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Beyond the heart - Exploring the therapeutic potential of PDE3 inhibitors

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ABSTRACT: Phosphodiesterases (PDEs) consist of an enzyme family of eleven groups responsible for the hydrolytic breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). cAMP and cGMP are important secondary messengers that regulate physiological functions. The widespread expression of PDE3 in tissues and organs makes it an attractive therapeutic target. For decades, PDE3 inhibitors have been acknowledged as significant pharmaceutical agents in the treatment of cardiovascular disorders due to their inotropic and vasodilatory actions. Emerging data, however, suggests that the potential therapeutic application of PDE3 inhibitors has gone beyond their traditional cardiovascular applications. This comprehensive review aims to explore the non-cardiovascular developments related to PDE3 inhibitors, exploring their mechanism of action, and clinical trials.

KEYWORDS: phosphodiesterase; PDE3 inhibitors; drug repositioning; respiratory disease; anti-inflammatory disease; anticancer; COVID-19.

1. INTRODUCTION

The history of PDE inhibitors begins with caffeine, followed by the discovery of theophylline, a caffeine analog. Theophylline was used for therapeutic purposes long before Sutherland and Rall's elucidation of their mechanisms of action in 1958 when they described the complex processes of cAMP signaling. Interestingly, it wasn't until nearly two decades later researchers realized the potential of new PDE inhibitors for clinical applications when the traditional drug discovery process was revolutionized through the employment of isolation and purification of biological targets [1,2].

Owing to their names, PDEs catalyze the hydrolysis of cAMP and cGMP, resulting in the production of AMP and GMP, respectively (Figure 1). cAMP and cGMP are secondary messengers within cellular signaling pathways [3,4]. These molecules are synthesized from ATP and GTP by adenylyl cyclase and guanylyl cyclase enzymes, respectively, following their activation by G-protein-coupled receptors and substances, such as natriuretic peptide and NO. Following their synthesis, cAMP and cGMP induce the activation of protein kinases, A (PKA) and G (PKG), respectively. This activation subsequently initiates a cascade of signaling events through protein phosphorylation and other pathways [5–7]. Furthermore, it is worth noting that cyclic nucleotide-binding proteins, such as EPACs (cAMP-activated guanine nucleotide exchange proteins), CNGCs (cAMP- and cGMP-gated ion channels), and PDEs like PDE-2, -5, and -6, are significantly involved in the transmission of signals (Figure 2) [6,8,9].

The cAMP and cGMP signaling pathways are essential for regulating various physiological processes, such as cardiovascular function, smooth muscle relaxation, immune response, reproduction, central nervous system activity, vision, platelet aggregation, cell growth and apoptosis; and as well as for the development of inflammatory diseases, erectile dysfunction, chronic obstructive pulmonary disease (COPD), hereditary retinal degeneration, diabetes, and tumor. In intracellular homeostasis, the concentrations of cAMP and cGMP are regulated by the relative rates of their synthesis and degradation. This process ensures a dynamic equilibrium is maintained, whereby the synthesis and hydrolysis of these molecules are balanced [3,10].

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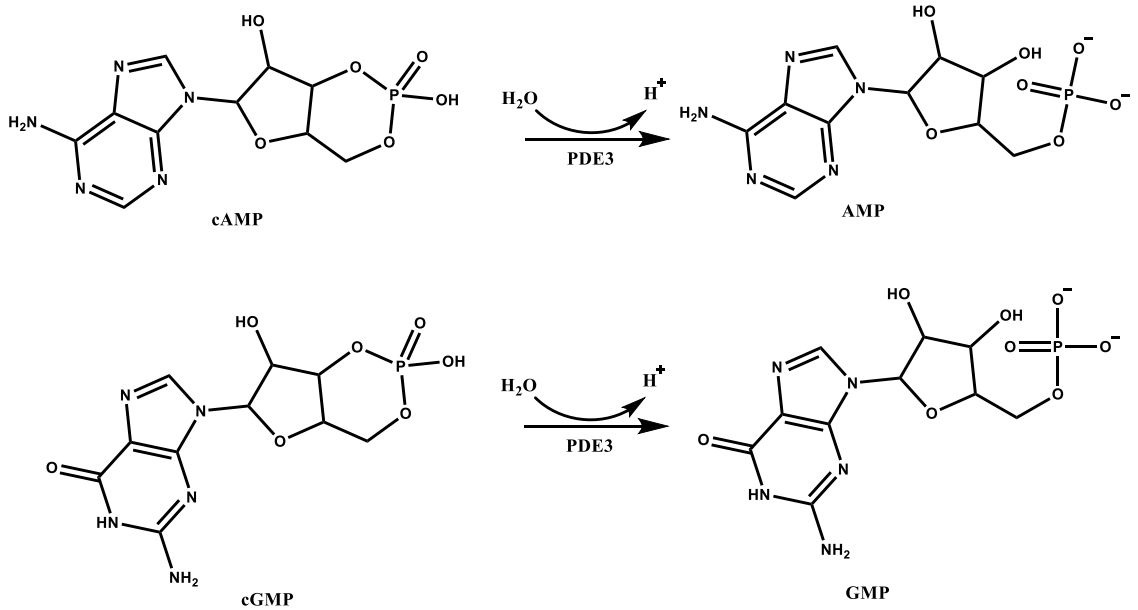

Figure 1: Hydrolysis of cAMP and cGMP to AMP and GMP by PDE3

PDEs are comprised of a total of 21 genes and exhibit functional differentiation into 11 distinct families. Each of these families exhibits diverse expression patterns across various tissues within the human body and can be categorized into three distinct classes according to their substrate preferences. PDE4, 7, and 8 predominantly degrade cAMP; whereas PDE5, 6, and 9 are specialized in the hydrolysis of cGMP. On the other hand, PDE1 – 3, 10, and 11 are considered versatile enzymes capable of hydrolyzing both cAMP and cGMP (Figure 2) [11–13]. Multiple studies revealed that over 100 unique protein products are transcribed from PDE genes because of the presence of alternative transcriptional start sites and splicing of gene products. This complexity consequently instigated investigations into the physiopathological importance of PDEs [3,8,11,13].

PDE3 is notable for its clinical significance in regulating cardiac and vascular smooth muscles, and platelet aggregation due to its strong affinity towards both cAMP and cGMP. For decades, it has been widely exploited as a pharmacological target in the management of cardiovascular disorders. However, due to its ubiquitous nature and critical roles in intracellular signaling, it is considered an attractive target in various diseases or disorders beyond cardiovascular-related diseases as recent studies prompt us to explore more domains by developing new PDE3 inhibitors for non-cardiovascular diseases and repositioning the present ones. The table below presents a comprehensive summary of the implication of PDE3 in non-cardiovascular diseases, corresponding known inhibitors, their respective modes of action, and any clinical trials conducted.

