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Review Article

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Phosphodiesterase-4 Inhibitors in COPD Therapy: A Review of Mechanisms, Limitations, and Emerging Opportunities

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Abstract: Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory disease with a high global morbidity rate and irreversible airflow limitation. Without addressing the underlying inflammation, current therapies mainly reduce symptoms. By examining the development, mechanisms, and therapeutic potential of phosphodiesterase-4 (PDE4) inhibitors in COPD, this review highlights developments, obstacles, and new approaches to clinical translation. PDE4 inhibitors suppress the release of inflammatory mediators and promote bronchodilation by increasing intracellular cyclic adenosine monophosphate (cAMP) levels. However, the extensive distribution of PDE4 in non-pulmonary tissues limits the use of treatment by causing gastrointestinal and neuropsychiatric side effects. The literature from 1977 to 2025 shows that while second-generation agents like roflumilast and cilomilast showed improved selectivity but only slight benefits, early compounds like rolipram showed efficacy but poor tolerability. Isoform-selective PDE4B targeting, inhaled delivery methods, and dual PDE3/4 inhibition are recent developments that present encouraging avenues for improving safety and efficacy. PDE4 inhibitors offer important mechanistic insight into COPD inflammation, despite the fact that clinical progress is still limited. Future developments will rely on better isoform specificity, optimized pulmonary formulations, and biomarker-guided patient selection. PDE4 inhibitors may progress from experimental anti-inflammatory drugs to precision treatments that can alter the course of COPD with these improvements.

Keywords: COPD; phosphodiesterase-4 inhibitors; inflammation; roflumilast; drug development.

1. Introduction

A major public health concern, chronic obstructive pulmonary disease (COPD) is one of the world's leading causes of morbidity and mortality. The Global Burden of Disease (GBD) Study 2021 estimates that 213 million people worldwide suffer from COPD, and the illness was the third leading cause of death globally in 2021, accounting for 3.7 million deaths (Jackson et al., 2023; Wang et al., 2025). Over 80% of COPD-related deaths occur in low- and middle-income countries (LMICs), where the burden is disproportionately higher. This is primarily because of air pollution, occupational exposures, and chronic smoking (Organisation, 2023). The World Health Organisation (WHO, 2023) cautions that as the population ages, COPD prevalence will continue to rise, particularly in areas with poor access to early diagnosis and preventive care (Mannino et al., 2024). In addition to its negative effects on health, COPD has a substantial financial impact, costing high-income nations over $50 billion a year in direct and indirect medical expenses as well as significant productivity losses globally (Mannino et al., 2024).

1.1. Chronic Obstructive Pulmonary Disease

Current COPD treatments are mostly symptomatic and do not stop the disease's progression, despite therapeutic advancements. The cornerstones of pharmacotherapy include long-acting bronchodilators, antimuscarinic drugs, and inhaled corticosteroids (either alone or in combination), which provide only slight reductions in airflow obstruction and the frequency of exacerbations (Bergantini et al., 2024; Janjua, 2020). Even with the best inhaled therapy, many patients still have a lower quality of life, frequent exacerbations, and a progressive decline in their lung function. Moreover, long-term exposure to corticosteroids raises the risk of metabolic disorders, osteoporosis, and pneumonia, underscoring the critical need for innovative anti-inflammatory strategies that address underlying disease mechanisms (Barnes, 2013).

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1.1.1. Mechanism of Inflammation in COPD

Although the exact mechanisms behind COPD are still unknown, chronic inflammation seems to play a significant part (**Fig. 1**).

Several structural changes in the lung parenchyma and small airways, including fibrosis, smooth muscle hypertrophy, goblet cell metaplasia, and lumen occlusion by mucus plugging, along with inflammation, are major factors in the airflow restriction and rapid decline of forced expiratory volume in one second (FEV1) seen in COPD (Barnes, 2019; Barnes, 2017; Barnes & Immunology, 2016; Zeng et al., 2024).

1.1.2. Differences Between Asthma and COPD

Asthma and COPD are diseases that cause chronic inflammation of the airways but have distinct characteristics (**Table 1**).

Table 1. Differences in the inflammation profile of asthma and COPD.

Asthma	COPD
Key inflammatory cells	
$CD4^+$lymphocytes	$CD8^+$lymphocytes
Eosinophils	Neutrophils
Mast cells	Macrophages
Neutrophils (severe asthma)	Eosinophils (exacerbation)
Upregulated cytokines/ chemokines	
IL-4, IL-5, IL-13	IL-8, IL-1
RANTES, MCP-1	Leukotriene B4, interferon -γ

Eosinophils, mast cells, and CD4 T lymphocytes are the main cell types involved in the inflammatory process in asthma, while more neutrophils, macrophages, and CD8 T lymphocytes are seen in COPD (Cukic, 2012; Sciurba, 2004; Tommola et al., 2017).Asthmatic patients have airway obstructions primarily caused by bronchoconstriction, which is the activation of smooth muscle and basal membrane thickening. These changes are positively associated with asthma attacks and bronchial hyperresponsiveness (Athanazio, 2012; Sköld, 2010).

