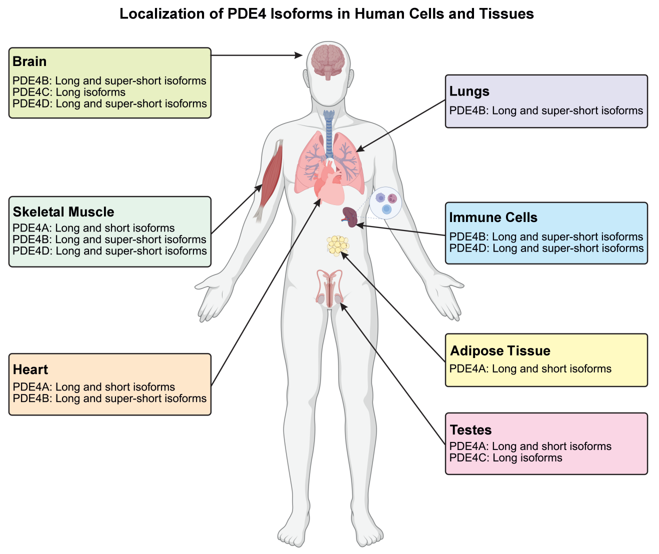

Fig. 2 Representation of PDE 4 isoforms in Human Cells and Tissues

in modulating cellular functions across different systems. This distribution allows for regulating cAMP levels in specific tissues, like the brain, lung, and immune cells, making PDE4 isoforms significant targets for therapeutic interventions. The presence of PDE4B in high concentrations within these tissues enables targeted treatments for neurological disorders, inflammatory diseases, and pulmonary conditions. The ability to selectively inhibit or modulate specific PDE4 isoforms in their localized environments offers a promising opportunity for developing precise and effective treatments for a wide range of diseases.

General PDE4B Structure

The structure of PDE4B has been studied through X-ray crystallography and molecular modeling. The catalytic domain of PDE4B is highly conserved among the PDE4 subfamilies, with a high degree of amino acid conservation[28]. The overall folding and secondary structures of PDE4B are like those of other PDE4 subfamilies. The active site of PDE4B usually has a metal ion (usually zinc or magnesium) and a hydrophobic pocket[29]. The active site is where the enzyme binds to its substrate cyclic adenosine monophosphate (cAMP) and hydrolyses it to AMP. PDE4B has a unique feature known as Control Region 3 (CR3), a C-terminal α-helix that can turn into multiple orientations. Small molecule ligands stabilize this region and are essential for the inhibitors' specific binding.

The sequence differences outside the active site contributing to PDE4B selectivity are primarily located in the Control Region 3 (CR3) and involve a single amino acid difference. Specifically, Leucine (Leu) is present at position 674 in PDE4B, whereas PDE4D has a Glutamine (Gln) at this position. These structural features, particularly the CR3 region and the H- and M-loops, are essential for understanding the selective binding of inhibitors to PDE4B and for designing selective inhibitors that can modulate its activity[30].

Structural features influencing inhibitor selectivity:

The PDE4 inhibitor design and development started in the 1980s. To successfully interact with a specific active site of PDE4, an agent must interact with an M pocket, two Q pockets, and an S pocket. M pocket is characterized by conserved hydrophobic and polar residues for divalent Zn2+ and Mg2+, critical for cAMP hydrolysis. Q pockets (inhibitor) are divided into hydrophobic P-clamp and conserved purineselective glutamine. Q pocket has two further pockets; Q1 is more petite, deeper, and contains hydrophobic residues, whereas Q2 is more prominent, protruding but hydrophobic. Most of the S pocket comprises hydrophilic residues and remains filled with a solvent, which helps form enzyme-inhibitor complexes. Different interactions like hydrophobic, coordination bonds with metal ions, and hydrogen bonding take place to occupy the specific active sites by inhibitors depending upon the nature of pockets of the PDE4[27,31]. According to several studies, PDE4B has two characteristics in common; one is a planar ring contained in the P-clamp hydrophobic residues (PHE446 on the roof, ILE410 and PHE414 on the floor) and H-bonding with invariant glutamine residue (GLN443). Usually, the Q pocket recognizes the cAMP. It forms a hydrogen bond, followed by forming a complex with metal in the M pocket by phosphate moiety, which induces hydrolysis of cAMP. Hence, the PDE4 inhibitors must occupy M and Q pockets to prevent cAMP hydrolysis[31]. Further, computational studies identified critical residues (lEU502 in PDE4B, GLU502 in PDE4D and PHE505, and PHE506 in both) for selectivity of PDE4B/PDE4D located in the CR3 region present outside the catalytic pocket, which has potential in designing selective inhibitors. This suggests exploring areas outside the catalytic domain, which is not conserved, like CR3, to design selective inhibitors[31]. Wang et al. 2007, observed that a key structural feature is a conserved residue of phenylalanine (Phe372) in the active site of PDE4 subfamilies which plays an essential role in the binding of an inhibitor. Inhibitors bind to this residue parallel or tilted, depending on their configurations. Also, PDE4B shows conformational flexibility at Met451, which might influence the inhibitor binding. The residues of PDE4B in active sites exhibit small positional shifts compared to other subfamilies. Comparatively, PDE4B and PDE4D have similar affinities for inhibitors making it more challenging to develop selective inhibitors for PDE4B over PDE4D[32]. A computational study using 3D-QSAR revealed that a more potent PDE4B inhibitor can be created using a heteroaromatic core having a sulphonyl group (with one H-bond acceptor), an aromatic ring, and benzoic acid moiety and suggested that could streamline the selective inhibitor designing[33]. The PDE4 inhibitors faced challenges due to side effects like nausea and vomiting. One possible explanation for this outcome is non-selective inhibitory effects on PDE4 subfamilies. Several studies on targeted knockouts, siRNA-mediated knockdowns, and dominant-negative strategies supported this theory. Such studies revealed that each PDE4 subfamilies and isoforms have different and specific functions. Hence the designing subfamily or isoform-specific inhibitors could be more promising for effective treatment without side effects[32].