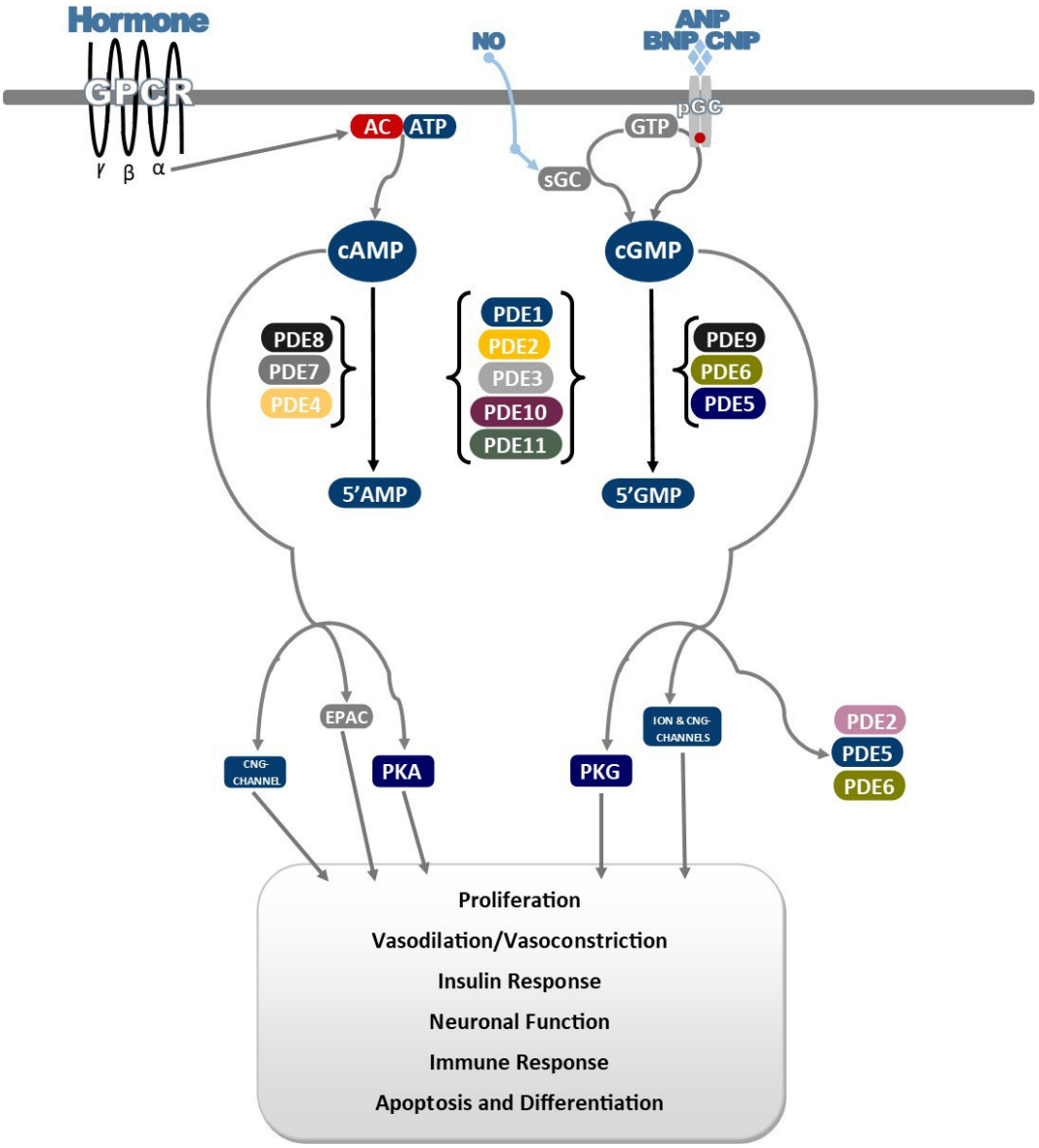

Figure 2: Cyclic nucleotide signaling and regulation [8]

Table. Implications of PDE3 in non-cardiovascular diseases and potential known inhibitors

Disease	Inhibitors	Mechanism of Action	Clinical Trials
Asthma	Enoximone	IL-8 and TNF-α inhibition [14]	-
COPD	Ensifentrine Motapizone	IL-8 and TNF-α inhibition [15]	Ensifentrine (NCT03443414) [16,17]
Colitis and Chron's Disease	Pumafentrine	TNF-α inhibiton[18]	-
Osteoarthritis	Pumafentrine Cilostazol	Reduction of chondrocyte IL-1β-induced nitrite accumulation [19]	Cilostazol (NCT04789837) [20]
Acute respiratory distress syndrome	Olprinone	Inhibition of IL-6 and IL-1β [21]	-
Diabetes	Milrinone Org 9935 SK&F 94120 ICI-118233 Siguazodan Pentoxifylline	Elevation of Ca^{2+} to enhance insulin secretion, inhibition of IL-1, IL-6, and TNF-α [22,23]	-
Hyperlipidemia	Cilostamide K-134	Activation of hormone-sensitive lipase [24,25]	-
Alzheimer's disease	Cilostazol	Activation of the proteolytic enzyme neprilysin[26], prevention of the accumulation of Aβ proteins and MDA[27]	Cilostazol (NCT02491268)[28,29]
Tauopathy	Cilostazol	Activation of the 26S proteasome to prevent the aggregation of tau protein [30]	-
Depression	Cilostazol	Activation of CREB/BDNF pathway [31]	Cilostazol (IRCT20090117001556N130)[32]
Autism	Cilostazol	Activation of CREB/BDNF pathway [33]	-
Photoaging	Cilostazol	Inhibition of p38 mitogen-activated protein kinases (MAPK) and NF-κB in response [34], Reduction of microphthalmia-associated transcription factor (MITF) expression [35]	-
Cancer	Cilostazol Cilostamide Anagrelide Zardaverine Quazinone DNMP	Although not well defined, the cAMP/PKA pathway may be the involved pathway[36–39]	-

2. OVERVIEW OF PDE3

The eleven identified families of PDE show variations in terms of their primary and secondary structure, substrate affinity, response to different types of effectors, and regulatory mechanisms. PDE3 is notable for its clinical significance in regulating the cardiac vascular system, tumorigenesis, inflammation, and cognition [40–43]. While PDE3 exhibits hydrolytic activity towards both cAMP and cGMP, it is interesting that the hydrolysis rate for cAMP is tenfold higher compared to cGMP. However, the affinity of PDE-3 towards cGMP is still significantly high and as a result, cGMP functions as a competitive inhibitor in the process of cAMP hydrolysis mediated by PDE3 [8,12]

In mammals, PDE3 occurs in two distinct isoforms, namely PDE3A and PDE3B. These isoforms exhibit structural similarities, with distinguished hallmarks of *N*-terminal hydrophobic regions (NHRs) responsible for enzyme localization, as well as a catalytic domain and a *C*-terminal domain. The primary distinctions between the PDE3A and PDE3B isoforms are attributed to the existence of a 44-amino acid residue segment within the catalytic domain and NHRs. The NHRs are an important segment that is exclusive to the PDE3 family, and they hold significant importance in designing the structures of PDE3 inhibitors [8,40,44,45].

PDE3A encodes three variants, namely PDE3A1, PDE3A2, and PDE3A3, with distinct molecular weights and specific phosphorylation sites [45,46]. These sub-isoforms are produced from the PDE3A gene during biosynthesis initiating from different sites. Consequently, these sub-isoforms exhibit amino acid sequences that are almost identical, with the exception of their NHRs. PDE3A1 is the longest isoform and possesses two distinct membrane-localizing domains, "NHR1" and "NHR2 and three phosphorylation sites (PS) namely (P1 - P3) [42]. PDE3A2 and PDE3A3 are relatively shorter isoforms, whereas PDE3A2 lacks NHR1

and upstream PS and PDE3A3 lacks NHR1, NHR2, and all three PS (Figure 3) [42,47]. Despite these differences, all three isoforms share a common C-terminal catalytic region, thereby exhibiting similar catalytic activity and sensitivity to inhibitors [8,42,48]. PDE3B has a single variant called the PDE3B1. It exhibits structural resemblances to PDE3A, such as NHR and PS, along with a C-terminal catalytic region. The C-terminal section exhibits a high similarity to that of PDE3A, leading to similar catalytic activity and susceptibility to inhibitors [42]. However, the *N*-terminal section shows variations leading to different intracellular localizations within cardiac myocytes. For example, PDE3A interacts with sarcoplasmic-reticulum (SR) proteins, whereas PDE3B is found near caveolin-3 near T tubule membranes [13,46,47]. This localization difference explains why inotropic responses to PDE3 inhibitors are absent in Pde3a-deficient mice but persist in Pde3b-deficient mice [49,50].

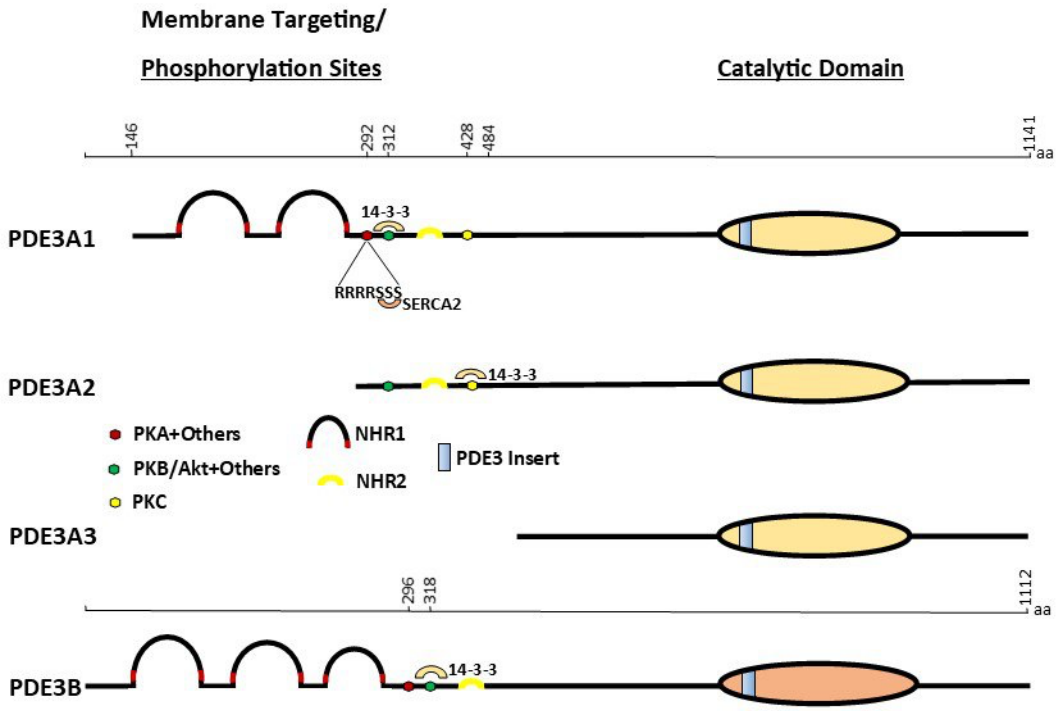

Figure 3 Structure and length of the PDE3 isoform [47]

PDE3s are widely distributed throughout various human tissues, albeit with distinct localization patterns exhibited by the two PDE3 isoenzymes. In mammals, the presence of PDE3A is typically observed in various tissues including platelets, the heart, corpus cavernosum smooth muscle, vascular smooth cells, megakaryocytes, oocytes, and placental muscle tissues. On the other hand, PDE3B is primarily identified as being significant in tissues involved in energy regulation, lipid metabolism, insulin signaling and glucose metabolism. These tissues include the liver, adipose tissue, spermatocytes, pancreatic beta cells, and the hypothalamus [8,13,46,51].