Reactive oxygen species from external toxic agents, particularly cigarette smoke, cause cell damage, which is linked to the decreased airway caliber seen in COPD patients (Bezerra et al., 2023; Stella et al., 2025). The process of airway narrowing leads to mucous hypersecretions and goblet cells (mucous metaplasia) in the small airways (Hayashi, 2012; Rubin, & Voynow, 2018; Rogers & biology, 2003).

1.1.3. Risk Factors for COPD

Approximately 80–90% of cases of COPD are caused by smoking, which is still the most important and well-established risk factor. Long-term tobacco smoke exposure causes oxidative stress, chronic inflammation, and an imbalance between proteases and antiproteases, all of which contribute to irreversible airway remodeling and alveolar wall destruction (emphysema) (Cohen et al., 1977; Hersh et al., 2011). Over many years, the inflammation thickens the walls of the airways and produces an excessive amount of mucus, which permanently alters the lung.

Exposures at work and in the environment are just as important as smoking. The risk of developing COPD is greatly increased by ongoing exposure to biomass fuel smoke, air pollution, industrial dust, and chemical fumes, especially in low- and middle-income nations where biomass fuels are frequently used for heating and cooking.

Other risk factors that hinder lung development and hasten functional decline in later life include low socioeconomic status, recurrent respiratory infections during childhood, and prolonged exposure to indoor pollutants (Kraïm-Leleu et al., 2016; Mannino & Buist, 2007). Even though it is uncommon, genetic susceptibility,

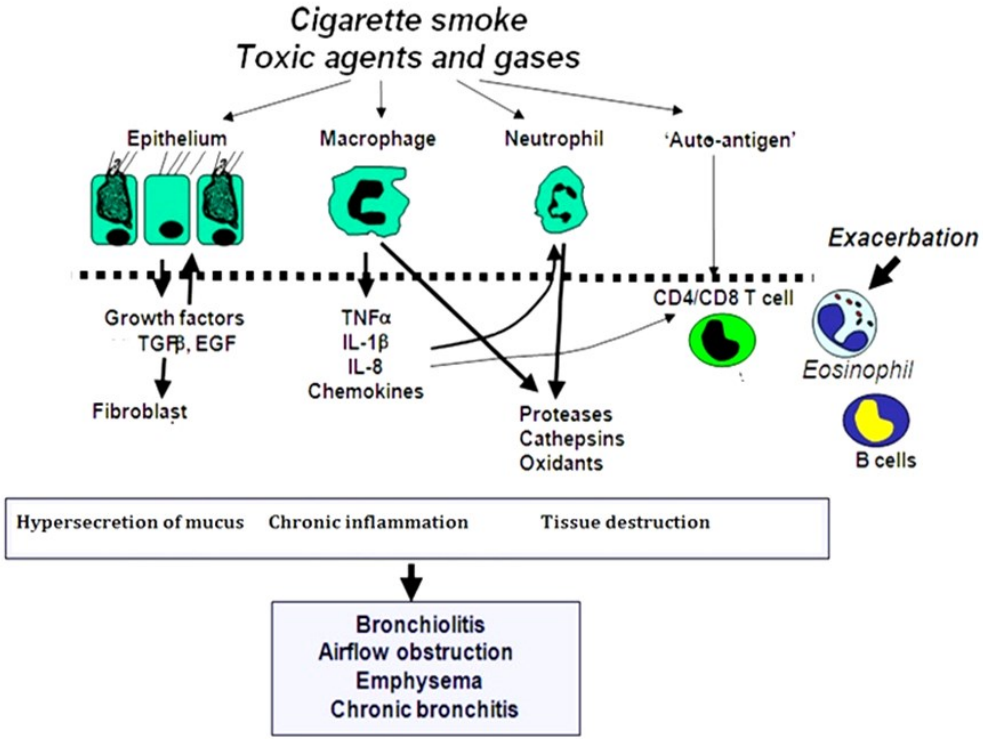


Fig. 1. Mechanism of action of Chronic obstructive pulmonary disease.

such as alpha-1 antitrypsin deficiency, is linked to early-onset emphysema in nonsmokers (Hersh et al., 2011). Furthermore, because of decreased lung elasticity and weakened immunity, aging, inactivity, and poor nutrition are associated with a quicker rate of disease progression (Albarrati et al., 2020).