Therapeutic Potential and Drug Development

Disease Associations

Pulmonary Fibrosis

PDE4B is involved in the progression of pulmonary fibrosis, specifically idiopathic pulmonary fibrosis (IPF). While specific genetic mutations of PDE4B in pulmonary fibrosis are not well-documented, their role in regulating inflammation is critical. PDE4B modulates cytokine production and myofibroblast conversion, key factors in lung fibrosis development. Several in vivo PDE4B inhibition studies have provided evidence for PDE4 regulation in pro-inflammatory and anti-inflammatory (anti-fibrotic) processes. It regulates by degrading cAMP and interacting with PKA and exchange factors directly activated by cAMP (EPAC1/2), which forms cAMP signalosomes for conducting various immune responses and pro-inflammatory cytokines. However, the mechanism underlying the anti-fibrotic effect of PDE4 inhibition is still not precise[17,34]. PDE4 inhibition studies highlighted the reduction of chemokines which recruit immune cells to the site of inflammation and exacerbate fibrosis, the reduction in lung injury maker (surfactant protein D), and the suppression of profibrotic gene expression in fibroblast cells that play a role in fibrosis. Further, PDE4B knockout mice failed to develop airway inflammations, reduction in T-helper 2 (Th2) cells, eosinophil infiltration, and pro-inflammatory TNF-α indication of its role in anti-inflammatory responses to allergies. Also, in the absence of PDE4B, fibroblast cells don't convert into myofibroblasts, contributing to extracellular matrix proteins in fibrosis[17]. Inhibiting PDE4B may serve as a therapeutic target by increasing cAMP levels, suppressing cytokine production, and preventing myofibroblast conversion, thus reducing inflammation and fibrosis[17,35] . Selectively targeting PDE4B offers a promising therapeutic strategy for pulmonary fibrosis, providing anti-inflammatory and antifibrotic effects with minimal systemic side effects.

Atopic Dermatitis

PDE4B has a significant function in the atopic dermatitis' inflammatory mechanisms. Although genetic predispositions are not well-documented, elevated PDE4B activity is a marker of atopic dermatitis (AD), exacerbating inflammation and contributing to the disease's chronic nature[36,37]. AD is a skin inflammatory disease marked by severe itching and the development of both acute and chronic eczematous lesions. Since cAMP is known to regulate immune responses and inflammations, its elevation suppresses monocytes and T cells. The activity of cAMP-PDE4 (A, B, C, and D) increases in an AD patient's mononuclear lymphocytes (MNL) and dermal fibroblast. The level of cAMP catalysis adenylate cyclase gets upregulated in MNLs, leading to increased cAMP production and PDE activity to maintain homeostasis. The increased cAMP will suppress immune cell overactivation, and the increased PDE will prevent cAMP from reaching higher levels. Also, high PDE in monocytes increases the production of prostaglandin E2, IL-6, and IL-10, causing an imbalance in Th1/Th2 cells. The global cytokine suppressor IL-10 in AD monocytes will decrease IFN_{γ} by Th1, shifting the Th1/Th2 cell ratio balance to the Th2 response, leading to an unregulated immune response[38].

Topical PDE4 inhibitors, like crisaborole, have been created and approved for treating mild to moderate atopic dermatitis, effectively reducing inflammation and improving symptoms. These inhibitors reduce the production of inflammatory cytokines like IL-4 and IL-13 and activate immune cells such as basophils and Th2 cells[36],[39]. The development of PDE4 inhibitors shows promise for managing atopic dermatitis by reducing inflammation and alleviating symptoms, with ongoing research to optimize these treatments.