3. OVERVIEW OF PDE3 INHIBITORS

The origins of PDE inhibitors can be traced back to the discoveries made by Henry Hyde Salter, an asthmatic, in 1860, whereby he documented the bronchodilator properties of caffeine (a xanthine) after drinking a cup of coffee. This discovery had triggered the interest of pharmaceutical industry in xanthines, leading to the isolation of theobromine and theophylline and the subsequent discovery of their diuretic properties from *in vivo* studies in 1887. In 1912, the inotropic properties of xanthines were discovered by J. Picjhler. However, the mechanism of actions of xanthines was not known was until 1958 when Sutherland and Rall discovered PDE and theophylline as a PDE inhibitor [1].

The development of selective PDE inhibitors started in parallel with the isolation of various isozymes of PDEs between 1960 – 1990. In 1961, dipyridamole was the first selective PDE3 developed as a therapeutic agent in the prevention of stroke. In 1978, amrinone was approved for the treatment of chronic heart failure. Structural modification of amrinone generated a second generation of PDE3 inhibitor, milrinone, that was approved for the short-term treatment of acute heart failure in 1987. In the same year, enoximone was also

approved for the treatment of congestive heart failure, followed by the discovery of zardaverine as a potent bronchodilator. Most of these inhibitors were discontinued due to the high mortality rate associated with their prolonged usage. Nevertheless, structural modification of these inhibitors led to the discovery of many inhibitors including cilostazol approved for the treatment of intermittent claudication in the end of the 20th century [1,13].

Chemically, PDE3 inhibitors are a diverse class of compounds that exhibit a range of nitrogen-containing scaffolds (Figure 4), including but not limited to, xanthines (theophylline), pyridazinone (zardaverine), pyrazinone (SK&F 94120), pyridinone (amrinone), imidazolinone (enoximone), quinolinone (ciostazol), and imidazoquinazolinone (lixazinone) [5,13].

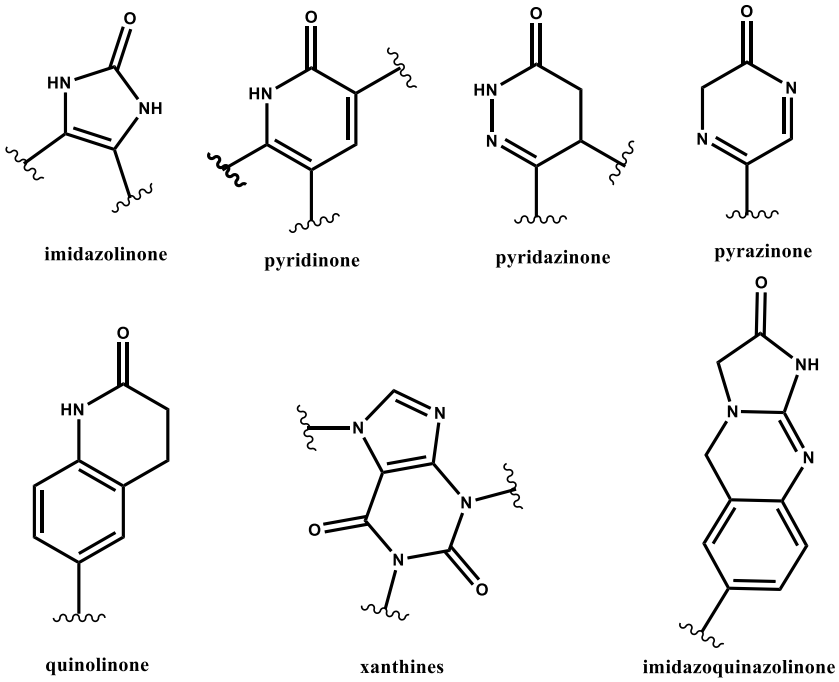

Figure 4 some chemical scaffolds present in PDE3 inhibitors.

4. IMPLICATION OF PDE3 IN VARIOUS DISEASES

4.1. Cardiovascular Diseases as the Starting Point

PDE3 inhibitors have been widely exploited for several decades as therapeutic agents in the management of cardiovascular disorders such as acute heart failure, cardiogenic shock, ischemic coronary heart disease, stroke and as vasodilators. The capacity to enhance myocardial contractility and vasodilation has served as a fundamental aspect of cardiac treatment. Examples of known selective PDE3 inhibitors include amrinone, milrinone, enoximone, levosimendan, CI-930, pimobendan, vesnarinone, cilostazol, cilostamide and lixazinone (Figure 5). Derivatives of these drugs are exploited in research studies to achieve positive inotropic, chronotropic, and antiarrhythmic effects when combined with other drugs [40,52–54].

The three sub-isoforms of PDE3A (PDE3A1 – A3) and PDE3B are expressed in cardiac myocytes. They are cGMP-inhibited cAMP PDE, and they are crucial in the termination of cAMP signaling. The widespread second messenger cAMP serves as a mediator of several external stimuli. Within the cardiovascular system, cAMP exerts regulatory control over a diverse range of physiological processes. Notably, it influences platelet aggregation, regulates the release of renin in the kidney, and participates in the modulation of contractility in cardiac myocytes. Furthermore, cAMP governs contractility and proliferation in vascular smooth muscle cells, among other functions [55].

The PDE3 enzymes, specifically the PDE3A, have a significant impact on regulating cAMP-mediated signaling in the human myocardium. This regulation influences myocardial contractility through complex pathways that involve the phosphorylation of proteins associated with calcium cycling inside cardiac muscle cells [42]. The findings from an *ex vivo* study involving mouse hearts carried out by Beca and coworkers indicate that the absence of the Pde3a gene results in a total elimination of inotropic responses caused by PDE3

inhibition. However, elevated levels of Ca^{2+} released from SR were observed due to the increase in cAMP level. Consequently, the contractility of the heart increased in the PDE3A-deficient heart, whereas no contractility enhancement was observed in the PDE3B-deficient one. This suggests that PDE3A plays a significant function in modulating cardiac contractility and not PDE3B [50,56].

In heart failure, cardiac myocytes undergo notable changes that influence their responsiveness towards signaling mechanisms. Heart failure is marked by a reduction in the density of β-adrenergic receptors and an elevation in the activity of Gαi and β-adrenergic receptor kinase [57]. Consequently, these changes result in a decrease in the production of cAMP. A reduction in levels of cAMP leads to a decrease in protein phosphorylation and a subsequent decline in the intensity of intracellular Ca^{2+} signals, commonly referred to as intracellular Ca^{2+} transients [42,57]. PDE3 inhibitors have been employed as a strategy to counteract these effects by preventing the degradation of cAMP, hence augmenting cAMP-dependent signaling inside the cardiac myocytes. For short-term therapy, the application of the inhibitors aims to enhance myocardial contractility in individuals with heart failure. However, extended usage, lasting months or more, increases sudden cardiac death mortality regardless of contractility. Overexpression of PDE3A may have benefits, according to studies [47,58]. Certain mutations that result in increased PDE3A activity are associated with severe hypertension, while paradoxically showing reduced levels of cardiac hypertrophy. These findings indicate that the inhibition of PDE3A may have negative consequences, whereas enhancing its activity may provide protective advantages against apoptosis and excessive hypertrophy [59].