All of these risk factors work together to highlight COPD as a complex illness that is impacted by lifestyle, environmental, and genetic factors in addition to smoking cessation.

1.1.4. Diagnosis of COPD

1.1.4.1. Lung Function Tests

Spirometry is the most common noninvasive lung function test. Measurements of relevance for COPD include the amount of air that can be forced out of the lungs in one breath after maximal inspiration (i.e., volume of air that can be exhaled in one breath after maximal inspiration) (i.e.,the FEV1 and FEV1/FVC ratio are FEV1, FEV1, and FEV1/FVC ratio, respectively (Brusasco et al., 2015; Neder et al., 2020).

In case of COPD, the FEV1/FVC ratio is < 0.7.

Measurements of FEV1 and FEV1/FVC must also be taken following two short-acting bronchodilator puffs to perform reversibility testing, which helps distinguish between the traditional asthmatic presentations (i.e., frequently completely reversible airway blockage) and COPD (i.e., permanent blockage of airflow) (**Table 2**) (Boutou et al., 2013; Donohue, 2005; Johns et al., 2014; Tantucci & Modina, 2012).

Table 2. Illustration of Spirometry analysis parameters for COPD.

Severity	FEV_1	FEV_1/FVC
Mild	>80% predicted	<0.7
Moderate	50%-79% predicted	<0.7
Severe	30%-49% predicted	<0.7
Very severe	<30% predicted	<0.7

1.1.4.2. Bronchoalveolar Lavage Fluid (BLF) and Induced Sputum Test

Sputum samples and bronchoalveolar lavage fluid from COPD patients have higher neutrophil counts. However, people with asthma have higher levels of eosinophils. The BLF, lung parenchyma, and airways have five to ten times as many macrophages (Nguyen-Ho et al., 2025; Peng, 2020; Yu et al., 2023).

1.1.4.3. Arterial Blood Gas Test

The amount of oxygen in blood drawn from an artery is measured. The findings provide insight into the severity of COPD and the necessity of oxygen therapy (Castro, 2024).

1.1.5. Treatment of COPD

The goals of managing COPD are to lessen symptoms, enhance quality of life, and prevent exacerbations and disease progression. Policymakers and healthcare systems continue to pay little attention to COPD, despite it being a major global cause of morbidity and mortality. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that pharmacological and non-pharmacological interventions customized to each patient's needs are necessary for effective management (Hanania et al., 2005; Kahnert, 2023).

The main goals of pharmacological therapy are to reduce inflammation and airflow restriction. The mainstay of treatment is bronchodilators, which improve exercise tolerance and airflow. These include both short- and long-acting β_2-agonists and antimuscarinic medications. Although their impact on the course of the disease is still minimal, inhaled corticosteroids are advised for patients who have eosinophilic inflammation or frequent exacerbations. Due to the predominance of neutrophils, macrophages, and CD8 T cells, which are less sensitive to corticosteroids than eosinophil-dominant asthma inflammation, ICS use in COPD only partially responds (Barnes, 2002).

Combination therapy improves symptom control and lowers the frequency of exacerbations. It usually involves long-acting bronchodilators (LABA/LAMA) or LABA/ICS. For patients with severe COPD who have a history of exacerbations and chronic bronchitis, PDE4 inhibitors like roflumilast have become additional anti-inflammatory options. PDE4 inhibition improves lung function and lowers inflammation, but its use is restricted due to systemic and gastrointestinal side effects (Barjaktarevic & Milstone, 2020).

Smoking cessation, pulmonary rehabilitation, immunization, oxygen therapy, and nutritional support are examples of non-pharmacological tactics that are still crucial parts of all-encompassing care. While pulmonary rehabilitation improves physical ability and quality of life, quitting smoking is the only intervention that has been shown to slow the progression of the disease.

Overall, no available therapy completely stops the progression of the disease, even though current treatments improve symptoms and lessen exacerbations. In order to alter the underlying pathophysiology and enhance long-term results for patients with COPD, future strategies seek to combine precision medicine techniques, biomarker-guided treatment, and targeted anti-inflammatory drugs.

1.1.6. Recent Approach

Among the novel anti-inflammatory drugs under development, phosphodiesterase 4 (PDE4) inhibitors have demonstrated remarkable efficacy in reducing the responses of different inflammatory cells by increasing cyclic 3′,5′-adenosine monophosphate (cAMP) levels (Peter, 2005; Barnes & Stockley, 2022).