Alzheimer's Disease

The onset and progression of numerous cognitively linked illnesses, including Alzheimer's disease (AD), are significantly influenced by PDE4B. PDE4B's function in the disease has been highlighted by identifying the gene as a genetic risk factor by genome-wide association studies (GWAS)[40]. GWAS studies identified genetic changes in PDE4B (SNPs rs556755587 and rs11208742) located in the upstream region of the gene, causing cognitive conditions[41]. PDE4B is highly expressed in the hippocampus, emerging as a key regulator of cognitive function[42]. PDE4B contributes to AD development by regulating the cAMP/PKA/CREB signaling pathway, leading to the development of amyloid-beta plaques, tau hyperphosphorylation, and changes in neuronal structure[43]. Its influence is present in the PDE4-cAMP signaling cascade, ultimately affecting the phosphorylation of the cAMP response element-binding protein (CREB), essential for memory and learning[11]. Despite no reduction in amyloid plaque burden, reduced PDE4B activity has shown protective effects on spatial memory and brain glucose metabolism in mouse models[40]. Experimental models and preliminary trials indicate that inhibiting PDE4B can prevent spatial memory deficits and maintain normal brain glucose metabolism. This is achieved by increasing cAMP levels, enhancing brain glucose metabolism, and reducing inflammation[40,44]. Studies investigating the impact of PDE4B modulation on cognition have given promising results. For instance, Sceletium tortuosum (Zembrin), a proprietary extract with PDE4B inhibitory properties, significantly improved executives' executive function and cognitive set flexibility in a randomized, double-blind, placebo-controlled crossover trial[45,46,47]. These findings suggest that PDE4B inhibition could protect against cognitive impairment in Alzheimer's and other dementias, making it a promising therapeutic target. Nevertheless, further research is necessary to explore the effectiveness and safety of selective PDE4B inhibitors in patients with various cognitive impairments.

One of the main pathogenic characteristics of AD is neuroinflammation, which is linked to both cognitive impairment and the amount of amyloid plaque. Rolipram's suppression of PDE4B is linked to less inflammation in AD models. Monocytes, macrophages, and microglial cells exhibit increased PDE4B expression in response to inflammatory stimuli, such as amyloid-beta ($A\beta$) peptides. Tumor necrosis factor-alpha ($TNF-\alpha$) production is decreased in mice deficient in PDE4B when exposed to inflammatory stimuli[41].

Schizophrenia

PDE4B is implicated in the pathophysiology of schizophrenia through genetic and biochemical pathways. It plays a critical role in mood regulation; by breaking down cAMP, PDE4B indirectly modulates the activity of neurotransmitters critical for mood, such as dopamine, serotonin, and norepinephrine[48]. The prefrontal cortex's altered dopamine neurotransmission, particularly the hypofunction of dopamine D1 receptors, is related to the psychotic symptoms and cognitive impairments that are frequently associated with schizophrenia. Genetic studies have linked PDE4B to schizophrenia, identifying chromosomal translocations and SNPs associated with the disorder[49,50,51]. PDE4B interacts with the disrupted schizophrenia 1 (DISC1) gene, a known risk factor for schizophrenia[50,51,52]. DISC1 is disrupted by a specific chromosomal translocation t (1;11) (q42; q14), which is associated with psychiatric conditions like schizophrenia, bipolar affective disorder, and relative affective disorders. cAMP is a secondary messenger in memory, learning, and mood, whereas PDEs inactivate the cAMP. Further, DISC1 interacts with PDE2A's by binding to its UCR2 domain; however, in the presence of high intracellular levels of cAMP, The PKA activates the PDE4 isoforms and phosphorylates URC1, which induces changes in conformation and enzymatic activity between URC1 and URC2. The increased level of cAMP reduces the DISC1 and dissolves the interaction of PDE2B and DISC1; this leads to an increase in PDE2B activity. This indicates that the PDE4B-DISC1 interaction is dynamically regulated by cAMP level through PKA activity, and the PDE4B can also be considered a genetic susceptibility factor for schizophrenia.[52]. Post-mortem studies show decreased PDE4B expression in schizophrenia patients. Animal models support PDE4B's role in schizophrenia, with mice having a mutant PDE4B showing reduced anxiety, increased exploration, and cognitive enhancements. Animal models deficient in PDE4B exhibit heightened anxiety-like behaviors, demonstrating that adequate PDE4B activity is essential for emotional stability. PDE4B's involvement in neuroinflammation, a process implicated in the pathology of mood disorders, further reinforces its potential as a therapeutic target. Neuroinflammatory mechanisms can disrupt brain function and contribute to depression and anxiety[53]. Increased cAMP levels due to PDE4B dissociation from DISC1 affect synaptic plasticity and cognitive functions. These findings highlight PDE4B's significant role in schizophrenia, suggesting that it can be a potential for its inhibition to improve cognitive function and reduce symptoms.