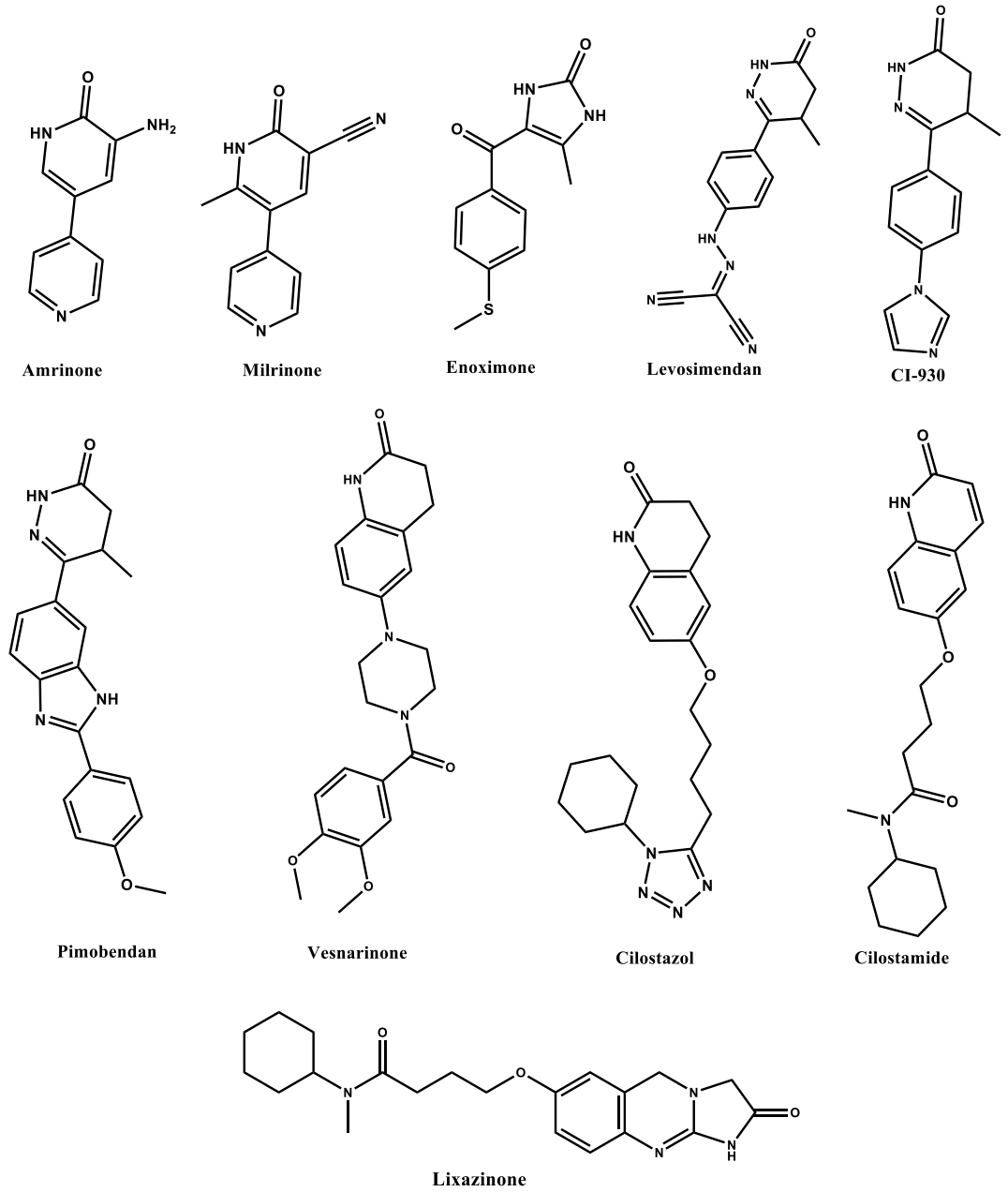

Figure 5 Known PDE3 inhibitors used in the treatment of cardiovascular diseases.

On the other hand, PDE2, 3 and 5 are the isoforms present in platelets where they hydrolyze the breakdown of cAMP and cGMP, and are responsible for the regulation of more than 90% of platelet function. cAMP and cGMP are well-known for their function in the inhibition of platelet aggregation [60]. When platelets are activated, they undergo structural changes, exposing a receptor called integrin αIIbβ3 on their surface. This receptor mediates protein-protein interactions leading to platelet aggregation and subsequent clot formation. cAMP exerts its antiplatelet activity by inhibiting the structural change, the activity of integrin αIIbβ3 and the subsequent suppression of the release of platelets. Therefore, by increasing cAMP levels, platelet aggregation can be inhibited [61,62]. However, other studies reported that dipyridamole and cilostazol exert their effects on platelet function through the inhibition of the reuptake of adenosine by red blood cells, leading to increased levels of adenosine in the plasma. Adenosine is a vasodilator and a nucleoside that increases cAMP concentration and subsequently inhibits platelet activity [60,62,63]. In addition, cilostazol effectively suppresses the expression of P-selectin on platelet surfaces, reduces the synthesis of thromboxane B2, and inhibits the release of platelet factor 4 [64,65].

4.2. Intermittent Claudication (IC)

IC is a condition that is characterized by the presence of atherosclerosis in the arteries in the lower extremities. IC deters patients from engaging in physical activities such as walking and exercising [66]. Multiple studies have communicated the overexpression of PDE3 in IC and PDE3 inhibitors have produced positive outcomes for the management of IC through the inhibition of platelet activation and relaxation of vascular smooth muscles. Cilostazol and pentoxifylline are the two PDE3 inhibitors that have received approval for the management of IC due to their notable improvement in patients' walking distance [66–68]. Ishiwata and coworkers assessed the effectiveness of parogrelil (NM-702) and cilostazol *in vitro*, *in vivo* and *ex vivo* studies. Parogrelil selectively inhibited PDE3 better than cilostazol with IC_{50}= 0.179 nM for PDE3A and 0.260 nM for PDE3B [69]. K-134, a derivative of cilostazol (Figure 6) and a selective inhibitor of PDE3 has completed Phase II clinical trials (NCT00783081) for the management of IC, and no safety concern has been raised [70].

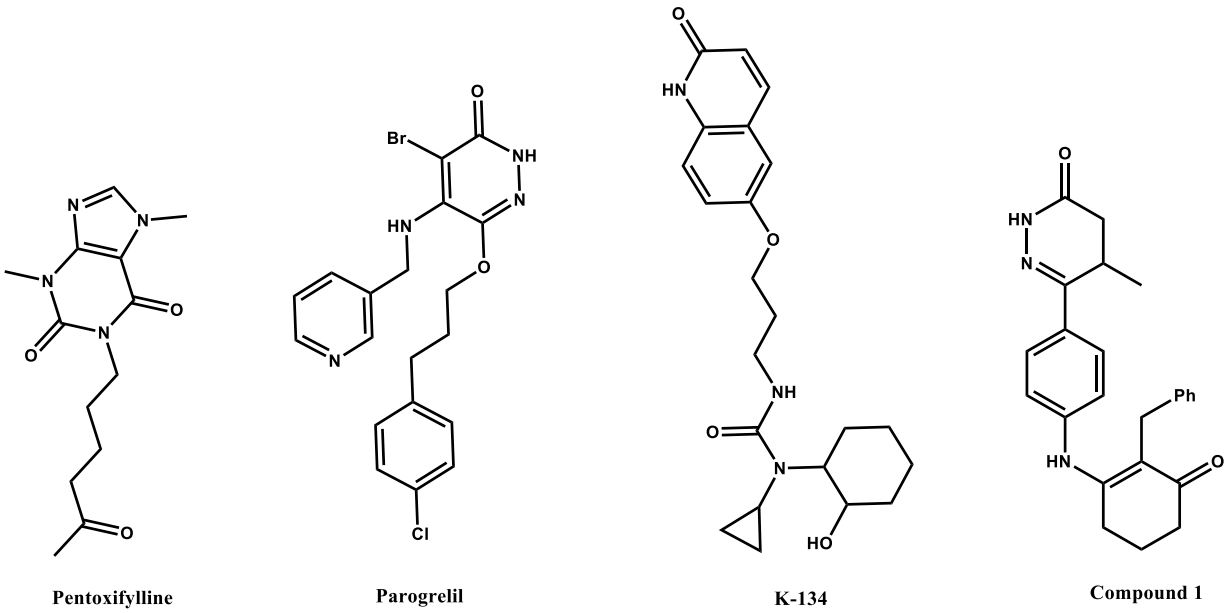

Figure 6: PDE3 inhibitors used in the treatment of IC and hyperlipidemia.