1.2. Phosphodiesterase Enzyme Superfamily

A promising class of anti-inflammatory drugs for the treatment of COPD is PDE4 inhibitors (**Table 3**). These substances increase intracellular cAMP signaling, which suppresses pro-inflammatory cytokines like TNF-α, IL-6, and IL-8 and promotes bronchodilation by specifically blocking PDE4, an enzyme that breaks down cyclic adenosine monophosphate (cAMP) (Torphy & Medicine, 1998). The only medication in this class that is currently approved is the oral PDE4 inhibitor roflumilast, which has been demonstrated to lower the frequency of exacerbations in patients with severe COPD linked to chronic bronchitis (Beasley et al., 2025). However, dose-limiting gastrointestinal and neuropsychiatric side effects limit its clinical use, requiring novel strategies like inhaled PDE4 inhibitors (e.g., CHF6001) as well as two PDE3/4 inhibitors (e.g., ensifentrine) to enhance tolerability and effectiveness (Maria Gabriella, 2021; Matera, 2020).

1.2.1. Structural Organization of PDEs

A catalytic domain, a long N-terminus that could have one or more structured domains, and an unstructured C-terminus are all present in every PDE (**Fig. 2.**) (Awrejcewicz, 2021; Brandao et al., 2022; Degerman, 1997).

The structured areas in PDEs' N-termini serve a variety of purposes. The GAF domains have been demonstrated to bind the cyclic nucleotides cAMP and cGMP, modulate PDE activity, and participate in PDE dimerization (Keravis & Lugnier, 2012;

Manganiello, 1999). The distinct substrate binding and dimerization functions of the GAF domains in each case are influenced by variations in the GAF-A and GAF-B domains of PDE2, PDE5, PDE6, PDE10, and PDE11 (Boswell-Smith, 2006; Francis et al., 2011). Crystallography has demonstrated direct contact between UCR and inhibitors attached to the PDE4B active sites, and the UCR domains control PDE4 activity, and PDE4D (PDB IDs: 3IAD, 3G4G, and 3G45) and 4WZI and 4X0F (Schultz & implications, 2009).

When compared to the canonical sequence, the PDE sequence is either truncated or differs due to multiple isoforms (caused by splice variants) of the PDE genes. The unstructured carboxy-terminal region or the amino-terminal region, where one or more structured domains may be missing, are where the truncations usually occur. Isomers lacking a catalytic domain will not function, and variations in the catalytic domain's sequence are not visible. The localization and activation mechanism of a PDE can also be impacted by sequence variations or truncation of amino-terminal domains, and it is of interest for drug discovery to develop inhibitors that are selective for particular isoforms (Bolger, 2021; Lorigo, 2021).

1.2.2. Phosphodiesterases 4

The most common cAMP-degrading enzyme expressed in inflammatory cells is PDE4, which is a phosphodiesterase. The PDE4 family includes 4 genes (PDE4A to D) with a unique chromosomal location per gene (Richter & Conti, 2004). Multiple splice variants are reported and categorized into two primary groups, the long and short forms, as a result of alternative splicing of the genes. Each subtype offers a conserved catalytic domain of about 270 amino acids, as well as two extra regions in the N-terminus called UCR1 (Upstream Conserved Region) and UCR2, which are either absent or present in the short and long forms, respectively (Russo, 1987). PDE4A, PDE4B, and PDE4D gene products are present in the majority of inflammatory and immune cells (Cheng et al., 1995; Wilhem, 1995).

1.2.2.1. Mechanism of PDE4 Action

Table 3. The Phosphodiesterases superfamily.

PDE Isoen-zyme	Number of Isoform	Substrate
PDE1	08	Ca2+/calmodulin Stimulated
PDE 2		cGMP-stimulated
PDE 3	04	cGMP-inhibited, cAMP-selective
PDE 4	20	cAMP-specific
PDE 5	03	cGMP-specific
PDE 6		cGMP-specific
PDE 7	03	cAMP-specific, high-affinity
PDE 8		cAMP-selective,
PDE 9 PDE 10 PDE 11	04 02 04	cGMP-sensitive, cAMP-selective, cGMP-specific cGMP-sensitive, dual specificity