Cancer Progression:

Out of all PDE subtypes, overexpression of PDE4B is highly known to be associated with hematological cancers like acute lymphoblastic leukemia, multiple myelomas, chronic lymphoblastic leukemias, and B-cell lymphoma. The normal mononuclear cells of peripheral blood upregulate the PDE4B expression when exposed to IL-2 and primary growth factors and promote CD4+ T-cell's cancerous cell proliferation and survival. The expression of PDE4B indicates its important role in cancer cell progression. The level of PDE4B also rises due to the negative feedback loop of elevated cAMP itself, for instance, in T-leukemic and B-lymphoblastoid cells on activating by cAMP analogs, 1-methyl-3-isobutylxanthine (IBMX), and dibutyl cAMP (dBcAMP). Similarly, when myeloma cells are treated with PDE4B inhibitors like rolipram, a significant rise of PDE4B can be observed due to abnormal accumulation of cAMP. The studies have found a link between PI3K/Akt Pathway inhibition and cAMP-mediated apoptosis. In colorectal cancer, PDE4B interacts with KRAS and promotes cell survival. However, PDE expression and activity are generally lower in neoplasia, but the overexpression of its subtype PDE4B indicates selective malfunctioning. It inhibits the Akt/mTOR pathway in colorectal cancers. Further, a few cases were reported with other types of cancer, viz. lung, liver, kidney, oral, skin, endometrium, and CNS. Unlike this, in the case of breast and castration-resistant prostate cancer, its expression was reportedly downregulated[54]. Overexpression of PDE4B causes immune cell infiltration to the tumor microenvironment and phosphorylates the PI3K/Akt pathway, leading to MYC hyperexpression and inducing the development of gastric cancer[6]. While PDE4B inhibition has proven therapeutic value in treating inflammatory diseases mentioned before, the potential implication of prolonged PDE4B downregulation in cancer development warrants consideration. For instance, particularly in the case of prostate cancer, decreased expression of PDE4B is observed in metastatic prostate cancer tissues, which causes the activation of the AR pathway, which is a hallmark of metastasis. Furthermore, studies performed to evaluate the effect of PDE4B in the LNCaP cell lines showed that downregulation/loss of PDE4B activated the PKA signaling pathway, leading to AR activation to promote cancer cell proliferation. This raises the need for careful evaluation of drugs, especially in populations at risk of cancers[55].

Current Inhibitors

Apremilast (CC-10004, Otezla)

PDE4B and other PDE4 isoforms are the oral PDE4 inhibitor apremilast targets. Apremilast inhibits these enzymes, raising intracellular cAMP levels that regulate the synthesis of inflammatory mediators, including IL-23 and tumor necrosis factor-alpha (TNF-α)[56,57]. This medication has been approved to treat psoriasis and psoriatic arthritis, showing promise in lessening the intensity and duration of these inflammatory diseases.

Crisaborole (AN2728, Eucrisa)

Crisaborole is a topical PDE4 inhibitor that features a unique boron configuration, which facilitates its effective penetration into the skin[58,59]. This drug specifically inhibits PDE4B, leading to a reduction in the inflammatory processes associated with atopic dermatitis. As a non-steroidal alternative for treating mild to severe atopic dermatitis, crisaborole relieves this persistent skin ailment.

Roflumilast (ARQ-151, Zoryve)

Roflumilast is recognized for its potency as a PDE4 inhibitor, being approximately 25-300 times more potent than Apremilast or Crisaborole, depending on the specific PDE4 isoform. Because it inhibits PDE4B and other PDE4 isoforms, intracellular cAMP levels rise, and various inflammatory mediators are modulated. Roflumilast is being studied for its possible application in treating psoriasis and atopic dermatitis. Chronic obstructive pulmonary disease (COPD) symptoms are already approved to be treated with it[60,61].

In Silico Studies

Utilizing innovative computational methods such as molecular dynamics (MD), molecular docking, simulations, and quantitative structure-activity relationship (QSAR) models, in silico studies of PDE4B inhibitors have been conducted. These methods are vital in the efficient discovery and optimization of PDE4B-specific inhibitors, paving the way for developing more effective treatments. Molecular docking aids in identifying potential inhibitors by predicting their binding affinity to the active site of PDE4B. Meanwhile, MD simulations assess the stability of these enzyme-inhibitor complexes under simulated physiological conditions. QSAR models play a crucial role in designing new inhibitors by analyzing the chemical structures of existing compounds and correlating these structures with their biological activity[69]. Several in silico studies have successfully identified novel molecules with promising potential as PDE4B inhibitors. These findings may result in the creation of more potent medicinal treatments for a number of illnesses, especially those that involve inflammation and neuroprotection