4.3. Hyperlipidemia

Lipolysis is a biochemical process that involves the enzymatic hydrolysis of triglycerides, stored fat molecules found in adipose tissue, producing fatty acids and glycerol that can be utilized by the body as a source of energy when glucose levels are low. Hormone-sensitive lipase (HSL) is responsible for the hydrolysis of stored fats and is activated via the cAMP-PKA pathway [24,25]. As a result, PDE3 inhibitors such as cilostamide can stimulate the process of lipolysis by increasing the concentration of cAMP in adipose tissues [24]. Many hyperlipidemic patients have hypertriglyceridemia which can be reduced with PDE3 inhibitors without the related adverse effects of HMG-CoA reductase. Besides Yokoyama and Aoki reported the hypotriglyceridemic effect of cilostazol and K-134 in an in vivo study conducted on mice [25]. In addition, a series of aryldihydropyridazinones and aryldimethylpyrazolones with 2-benzyl vinylogous amide derivatives were investigated for selective PDE3B inhibition and subsequent lipolytic properties. Compound 1 was discovered to stimulate lipolysis in adipocytes, increase metabolic rate in rats, and lower blood pressure [71].

4.4. Inflammatory diseases

cAMP activates cAMP-dependent PKA by binding to its regulatory subunits, triggering a signaling cascade. Intracellular PKA controls cell maturation and promotes the generation of anti-inflammatory signals that counteract the generation of inflammatory substances [72]. According to the literature, higher levels of cAMP promote the synthesis of anti-inflammatory substances like IL-10 [73,74]. Furthermore, CREB, a vital protein that regulates the reactions of the immune system to inflammation is activated through phosphorylation with the help of the cAMP-dependent PKA. The activation of CREB reduces inflammation and protects tissues. This is because phosphorylated CREB binds to the NF-κB (nuclear factor kappa-light-

chain-enhancer of activated B cells) complex and thus, prevents the binding of CREB. This interference has been proposed to directly inhibit the activation of NF-κB, leading to a decrease in proinflammatory responses such as the production of TNFα (tumor necrosis factor-alpha), IL-6 and IL-1β [75]. Besides, low levels of cAMP lead to inflammation by increasing the levels of pro-inflammatory substances like IL-8, IL-12, IL-17, IL-22, IL-23, and TNFα. Consequently, increasing cAMP levels by blocking the activity of PDEs has been a potential strategy for developing anti-inflammatory agents [73].

Crohn's disease (CD) and ulcerative colitis (UC) are chronic conditions affecting the gastrointestinal tract and are distinguished by a dysregulation in the levels of proinflammatory and anti-inflammatory cytokines. The overexpression of TNF-α has been observed in individuals with CD and UC. Inhibiting TNF-α using anti-TNF-α antibodies has proven to be an efficacious therapeutic approach for managing CD and UC. However, prolonged use of antibodies comes with immunosuppression as a side effect [18,76]. Rieder and coworkers studied the anti-inflammatory properties of roflumilast, a selective PDE4 inhibitor, and pumafentrine, a dual PDE3/PDE4 inhibitor (Figure 7), in the colitis model in mice. Pumafentrine reduced the production of TNF-α and improved clinical scores according to the findings [18].

Osteoarthritis (OA) is an inflammatory disease characterized by cartilage deterioration due to abnormal functioning of chondrocytes in the joints. Among the key cytokines that participate in cartilage deterioration is IL-1β. IL-1β stimulates the production of cartilage-degrading substances like NO. PDE inhibitors exhibit chondroprotective effects by reducing chondrocyte IL-1β-induced nitrite accumulation [77]. Pumafentrine is effective in reducing the severity of arthritis in mice. It has shown a synergistic effect when used in combination with methotrexate [19]. Cilostazol is currently in a recruitment status in a phase I study as an adjunct to conventional therapy in OA patients [20].

Asthma and chronic obstructive pulmonary disease (COPD) are chronic respiratory disorders characterized by bronchoconstriction and airway inflammation. [78]. These two diseases affect all ages and can cause symptoms that greatly affect the daily life of a person. Asthma and COPD are not fully curable and for over four decades, the treatment strategies have not changed much. Patients taking the available improved therapies still experience symptoms that affect their daily lives. Thus, new treatments are needed to help patients feel better, improve their lives, and manage their symptoms more effectively [17,79].

PDE3 and PDE4 are among the targets explored in the quest for new therapy against asthma and COPD [80–82]. PDE3 acts on both cAMP and GMP in airway smooth muscle cells, macrophages, dendritic cells, epithelial cells, lymphocytes etc. whereas PDE4 acts only on cAMP and is involved in inflammatory cell activation in similar immune cells [41]. The simultaneous inhibition of PDE3 and PDE4 exhibited an additive and synergistic effect in reducing inflammation and bronchoconstriction, surpassing the individual administration of PDE3 or PDE4 inhibitors. [17,74,83–86]. Milara et al. studied the effects of selective inhibitors of PDE3 and PDE4, motapizone and rolipram, respectively. Separate inhibition of PDE3 or PDE4 in human alveolar macrophages exposed to lipopolysaccharide (LPS) reduced IL-8 and TNF-α cytokine secretion by about 20%. Dual inhibition of PDE3 and PDE4 simultaneously resulted in a synergetic effect, decreasing the IL-8 and TNF-α cytokine secretion by up to 90%. This shows that combined inhibition of PDE3/4 shows promise as a strong anti-inflammatory approach in respiratory disorders [15]. A phase II clinical trial (NCT02427165) conducted by Bjermer et al. revealed that ensifentrine (RPL554) a dual PDE3/PDE4 inhibitor displayed dose-dependent bronchodilation and was as efficient as a therapeutic dose of nebulized salbutamol. Additionally, ensifentrine was equally well-tolerated at all doses and did not exhibit the anticipated typical salbutamol-related side effects [16]. In another phase III clinical trial, ensifentrine demonstrated a safety profile similar to a placebo. The study concluded that ensifentrine has the potential to be a valuable and complementary treatment option for COPD patients, effectively addressing the limitations of current treatment methods [17].

Another respiratory inflammatory disease is acute respiratory distress syndrome (ARDS). It is a common disease where lung tissue becomes inflamed, leading to lung dysfunction [87]. Kosutova et al. conducted an in vivo study to evaluate the anti-inflammatory properties of olprinone, a PDE3 inhibitor. The findings indicated a notable decrease in the levels of IL-6 and IL-1β and therefore, olprinone may serve as a promising drug candidate for the treatment of ARDS [21].

Recently, coronavirus disease-19 (COVID-19), a viral respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide and caused millions of cases and deaths. It is mainly characterized by hyperinflammation caused by "cytokine storm", cough, shortness of breath, pneumonia, and coagulation biomarkers [88–90]. One of the strategies applied against COVID-19 was focused on reducing hyperinflammation to prevent multiple organ dysfunction syndrome. With the anti-inflammatory and bronchodilatory properties, PDE3 inhibitors became attractive candidates against COVID-19 [89,91]. Pentoxifylline and ibudilast which are nonselective PDE inhibitors, ensifentrine, a dual PDE3/4 inhibitor and dipyridamole, a PDE3 inhibitor, are being studied in various COVID-19 clinical trials [92].

Moreover, computational chemistry studies conducted on cilostazol, other antiplatelets and recent antiviral drugs used against COVID-19 by Abosheasha and El-Gowily disclosed that cilostazol demonstrated the highest binding affinity against the main protease (Mpro), which is an important druggable target of SARS-CoV-2 [93].