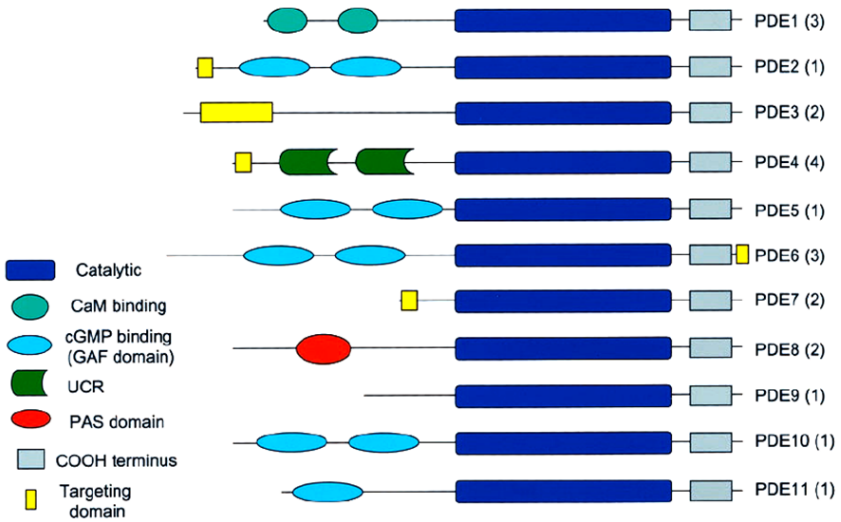


Fig. 2. Schematic representation of the structural domains of the 11 phosphodiesterase (PDE) families. Each PDE family possesses a conserved C-terminal catalytic domain (blue) and variable N-terminal regulatory domains, which contribute to functional diversity. Domain types include calmodulin (CaM)-binding (green), cGMP-binding GAF domains (cyan), upstream conserved regions (UCR, dark green), PAS domains (red), C-terminal extensions (grey), and targeting domains (yellow). The numbers in parentheses indicate the number of known gene isoforms in each PDE family.

In inflammatory cells, cAMP functions as a negative regulator of the main activating pathways, including T-cell cytokine release. Alternatively, cAMP-specific PDE isozymes control cAMP levels; PDE4 is primarily expressed in immune and inflammatory cells. These cells' PDE4 is effectively inhibited to raise intracellular cAMP levels, which in turn trigger particular protein phosphorylation cascades that produce a range of functional responses. This in turn prevents immune cells from activating anti-inflammatory mediators like IL-10 and releasing inflammatory mediators like cytokines like tumor necrosis factor-R (TNF-R), interleukin-2 (IL-2), interleukin-12 (IL-12), leukotriene B4 (LTB4), and interferon-γ (IFN-γa). It has been a major pharmaceutical focus to develop PDE4 inhibitors as therapeutic agents because cellular mediators are important in inflammatory diseases like asthma and COPD (as well as rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, and multiple sclerosis). Furthermore, bronchodilation, which is advantageous for the treatment of respiratory conditions like COPD, was brought about by the augmentation of intracellular cAMP levels through the inhibition of PDE4 activity (Kim et al., 2021; Schafer & Day, 2013).

1.2.2.2. PDE4 Inhibitors

First and Second generation PDE4 inhibitors - Preclinical research using first-generation compounds that selectively inhibit PDE4 and are typified by archetypal rolipram has shown remarkable efficacy in animal models of pulmonary inflammation. However, it was discovered that these drugs were linked to serious class-related adverse effects, including nausea, vomiting, and gastric acid production, which were brought on by the inhibition of PDE4 in the parietal glands and the Central Nervous System (CNS), respectively. These results made the creation of PDE4 inhibitors with a better therapeutic ratio necessary (Giembycz, 1992; Hatzelmann, 2001; Torphy & Medicine, 1998).

Cilomilast and roflumilast, the most clinically developed selective PDE4 inhibitors, have a better side effect profile than theophylline and first-generation drugs. Knowing that PDE4 exists in two different conformations, low-affinity rolipram-binding PDE4 (LPDE4; which predominates in immunocompetent cells) and high-affinity rolipram-binding PDE4 (HPDE4; which predominates in the parietal glands and CNS) these compounds were created. Second-generation drugs (like cilomilast) mainly target LPDE4, which improves the therapeutic index, in contrast to rolipram, which targets HPDE4. However, Roflumilast was approved in 2013 for the treatment of COPD, while Cilomilast failed in phase III clinical trials. However, it also has adverse effects,such asan upset stomach. Cilomilast and Roflumilast are PDE4D inhibitors that selectively block the enzyme. According to certain reports, selective PDE4B inhibition reduces inflammation while selective PDE4D inhibition induces vomiting (Barnette et al., 1998; Blauvelt et al., 2023; Montana & Dyke, 2002; Torphy & Medicine, 1998).

Therefore, the creation of novel compounds that are selective for a single subtype is one of the recent strategies that are typically used to obtain strong and selective inhibitors with an enhanced therapeutic index.

2. Methods of Literature Retrieval

This review aims to give a thorough assessment of PDE4 inhibitors in the treatment of COPD by looking at their pharmacological development, clinical results, and mechanistic justification. This paper highlights the developments, constraints, and prospects for PDE4-targeted drug development by combining results from preclinical, clinical, and computational studies published between 1977 and 2025. Emerging approaches that may improve the accuracy and therapeutic impact of PDE4 inhibitors in the treatment of COPD, such as isoform-selective inhibition, pulmonary delivery systems, and biomarker-guided patient selection, are given particular attention.