Identification of GSK256066

A notable investigation conducted by Woodrow et al. examined the synthesis of quinoline-3-carboxamides as effective and targeted inhibitors of PDE4B[70]. GSK256066, a potent molecule with a pIC50 of 11.1 and remarkable selectivity against other

Table 3: Overview of PDE4 current Inhibitors, detailing their Usage, Molecular Formula, logP, and Common Adverse Effects

Drug	Usage	Molecular Formula	logP	Common Adverse Effects	IC50 Value	References
Apremilast	Psoriatic Arthritis,	C22H24N2O7S	1.8	Nausea Diarrhea Vomiting Headache Abdominal Pain Depression Weight Loss NasopharyngitisURTI	No data available	[62], [63], [64]
Crisaborole	Atopic Dermatitis	C14H10BNO3	2.6	Mild application site reactions Nasopharyngitis Insomnia Upper respiratory tract infection Headache Muscle strain, Gastrointestinal symptoms Weight Loss	PDE4B1= 55, PDE4B2=61	[65], [66], [67]
Roflumilast	Chronic Obstructive Pulmonary Disease	C17H14Cl2F2N2O3	4.6	Diarrhea Headache Insomnia Nausea Application site pain URTI Urinary Tract Infection	No data available	[64], [68]

PDE isoforms, was discovered as a result of this research. GSK256066 was developed as an inhalable PDE4 inhibitor to mitigate systemic side effects, like emesis, frequently associated with oral PDE4 inhibitors. The compound showed promising results in biological assays, including inhibiting TNF-α production in human peripheral blood mononuclear cells (PBMCs), positioning it as a potential candidate for treating inflammatory diseases like asthma and COPD.

Neuroprotective PDE4 Inhibitors

Peng et al. further report on developing PDE4 inhibitors through in silico methodologies to enhance therapeutic efficacy while minimizing adverse effects like nausea and vomiting. Among their notable discoveries is the compound (S)-Zl-n-91, which exhibited potent neuroprotective activity with IC50 values of 12 nM for PDE4D and 20 nM for PDE4B. This compound demonstrated significant neuroprotection in in-vitro trials using ICR mice, indicating its potential for further exploration in neurological research. Chemical 14, a noteworthy chemical, has shown effectiveness in enhancing learning and memory by PDE4 inhibition and modulation of important cAMP-mediated signaling networks, including the EPAC/ERK and cAMP/PKA/CREB pathways[71]. Compound 14's involvement in improving cognitive function has been well-established in preclinical research despite the lack of definite IC50 values.

AstraZeneca's Optimization of Novel Inhaled PDE4 Inhibitors

A research team at AstraZeneca also made significant contributions by optimizing novel inhaled PDE4 inhibitors. Among their discoveries were compounds 12a and 12b, which demonstrated high potency, with human PDE4B enzyme pIC50 values of 10.6 and 10.7, respectively[72]. In preclinical animals, these drugs demonstrated significant suppression of pulmonary inflammation, with ED80 values of 0.02 and 0.06mg/mL nebulizer concentration, signifying 0.2 and 0.6μg/kg lung-deposited dosages, correspondingly. In silico studies are crucial for accelerating drug discovery, mainly targeting enzymes like PDE4B. These computational methods efficiently identify and optimize potential inhibitors, saving time and resources compared to traditional experimental approaches. By predicting molecular interactions and stability, in silico techniques streamline the formation of more potent and selective PDE4B inhibitors, leading to safer and more effective treatments.

Long-term systemic effects of PDE4B inhibition:

cAMP has a pleiotropic effect and causes several inflammatory and cognitive diseases; this has led to the development of PDE inhibitors to reduce the degradation of cAMP. Out of all isotypes, PDE4 plays a more fundamental role in regulating endothelial and epithelial barrier stability, hence making its

Table 4: Overview of Novel Molecules reported from In-Silico Studies, ChEMBL ID, SMILES, and IC-50.