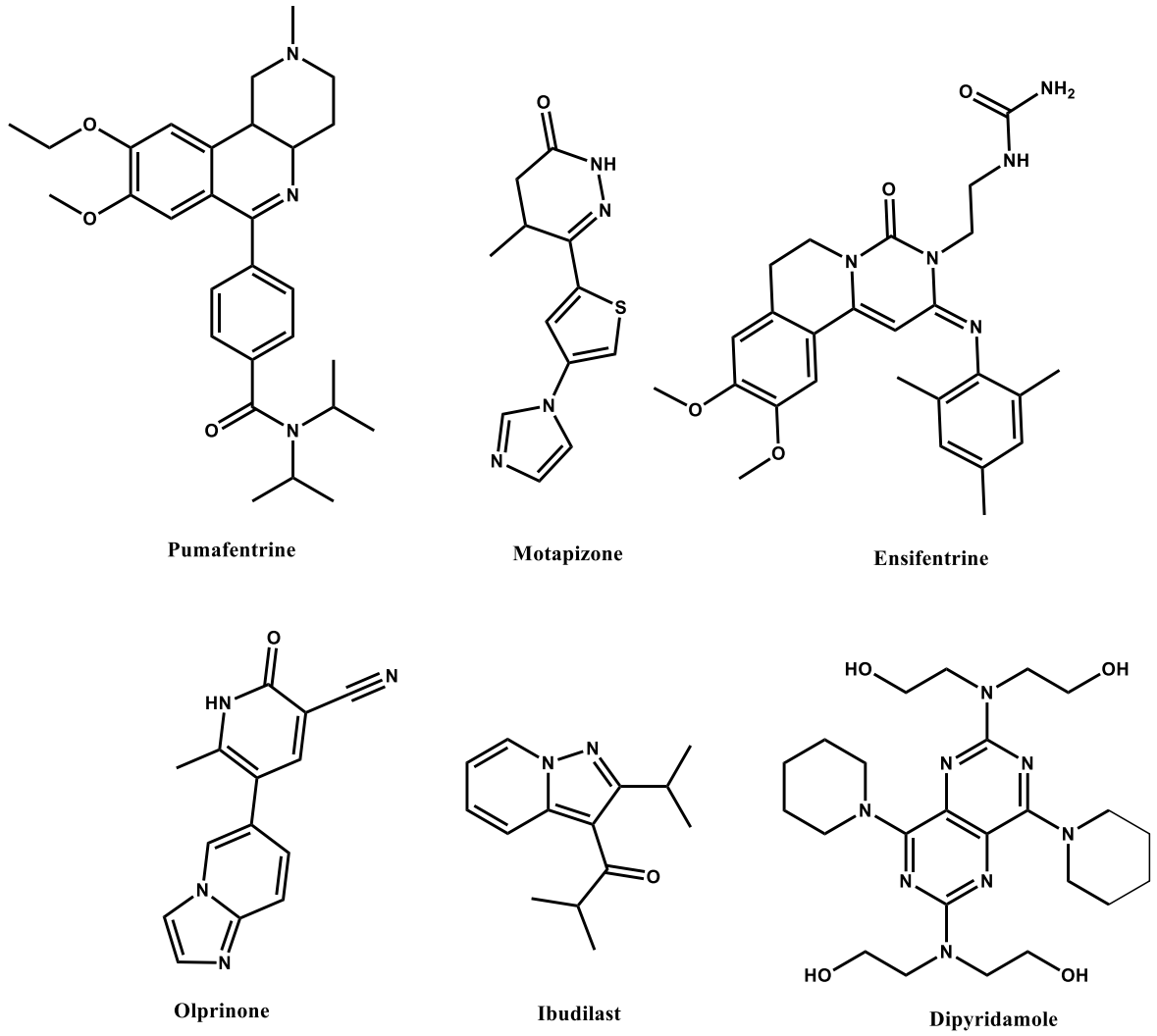

Figure 7: PDE3 inhibitors used in inflammatory disorders.

4.5. Neurological Disorders

Mild cognitive impairment (MCI) is an intermediate phase between the cognitive changes of typical aging and early dementia. It is characterized by a cognitive decline exceeding what is expected for someone's age and education level. It may progress to dementia and Alzheimer's disease if left untreated [94,95]. In the brain, cAMP and cGMP play crucial roles in neurodevelopment and maintaining synaptic plasticity, which helps with learning and memory. They play a role in axon growth and guidance. The levels of cAMP and cGMP are important for shaping neuronal circuits and affecting processes like neuronal migration, neuroprotection and neuroplasticity [6,96–99]. Besides, Yanai et al reported that cilostazol improved learning and memory in mice by increasing cAMP concentration [100]. In another study by Yanai et al., cilostazol reversed spatial memory impairment in aged male mice, increased glucose uptake in the brain and reduced neuroinflammation that can cause neurodevelopmental disorders [101].

Amyloid β (Aβ) proteins play a role in the production of reactive oxygen species and NO in individuals with Alzheimer's type dementia. These chemicals are responsible for inducing an excessive level of oxidation in proteins and lipids within neurons, which may potentially be associated with impairments in learning and memory [102]. A study conducted by Hiramatsu et al. examined cilostazol's potential effectiveness for

dementia related to cerebral ischemia. The study investigated if cilostazol could improve learning and memory problems caused by $A\beta_{25-35}$ in mice and compared its effects to aspirin. $A\beta_{25-35}$ causes accumulation of malondialdehyde (MDA) and IL-1β in the frontal cortex and hippocampus. The findings revealed that Cilostazol helped improve memory and cognition affected by $A\beta_{25-35}$ by preventing the accumulation of MDA, whereas aspirin did not show any improvements [27]. A different study demonstrated coherent results in which cilostazol improved behaviors and memory in Alzheimer's disease-like cognitive decline by preventing the accumulation of Aβ proteins. Cilostazol increases the level of the proteolytic enzyme neprilysin [26]. Cilostazol decreased cognitive decline in two different studies on Alzheimer patients in a phase II clinical trial (NCT02491268) [28,29]. Multiple studies have confirmed the positive effect of cilostazol on memory performance in Alzheimer's and dementia cases and have associated this activity with the inhibition of PDE3 [98]. Cilostazol was found to reduce sporadic cerebral amyloid angiopathy, which is a prevalent age-related cerebral small vessel disease mostly present in Alzheimer's patients. It is mainly characterized by symptomatic intracerebral hemorrhage which may be caused by antiplatelet drugs. However, despite its antiplatelet activity, cilostazol did not induce intracerebral hemorrhage [103]. In fact, in a study conducted on mice, Kitashoji et al. reported that cilostazol could reduce intracerebral hemorrhage associated with oral anticoagulants [104].

Additionally, Schaler and Myeku conducted an *in vivo* study to examine the impact of cilostazol on tauopathy and cognitive decline. [30]. Tauopathy is a collection of neurodegenerative disorders marked by an abnormal increase in the phosphorylation of these tau proteins causing them to accumulate into aggregates. These aberrant aggregates consequently form neurofibrillary tangles, which can interfere with the normal functioning of neurons and result in a decline in cognitive abilities [30,105]. By inhibiting PDE3, cilostazol activates the cAMP/PKA pathway, leading to the activation of the 26S proteasome and subsequent enhancement of its proteolytic activity. The proteasome breaks down abnormal or misfolded proteins, such as aggregates of tau protein, thereby reducing the severity of tauopathy and ameliorating cognitive impairment [30].

On the other hand, cAMP and cGMP activate PKA and PKG, which start downstream pathways by modifying important proteins, that affect learning, memory, neurodevelopmental disorders, and psychiatric disorders. Examples of these proteins include CREB [98,100,106]. Activation of CREB by cAMP-dependent PKA enhances the gene expression of neuroprotective substances including the brain-derived neurotrophic factor (BDNF), a key neurotrophin in the brain. BDNF regulates neurogenesis, proliferation, and survival of neural stem [107–110]. Besides multiple studies have communicated the implication of the CREB/BDNF pathway in the etiology of major depressive disorder (MDD) [111]. Activating the CREB/BDNF pathway is a promising strategy for the treatment of post-stroke depression [108,110,112]. Besides, Kim et al. investigated the post-ischemic stroke antidepressant properties of cilostazol in mice with chronic mild stress. The findings revealed that cilostazol reduced the depressive behaviors of the mice by preventing neurodegeneration and promoting neurogenesis via the activation of the CREB/BDNF pathway [31]. In a clinical trial evaluating the safety and effectiveness of cilostazol and sertraline for MDD, the findings demonstrated that the combination of cilostazol and sertraline led to a statistically significant reduction in Hamilton depression rating scale (HAM-D) scores and an increase in remission rates when compared to the placebo group [32].

Moreover, Luhach et al. investigated the role of cilostazol in attenuating behavioral and biochemical deficits in a rat model of autism spectrum disorder (ASD). According to the study, cilostazol exhibited positive effects on symptoms associated ASD, including repetitive behavior, deficits in social behavior, anxiety, and hyperlocomotion. These effects are likely attributed to the activation of the CREB/BDNF pathway. Additionally, the anti-inflammatory and neuroprotective properties of cilostazol helped to reduce ASD-related brain inflammation and oxidative stress [33].

4.6. Diabetes

Although the antidiabetic mechanism of PDE3 inhibitors is not fully elucidated, studies have revealed that NO causes an increase in cGMP levels, which inhibits PDE3 in human islets of Langerhans. As a result, the cAMP levels increase. cAMP amplifies insulin secretion by Ca^{2+} elevation and triggering signals in β-cells, and this mechanism may be involved in the insulin secretagogue effect of NO. cAMP lowering agents such as PDE3 decrease insulin secretion and therefore, increasing the cAMP level with PDE3 inhibitors stimulates insulin secretion, making them potentially helpful for type 2 diabetes [45,113–117]. Many studies have revealed the presence of both PDE3 isoforms together with other PDE isoforms in the β-cells, however, PDE3B demonstrates a more prominent role in β-cells functionality. A multitude of animal tests have provided compelling evidence indicating that PDE3B plays a pivotal role in the metabolic functions of diverse organs, such as the liver, adipocytes, and pancreatic β-cells. Consequently, PDE3B is widely recognized as an essential

factor in the complex mechanism of insulin secretion irrespective of the species being examined [118]. Härndahl et al. have revealed that the upregulation of PDE3B in pancreatic β-cells caused a reduction in cAMP levels and subsequent impairment of insulin release induced by glucose and glucagon-like peptide-1 (GLP-1) [119,120].