3. Review of Literature

The development of PDE4 inhibitors for COPD has progressed in distinct phases. Early first-generation compounds demonstrated strong efficacy but were limited by adverse effects. This led to the design of second-generation inhibitors with improved tolerability, followed by next-generation approaches aiming for subtype selectivity and reduced side effects. In addition, computational and structural studies have provided key insights into inhibitor design. The literature is therefore reviewed below in four categories: first-generation, second-generation, next-generation/subtype-selective inhibitors, and computational/structural studies.

3.1. First and Second Generation PDE4 Inhibitors

PDE4 inhibitor development has gone through several stages characterized by tolerability, selectivity, and potency optimization. The proof-of-concept that PDE4 inhibition could reduce inflammation by raising intracellular cyclic adenosine monophosphate (cAMP) and lowering pro-inflammatory cytokines like TNF-α, IL-8, and leukotrienes was established by the first-generation inhibitors, such as rolipram (Hatzelmann et al., 2001; Torphy & Medicine, 1998). Early research showed that rolipram and its analogues had strong anti-inflammatory effects in animal models of airway disease; however, dose-dependent side effects, such as nausea, vomiting, and gastric hypersecretion, which were primarily linked to PDE4 inhibition in the gastrointestinal tract and central nervous system, limited the drug's clinical utility (Giembycz et al., 1992).

Several first-generation analogues, including triarylethane derivatives, indan-1,3-dione derivatives, indole N-oxide, and phthalazine analogues, were created in order to get around these restrictions and increase safety and selectivity. These analogues had altered physicochemical characteristics intended to reduce penetration into the CNS, hence lowering the risk of emesis, while still having the anti-inflammatory effectiveness of rolipram (Alexander et al., 2002; Michael et al., 1994; Barnette et al., 1998; Blauvelt et al., 2023; Burnouf & Pruniaux, 2002; Crocetti et al., 2022; He et al., 1998; Hulme et al., 1998). Catechol or methoxy substituents play a crucial role in improving binding affinity to the PDE4 catalytic site while affecting lipophilicity and tolerability profiles, according to structure-activity relationship (SAR) studies. The majority of these early compounds failed to advance despite encouraging preclinical results because of insufficient therapeutic windows and metabolic instability.

Wei et al. (1998) synthesized a novel series of 2,2-disubstituted indan-1,3-dione-based PDE4 inhibitors. On evaluation, they found that several analogues were non-emetic in the canine emesis model, unlike the classical PDE4 inhibitors (He et al., 1998). Prioritized the compounds and, through a focused synthesis campaign, developed compounds 12a and 12b. These both showed striking anti-inflammatory activity (**Fig. 12.**) (Revelant et al., 2014).

Hulme et al. (1998) described the synthesis and *in vitro* and *in vivo* evaluation of a novel series of indole N-oxide PDE4 inhibitors. These showed excellent *in vivo* activity for inhibition of TNF-α levels in LPS-challenged mice (**Fig. 3**.).

Napoletanoet al. (2000) described the synthesis and *in vitro* evaluation of a novel series of Phthalazine PDE4 inhibitors. Though the compounds represented conformationally constrained analogues of Piclimilast and RP 73401, some showed reduced side effects (**Fig. 4**) (Michael et al., 1994).

Giembyczet al. (2001) reviewed Cilomilast, a second-generation PDE4 inhibitor for treatment of asthma and COPD (**Fig. 5**.).

Alexander et al. (2002), the discovery, synthesis, and biological activity of a series of triarylethane PDE4 inhibitors. SAR studies for compound CDP840 were also presented. This compound was found to be non-emetic (**Fig. 6.**).

Burnouf et al. (2002) highlighted recent data of the most advanced clinical candidates and SAR relationships of the recent structural series reported.

Kim et al. (2003) synthesized and performed SAR analysis of a new series of catechol hydrazines for developing an effective PDE4 inhibitor as an anti-asthmatic. These compounds showed a significantly improved Rolipram binding profile compared with Rolipram, a prototype PDE4 inhibitor.

Better pharmacokinetics, increased selectivity for the low-affinity rolipram-binding site (LPDE4), and fewer central side effects were the hallmarks of the second-generation PDE4 inhibitors. The two most clinically developed of these were roflumilast (Daxas) and cilomilast (Ariflo) (Xu et al., 2000). By specifically blocking PDE4D isoforms, clomilast showed enhanced gastrointestinal tolerability and strong anti-inflammatory activity; however, phase III trials did not yield enough results. On the other hand, severe COPD linked to chronic bronchitis and frequent exacerbations can be treated with roflumilast, a selective PDE4 inhibitor with a longer half-life and higher potency (Blackburn-Munro, 2004; Manallack, 2005; McIntyre et al., 2004).