No	ChEMBL	SMILES	IC-50/nM	Reference
1	CHEMBL570015	COc1cccc(Nc2c(cnc3c(C)cc(cc23)S(=O)(=O)c2cccc(c2)C(=O)N(C)C)C(N)=O)c1	0.00794	[70]
2	CHEMBL4744560	COc1ccc(-c2nc(C(=O)NCc3coc4ccccc34)c(o2)[C@@H](C)N)c2ccc(nc12)C(F)(F)F	0.01	[71]
3	CHEMBL4794267	Cn1nc(cc1C(F)(F)F)C(=O)NC1CCC(CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(CCCN2CCNCC2)cc1	0.01	[71]
4	CHEMBL570015	COc1cccc(Nc2c(cnc3c(C)cc(cc23)S(=O)(=O)c2cccc(c2)C(=O)N(C)C)C(N)=O)c1	>0.0100	[72]
5	CHEMBL3287987	Cc1cc(nn1C)C(=O)N[C@H]1CC[C@H](CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(O)cc1CN1CCCOCC1	0.01	[72]
6	CHEMBL569791	COc1cccc(Nc2c(cnc3ccc(cc23)S(=O)(=O)c2cccc(c2)C(=O)N(C)C)C(N)=O)c1	0.01	[70]
7	CHEMBL3986586	CCn1nc(cc(NC(=O)Nc2c(Cl)cncc2Cl)c1=O)-c1cccc(c1)-c1cccc(c1)C(=O)NCCN1CCOCC1	0.014	[73]
8	CHEMBL3287739	Cc1cc(nn1C)C(=O)N[C@H]1CC[C@H](CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(O)cc1CN1CCOCC1	0.0158	[72]
9	CHEMBL3287995	Cc1cccc2nc(cn12)C(=O)N[C@H]1CC[C@H](CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(O)cc1CN1CCOCC1	0.0158	[72]
10	CHEMBL3287991	Cc1csc(n1)C(=O)N[C@H]1CC[C@H](CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(O)cc1CN1CCOCC1	0.0158	[72]
11	CHEMBL3288029	C[C@H]1CN(Cc2ccc(c(CN3CCOCC3)c2)-c2cccc(Oc3ncc(F)cc3C(=O)N[C@@H]3CC[C@@H](CC3)NC(=O)c3nc(C)cs3)c2)C[C@@H](C)N1	0.02	[72]
12	CHEMBL3288027	C[C@H]1CN(CCCc2ccc(cc2)-c2cccc(Oc3ncc(F)cc3C(=O)N[C@@H]3CC[C@@H](CC3)NC(=O)c3cc(C)n(C)n3)c2)C[C@@H](C)N1	0.02	[72]
13	CHEMBL3288024	C[C@H]1CN(Cc2cc(ccc2O)-c2cccc(Oc3ncc(F)cc3C(=O)N[C@@H]3CC[C@@H](CC3)NC(=O)c3cc(C)n(C)n3)c2)C[C@@H](C)N1	0.02	[72]
14	CHEMBL3287994	Cc1cccc(n1)C(=O)N[C@H]1CC[C@H](CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(O)cc1CN1CCCOCC1	0.02	[72]
15	CHEMBL3287990	Cc1nc(cs1)C(=O)N[C@H]1CC[C@H](CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(O)cc1CN1CCCOCC1	0.02	[72]
16	CHEMBL3288030	C[C@H]1CN(Cc2ccc(c(CN3CCOCC3)c2)-c2cccc(Oc3ncc(F)cc3C(=O)N[C@@H]3CC[C@@H](CC3)NC(=O)c3cc(C)ccc3O)c2)C[C@@H](C)N1	0.02	[72]
17	CHEMBL3287999	Oc1ccc(c(CN2CCCOCC2)c1)-c1cccc(Oc2ncc(F)cc2C(=O)N[C@@H]2CC[C@@H](CC2)NC(=O)c2cn3cc(F)ccc3n2)c1	0.02	[72]
18	CHEMBL1830791	CC1(C)CCc2c(Nc3c(Cl)cncc3Cl)nc3oc4c(NCc5cccnc5)ncnc4c3c2C1	0.02	[74]
19	CHEMBL571381	COc1ccc(cc1)S(=O)(=O)c1cc(C)c2ncc(C(N)=O)c(Nc3cccc(OC)c3)c2c1	0.02	[70]
20	CHEMBL3287988	Cc1nc(cs1)C(=O)N[C@H]1CC[C@H](CC1)NC(=O)c1cc(F)cnc1Oc1cccc(c1)-c1ccc(O)cc1CN1CCOCC1	0.02	[72]

inhibition a more promising therapy. However, the risk of severe side effects is high because PDE4 is present in numerous tissues[75]. Over 300 million people worldwide have asthma and chronic pulmonary disease (COPD), leading to 461,00 yearly fatalities and significant financial burden, emphasizing the need for innovative, efficient treatments. PDE inhibitors, like theophylline, continue to be in use. However, it is not advised for all patients because of its limited tolerance margin and serious adverse effects, including a strong pharmacological CYP1A2 enzyme interaction. Since 2011, another inhibitor drug called roflumilast has been used as an add-on treatment for COPD patients with frequent worsening symptoms[75]. Roflumilast, like selective inhibitors, could be used for asthma, but it is still not recommended due to conflicting trials and lack of data. In the case of skin inflammation, treatment is generally restricted to generic immunosuppressants and topical therapy despite its association with side effects and poor effectiveness[75]. Rolipram causes side effects related to CNS and gastrointestine[27]. Initially, PDE4 inhibitory drugs failed in clinical trials because of nausea and emesis, and others include fatigue, dyspepsia, headache, nasopharyngitis, and gastroenteritis. Studies done using rodents showed necrosis in mesenteric arteries (Mesenteric vasculitis) when using a second-generation inhibitor, cilomilast, and the drug is in phase III trial. Apremilast showed headache, nausea, and pharyngitis. The first and only drug approved by FDS is Roflumilast to treat COPD, but it has a higher chance of causing back pain, headache, weight loss, diarrhea, and decreased appetite. Several flavonoids like Diocletian were also seen inhibiting the PDE4 and anti-inflammatory by interacting with multiple pathways. However, they were causing side effects like vomiting, nausea, and dizziness[69].