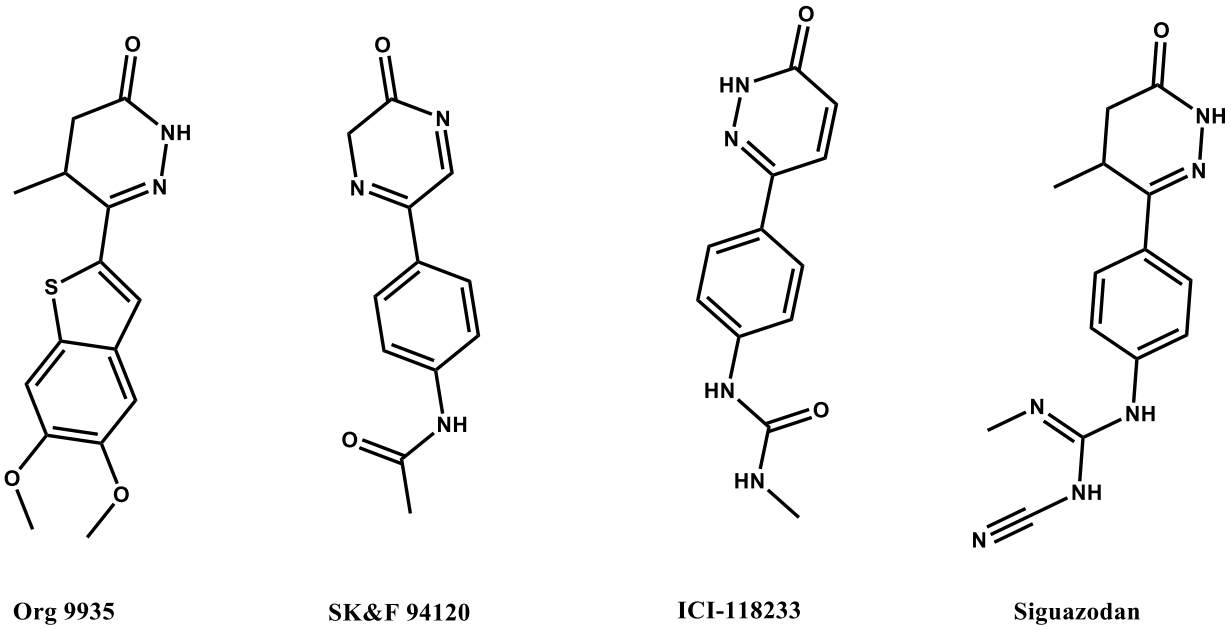

Figure 8: PDE3 inhibitors showing antidiabetic activity

On the other hand, Han P. and coworkers evaluated the effect of PDE3 inhibition on insulin secretion using a selective PDE3 inhibitor, milrinone. Milrinone inhibited PDE3 activity in fractionated soluble βTC3 cell lines and this inhibition was consistent for approximately 70%. Nevertheless, despite this inhibition, milrinone did not exhibit any notable augmentation in insulin secretion upon exposure to a glucose concentration of 16.7 mM. However, when incubated mouse pancreatic islets were studied under the same conditions, a different outcome was observed, whereby the insulin secretion was increased twofold [121]. Another study conducted by Shafiee-Nick et al. demonstrated that selective PDE3 inhibitors like Org 9935, SK&F 94120, ICI-118233 and siguazodan (Figure 8) exhibited significant inhibition of PDE3, resulting in a concentration-dependent increase in insulin release (up to 40% increase) when exposed to a stimulating glucose concentration of 10 mM. However, no such increase was observed when exposed to a glucose concentration of 3 mM [22]. Pentoxifylline exhibits inhibitory activity against PDE, leading to a decrease in the generation of IL-1, IL-6, and TNF-α. These cytokines contribute to the development of micro and macrovascular complications in diabetes, insulin resistance, and atherosclerosis, indicating the potential antidiabetic effect of pentoxifylline in diabetic neuropathy [23]. Pentoxifylline has been found to reduce oxidative stress in diabetic animal models [122,123].

4.7. Renal Diseases

The etiology of acute kidney injury is complex and multifactorial. One of the causes is snakebites. Marinho et al. studied the renoprotective effects of cilostazol against nephrotoxicity caused by *Bothrops alternatus* snake venom (BaV). BaV increases the production of TNF-α and IL-1β, which play an important role in nephrotoxicity. Cilostazol suppresses pro-inflammatory cytokine production. Marinho et al. hypothesized the implication of PDE3 in nephrotoxicity generated by BaV because cilostazol was found to significantly mitigate the effects of BaV-induced nephrotoxicity [124]. As reviewed by Bhanot et al. and Leehey, pentoxifylline has demonstrated a renoprotective effect in many studies by preventing proteinuria and the generation of reactive oxygen species [23,125].

4.8. Skin Disorders

Photoaging of human skin is a disorder mainly caused by chronic exposure to UV A and B radiation, and to wavelengths beyond the UV spectrum [126]. It is mainly characterized by dyspigmentation, skin roughness, and precancerous changes [127]. Kim et al. investigated the anti-photoaging properties of cilostazol in UV B-irradiated hairless mice. The findings revealed that the administration of cilostazol resulted in a decrease in wrinkle formation and skin thickness in UVB-exposed mice. In addition, molecular research revealed that cilostazol exhibited significant inhibition of the activation of MAPK and NF-κB in response to UVB irradiation [34]. Furthermore, Wei and coworkers investigated the effects of cilostazol on melanogenesis and revealed that cilostazol stimulates the synthesis of melanin and enhances the activity of tyrosinase enzyme and gene expression. The mechanism of action of cilostazol was believed to be via increasing MITF expression, which regulates melanocyte differentiation and pigment generation because SiRNA-mediated knockdown of MITF nullified cilostazol's melanogenic effects. In addition, the application of H-89, a PKA inhibitor, caused a decline in MITF expression, indicating that the cAMP-dependent PKA pathway is important for cilostazol-induced MITF expression [35].

4.9. Alopecia

Alopecia is a condition marked by hair loss, primarily in the scalp, but it can also affect other areas of the body. Treatment can be attained through the stimulation of hair follicle (HF) growth using various pharmacological agents that facilitate hair growth. HFs and HF stem cells play a significant role in the biological processes of wound healing and re-epithelialization. As the wound heals, there is an increase in vasodilation, and this augments cutaneous blood flow. Consequently, the stimulation of cutaneous blood flow in patients with alopecia can potentially enhance blood circulation in the microenvironment of hair follicles, leading to hair growth and hypertrichosis. Although PDE3 has been identified in human HF through mass spectrometry-based analysis of the human proteome, its implication in alopecia is not fully elucidated [128]. Nevertheless, Choi and coworkers communicated that cilostazol enhanced vasodilation by increasing intracellular cAMP levels in vascular smooth muscle cells, leading to an augmentation in microcirculation in human balding scalps. As a result, cilostazol promotes hair shaft elongation and improves the proliferation of human hair matrix keratinocytes [128].

4.10. Cancer

Advancement in research of molecular and cellular biology has provided insights into the mechanisms underlying cancer development. It has been observed that genetic and epigenetic changes can trigger the activation of specific signaling pathways, leading to uncontrolled cell growth and the initiation of carcinogenesis. Cancer cells, therefore, regulate the cyclic nucleotide signaling for proliferation and functioning. Cancer is associated with a range of modifications that result in the activation or inactivation of cAMP and cGMP signaling pathways [8,9,51,129,130].

Pitar and coworkers investigated the relationship between cGMP and cancer by studying the effects of guanylyl cyclase C agonists on the progression of human colon carcinoma cells. The study revealed that these agonists can inhibit the proliferation of certain colon carcinoma cells without inducing apoptosis or necrosis. Although the mechanisms of action of these agonists against colon carcinoma cells remain unclear, the study suggested that they probably exerted their anticancer activity actions are mediated through cGMP-specific downstream effector [131]. In addition, two different studies have communicated the presence of low levels of cAMP in cancer cells and that increasing cAMP levels lead to anticancer activity against skin cancer [132] and chronic lymphocytic leukemia through PKA-induced apoptosis [133]. Besides, Murata et al. investigated the anticancer activity of cilostazol, a PDE3 inhibitor, against colon cancer. The team has found that cilostazol prevents metastasis by inhibiting PDE3, causing an increase in the levels of cAMP in colon cancer cells, which in turn suppresses trans-cellular migration [134]. Recently, Sim et al. reported the anticancer activity of cilostazol via the activation of the cAMP/PKA pathway against hepatocellular carcinoma. In fact, the combination of cilostazol with cisplatin displayed a wider anticancer property against various cancer cells, including cisplatin-resistant cells [135]. In addition, Murata et al. assessed the anticancer activity of cilostamide, revealing that it inhibited the proliferation of the human neoplastic submandibular gland by inhibiting PDE3 [43].