Roflumilast inhibits the release of cytokines and chemokines like TNF-α, IL-8, and leukotriene B4 by increasing intracellular cAMP levels in inflammatory and structural lung cells. Although roflumilast has been shown in clinical trials to improve FEV_1, decrease the frequency of exacerbations, and reduce systemic inflammation, its widespread use is limited by side effects like weight loss, insomnia, and gastrointestinal disturbances (Katharine, 2009; Hara-Yokoyama, 2013).

In order to increase potency and selectivity, second-generation compounds incorporate heterocyclic scaffolds such as pyridinecarboxamides, aminophthalic acids, and thiadiazolecarboxylic acids, which interact with the conserved glutamine residue (Gln369) within the PDE4 catalytic pocket through hydrogen bonding. The mechanistic basis of inhibitor binding has also been revealed by crystallographic analyses of PDE4B2B and PDE4D catalytic domains, providing a foundation for subsequent isoform-selective and inhalable PDE4 inhibitors.

Hassell et al. (2000) determined three three-dimensional structures of the catalytic domain of phosphodiesterase 4B2B to 1.77Å resolution.They suggested the mechanism of action and basis for specificity of inhibitors (**Fig. 7**.).

Ochiaiet al. (2004) designed and synthesized hydrophilic analogues based on the hypothesis that dose-limiting side effects of PDE4 inhibitors are mediated via the CNS. These piperidine derivatives were found to possess improved therapeutic potential (**Fig. 8.**).

McIntyreet al. (2004) established that Tetomilast inhibits superoxide production by human neutrophils and also has PDE4 inhibitory activity. Thus, it can be used in the treatment of ulcerative colitis and COPD (**Fig. 9.**).

Vignola et al. (2004) reviewed selective PDE4 inhibitors as a therapeutic advance in the treatment of COPD, due to their novel mechanism of action and potent anti-inflammatory effects coupled with a good safety and tolerability profile.

Manallacket al. (2005) summarized the available crystal structures of the PDEs and, in doing so, presented a detailed description of the PDE active site (**Fig. 10.**).

Athanazioet al. (2012) highlighted the similarities and differences between asthma, COPD, and bronchiectasis in terms of the risk factors, pathophysiology, symptoms, diagnosis, and treatment.

Fig. 3–10 collectively illustrate representative first- and second-generation PDE4 inhibitor scaffolds, their key structure–activity relationships, and the crystal architecture of the PDE4 catalytic site.

Understanding the therapeutic potential and difficulties of PDE4 inhibition in inflammatory airway diseases was made possible by the combined efforts of first- and second-generation inhibitors. The need for isoform-selective, dual-target, and inhaled PDE4 inhibitors is being investigated in next-generation designs, despite the fact that early compounds showed pharmacological promise. Adverse effect profiles and limited efficacy highlighted this need.

3.2. Next Generation PDE4 Inhibitors (selectivity, isoform targeting, multi-target approaches)

Next-generation inhibitors were created with improved PDE4B selectivity, dual PDE3/4 activity, and inhalable delivery to reduce systemic exposure, building on previous limitations (Banner Press, 2009; Brullo et al., 2015; Hagen et al., 2014; Yanagishita, et al., 2013; Jansen et al., 2016; Revelant et al., 2014). Triazine, triazole, and fluoropyridinyl scaffolds optimized binding to the conserved Gln369 residue within the catalytic domain, while compounds like CHF6001 and ensifentrine showed strong local anti-inflammatory and bronchodilatory efficacy with improved safety profiles in clinical trials. These design advancements signal a move toward phenotype-specific COPD treatment and precision pharmacology.

Banner et al. (2009) suggested that combined inhibition of PDE3 and PDE4 inhibitors has additive and synergistic anti-inflammatory and bronchodilator effects versus inhibition of either PDE3 or PDE4 alone. Given that synergy has been seen in terms of efficacy endpoints, an obvious concern is that synergy may also be observed in side effects. Interestingly, however, no synergy or additive effects with a combination of a PDE3 and PDE4 inhibitor in a cardiomyocyte assay were observed. Inhibition of PDE3 and PDE4 isoenzymes is advantageous in comparison with selective inhibition of the PDE4 isoenzyme (Banner et al., 2009).