Limitations and challenges faced in developing PDE4B-specific inhibitors:

Several attempts were made in past to create PDE4 inhibitors which can differentiate between subfamilies of PDE4 to minimize the side effects, however on few were approved due to lack of structural information of all subfamily's active sites[32]. Due to similarity in structures, there suggested a similar binding energy and the structural pockets where inhibitors binding sites are deep seated making itself selectivity determinant[32]. Over the decade, PDE4 inhibitors have been extensively studied for treating human diseases, but many have been terminated due to emesis side effects because of poor PDE4 subfamilies' selectivity, making it desirable to design novel isotype-selective PDE4 inhibitors[5]. Since PDE4 isoforms are so similar, there aren't many isoform-selective inhibitors, which means that new PDE4 isoform-selective inhibitors will need to be developed[5]. Till date only four PDE4 inhibitors are approved viz. roflumilast (COPD), apremilast (arthritis), crisaborole (atopic dermatitis) and ibudilast (krabbe and bronchial asthma). Several others are discovered and under trials like rolipram (multiple sclerosis and depression), orismilast (psoriasis and atopic dermatitis), ensifentrine a dual-selective inhibitor (COPD), zatomilast (Alzheimer and Fragile X syndrome), cilomilast for GSK256066 (COPD, rhinitis and asthma), tanimmilast (COPD), tetomilast (Crohn's disease and ulcerative colitis), and revmilast (rheumatoid arthritis) and mufemilast (psoriasis and ulcerative colitis)[5].

Since the 1980s, the development of new PDE4 inhibitors has been rapid, with milestone discoveries like theophylline, rolipram 1, roflumilast 2, and apremilast. Theophylline is one of the earliest discovered for asthma and COPD, due to its poor activity and no selectivity for distinct PDE subfamilies, it is not employed as a primary agent except for situations in which other conventional bronchodilator medications are ineffective. Rolipram was used as an anti-inflammatory action however, its usage was stopped due to severe adverse effects on the central nervous system and gastro intestine. Lately, it has been employed in prototype compounds to assess the efficacy of novel PDE4 inhibitors[27]. Later, roflumilast 2 showed high inhibition and good selectivity without any side effects and was clinically approved. These agents have shown weak activity and no selectivity towards different PDE subfamilies, making them less effective in managing asthma and COPD. However, their clinical use has been hampered by severe side effects. After this apremilast (psoriatic arthritis, crisaborole (atopic dermatitis and ibudilast (Krabbe disease) also got approved[27].

Potential of combining PDE4B inhibitors with therapeutic agents:

An approved inhibitor oral drug ampremilast was used for treating psoriasis, although it shows sufficient results but it usually causes side effects like diarrhea, nausea, headache and its extended might cause depression. To mitigate this roflumilast was given in trials, given positive results by lowering the side effects, but an unexpected outcome of this combination appeared, increasing risk of respiratory infections. The link between PDE4 dependent pathway and alterations is still not clear as the inflammatory response in these conditions might be linked to PDE4 or its isotype signaling. Hence, more comprehensive study is required to improve patient's quality of life[75]. Because PDE4 expresses in many tissues and increases the chances of more side effects hence a key challenge is finding ways to target treatment tissue and cell specific, so they only affect the areas that need treatment. This will help making therapies more effective and reduce side effects[75]. Further, inhibitors of dual PDE4, such as PDE3/PDE4 and PDE4/PDE7, exhibit synergistic actions, raising cAMP and cGMP levels and enhancing physiological functions. Therefore, new PDE4 inhibitors may result from the simultaneous inhibition of several subfamilies. Also, it may be possible to lower dosage and minimize side effects by combining PDE4 inhibitors with other anti-inflammatory medications. The recent advancements in computer-aided drug designing with molecular docking studies and crystal structures offered useful information for such creating novel PDE4 inhibitors[76]. The combination therapy of roflumilast and inhaled corticosteroid/LABA fixed-dose combination (FDC) has shown significant improvement in COPD treatment. In a clinical trial of phase IV, 1:1 randomized patient was given roflumilast or placebo, plus corticosteroid, roflumilast reduced the rate of COPD acute exacerbations by 18% compared to placebo. This therapy also improved lung function and health status in COPD patients. Therefore, combining PDE4 inhibitors with inflammatory airway diseases proved effective, showing comparable efficacy to LABA and LAMA combination therapy[77].