Abadi et al. prepared a series of 1,2-dihydropyridine and evaluated their PDE3A inhibitory properties and anticancer activity against colon cancer cell line, HT-29. Compound 2 exhibited the strongest PDE3 inhibition with an IC_{50} of 27 µM, whereas compound 3 displayed the strongest inhibition against HT-29 with an IC_{50} of 3 µM. The results did not show any direct correlation between anticancer properties and PDE3

inhibition of the compounds [129]. In another study, the team synthesized 3-cyano-2-pyridone, 3-cyano-2-aminopyridine, pyrido[2,3-d]pyrimidin-4(3*H*)one and pyrido[2,3-d]pyrimidin-4-amine derivatives, evaluated their PDE3B inhibitory and anticancer properties against HT-29 colon tumor cell line. Compound 4 with the pyridone scaffold and compound 5 with the pyrido[2,3-d]pyrimidin-4(3*H*)-one scaffold (Figure 9) that inhibited both cAMP and cGMP hydrolysis showed the best anticancer effect, indicating that both cAMP and cGMP play a role in the anticancer activities of PDE3 inhibitors [136]. Davari et al. synthesized a range of pyridine derivatives with notable inhibitory activity against PDE3. The compounds were also evaluated for their anticancer properties against breast cancer cell line, MCF7. The results showed a direct correlation between their PDE3 inhibition and their anticancer activities with compound 6 showing the strongest PDE3A inhibitory activity of IC_{50} = 3.76 ± 1.03 nM and anticancer activity of IC_{50} = 34.3 ± 2.6 µM [137].

After confirming the expression and implication of PDE3A and Schlafen12 (SLFN12) in gastrointestinal stromal tumors, Vandenberghe et al. reported the anticancer properties of cilostazol and DNMDP via PDE3A and SLFN12 inhibition [37]. Similar results were reported by An et. after investigating the anticancer properties of anagrelide against a panel of 31 different types of cancer cell lines. Anagrelide exerted its anticancer activity through PDE3A and SLFN12 inhibition and subsequently, the induction of cell cycle arrest and apoptosis [39]. Nazir et al. reported the overexpression of PDE3A in various 10 solid cancer cells and a correlation between PDE3A expression and their sensitivity towards PDE3 inhibitors such as Zardaverine and Quazinone [38]. Hao et al. investigated the implication of PDE3A in the progression of breast cancer its potential as a druggable target, and the anticancer activity of cilostazol. The results revealed overexpression of PDE3A in breast cancer tumors, that it contributes to metastasis by activating inflammatory pathways and inhibiting the cAMP/PKA pathway. Cilostazol demonstrated anticancer and antimetastatic activity in breast cancer both *in vitro* and *in vivo* studies via PDE3A inhibition [36]. Furthermore, Shekouhy et al conducted a synthesis of nucleobases-containing tetrazole hybrids and examined their PDE3A inhibitory activities and anticancer properties. Similar to Davari et al., a clear correlation between PDE3A inhibitory activities and anticancer properties of these compounds was observed, supporting the implication of PDE3 in tumorigenesis. Compound 7 showed a better PDE3A inhibition than cilostazol with IC_{50} of 1.89 ± 0.75 nM. Similarly, the same compound showed better anticancer activity against MCF-7 than methotrexate with IC_{50} of 25.71 ± 3.85 µM [138]. On the other hand, MacKeil et al. reported the angiogenic activity of cilostamide through the inhibition of PDE3. However, the group confirmed that silencing PDE3B, but not PDE3A, markedly impairs sprouting. This explains that cilostamide exerts its angiogenic activity by inhibiting PDE3B [139].

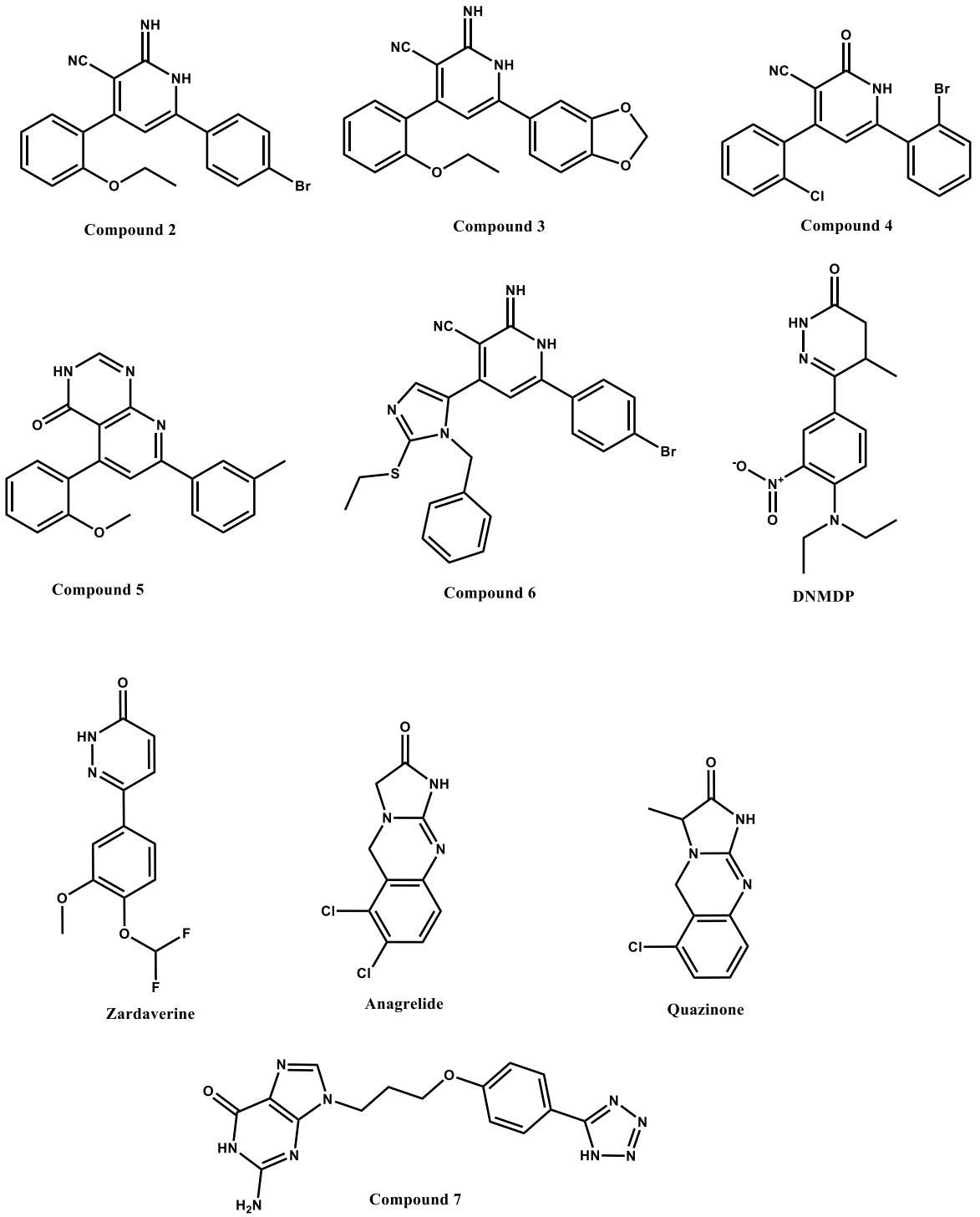

Figure 9: PDE3 inhibitors showing anticancer activity.

5. CONCLUSION

In conclusion, this review expands our understanding of the diverse therapeutic potential of PDE3 inhibitors beyond their traditional cardiovascular applications as various research revealed additional therapeutic potential for different medical conditions including, but not limited to, various inflammatory disorders, diabetes, and cancer. By exploring the cellular pathways modulated by PDE3, this review has provided insights into the mechanisms of action of PDE3 inhibitors and their potential for drug repositioning. Besides, PDE3 is widespread throughout the body and their precise roles in various diseases remain to be fully elucidated. As a result, further investigations, drug repositioning of PDE3 inhibitors and clinical trials are necessary to fully realize their potential in the management of various non-cardiovascular diseases. Future research should prioritize the identification of promising PDE3 inhibitors for specific diseases, as well as the

optimization of their pharmacokinetic and their cardiovascular related toxicities. Overall, this review has made a significant contribution in enhancing our comprehension regarding the various therapeutic applications of PDE3 inhibitors, while also offering a clear direction for forthcoming investigations in this area.

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