Preclinical and clinical advances in PDE4 Inhibitors

Research has demonstrated that the PDE4 inhibition efficiently reduces a wide range of inflammatory reactions both in vivo and in vitro. Moreover, a large number of PDE4 inhibitors in development work well in animal models of inflammatory conditions like asthma, IBD, psoriasis, rheumatoid arthritis and COPD. Rolipram medication is known to reduce proinflammatory cytokines (TNF-α) and interleukin (IL-6), suppresses inflammation, sepsis and increases anti-inflammatory factor (IL-10) production. It also improves endotoxin-induced cardiac dysfunction. Rolipram and apremilast also decreases M2 macrophage differentiation and reduce skin fibrosis by interfering with IL-6 release from macrophages. Roflumilast is and effective anti-inflammatory drug for regulating airway inflammation by inhibiting NF-κB, p38 mitogen-activated protein kinase and JNK activation. In animal model study, it reduced resistance in guinea pigs by lowering the circulating leukocytes, eosinophils, and pro-inflammatory cytokines (IL-4, IL-5, and TNF-α). Also, in asthmatic mice models it inhibited airway inflammation, remodeling and airway hyperreactivity. Further, in diabetic rats, it improved bladder dysfunction and lowered inflammations. During the preclinical studies on psoriatic and arthritis mice models, apremilast has shown reduced the epidermal thickness and suppressed abnormal proliferation by reducing TNF-α, IL-2, IL-23 and ICAM1. It also alleviates murine ulcerative colitis by modulating mucosal immunity and suppressing pulmonary inflammation. Ibudilast is an oral PDE4 inhibitor for stroke and asthma and rheumatoid arthritis. It is also seen to reduce acute respiratory distress syndrome in mice and mitigates Alzheimer's disease by targeting inflammation and ubiquitin/protease pathways.[77]. An oral PDE4B inhibitor, BI 1015550, was investigated in a second-phase, placebo-control trial on 147 idiopathic pulmonary fibrosis (IPF) patients at a dosage of 18mg for 12 weeks. This study was successful since BI1015550 stabilized lung function by preventing reduction in forced vital capacity (FVC), making it more reliable for future validation in phase 3. BI 1015550 has shown its anti-inflammatory activity in animal models inhibiting TNF-α and IL-2[17]. Recently, a polymethoxyflavone, Nobiletin (5,6,7,8,3',4'-hexamethyl flavonoid) has been isolated from Citri Reticulatae Pericarpium in China and discovered that it targets PDE4B during animal model studies and cause its inhibition. Nobiletin is frequently used for chronic inflammations, cancer and allergic conditions. It can reduce the hyperresponsiveness of airways in asthma by suppressing TGB-β1 activated cell proliferation and activates the cAMP-PKA-CREB pathway[78]. Hence, these PDE4 inhibitors are showing success in preclinical animal model giving a suggesting their potential in treatment of inflammatory conditions. Even after the effective response in reducing inflammations by Rolipram, it causes side effects related to CNS and gastro intestine[27]. Similarly, Cilomilast a second-generation inhibitor showed promise in initial clinical trials by improving renal dysfunction in cisplatin-induced acute kidney injury however it caused severe gastrointestinal side effects and caused it termination. Another PDE4 inhibitor called tofimilast has been evaluated for asthma treatment but failed to show sufficient efficacy in the clinical trials and its development was then terminated[27].

Conclusion

Phosphodiesterase 4B (PDE4B) has emerged as a critical enzyme with significant implications across various physiological and pathological processes. Its regulatory role in inflammation, cognition, and mood showcases its therapeutic potential in addressing conditions like pulmonary fibrosis, atopic dermatitis, Alzheimer's disease, and schizophrenia. The detailed structural understanding of PDE4B has facilitated the development of selective inhibitors, like Apremilast, Crisaborole, and Roflumilast, which have shown promising results in clinical settings. Furthermore, new PDE4B inhibitors have been found through in silico research, opening the door to more precise and successful therapeutic approaches. Further investigation into the mechanisms underlying PDE4B and its inhibitors could improve our capacity to diagnose, treat, and manage a broad range of illnesses, ultimately leading to better patient outcomes and quality of life.

Acknowledgements

This article was independently authored, without financial support, funding, or external sponsorship involved. There were

no costs incurred in the preparation of this manuscript, and I declare that there are no conflicts of interest related to its content or publication. My sole aim is to contribute to the advancement of knowledge in this field.

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