Reddy et al. (2013) synthesized several novel imidazophenoxazine-4-sulfonamides as potential inhibitors of PDE4 (**Fig. 11**) (Yanagishita, et al., 2013). Savi et al. (2014) performed rational lead optimization and built a Free-Wilson model to predict PDE4 potency. Using this model and human protein binding predictions, they Hagen et al. (2014) reported a series of structure-activity relationships that demonstrated the triazine core can be used to generate subtype-selective inhibitors of PDE4B versus PDE4D (**Fig. 13**.) (Hagen et al., 2014).

Jansen et al. (2015) presented a comparative analysis of crystal structures across the PDE superfamily and provided a comprehensive structure-based PDE–ligand interaction map that highlighted conserved and PDE subtype-specific interactions in the PDEStrI An database.

Brulloet al. (2015) designed selective PDE4D inhibitors and have synthesized them, replacing the 3-methoxy group with a 3-difluoromethoxy isoster moiety in catecholic structures given below (**Fig. 14**.). Fig. 11–14. depict representative next-generation PDE4 scaffolds, structure–activity models, and subtype-selective binding interactions.

3.3. Combinatorial / Docking & Computational Approaches

By elucidating active-site geometry and isoform-specific interactions, computational research and molecular docking have significantly aided rational PDE4 inhibitor desig. The binding conformations of rolipram and related inhibitors within the PDE4

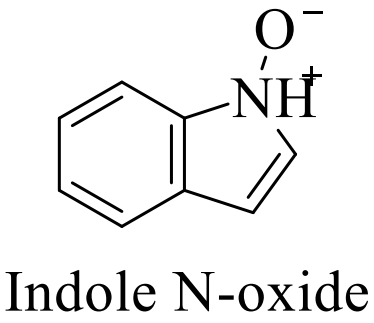


Fig. 3. Indole N-oxide.

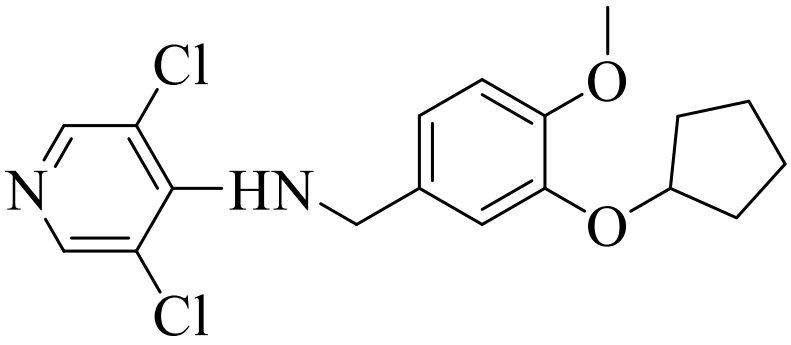


Fig. 4. (4S,4aS,5aS,6S,12aS)-7-Chloro-4-(dimethylamino)-1,10,11,12a-tetrahydroxy-6-methyl-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide.

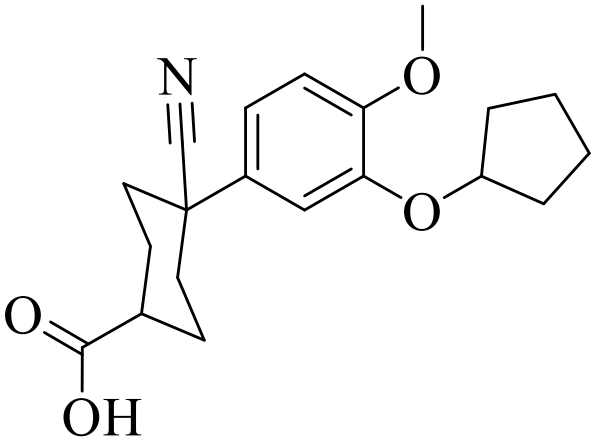


Fig. 5. Hydroxynicotinic acid (hydroxy-pyridinecarboxylic acid).

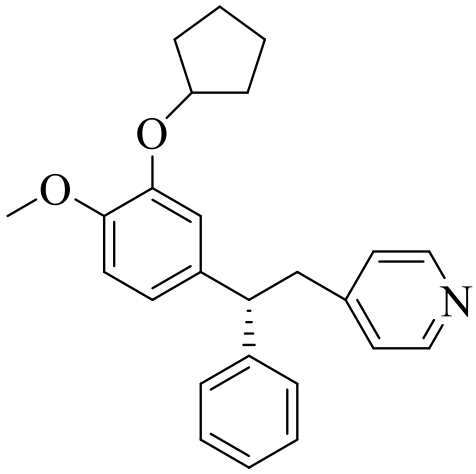


Fig. 6. Triarylethane derivatives.

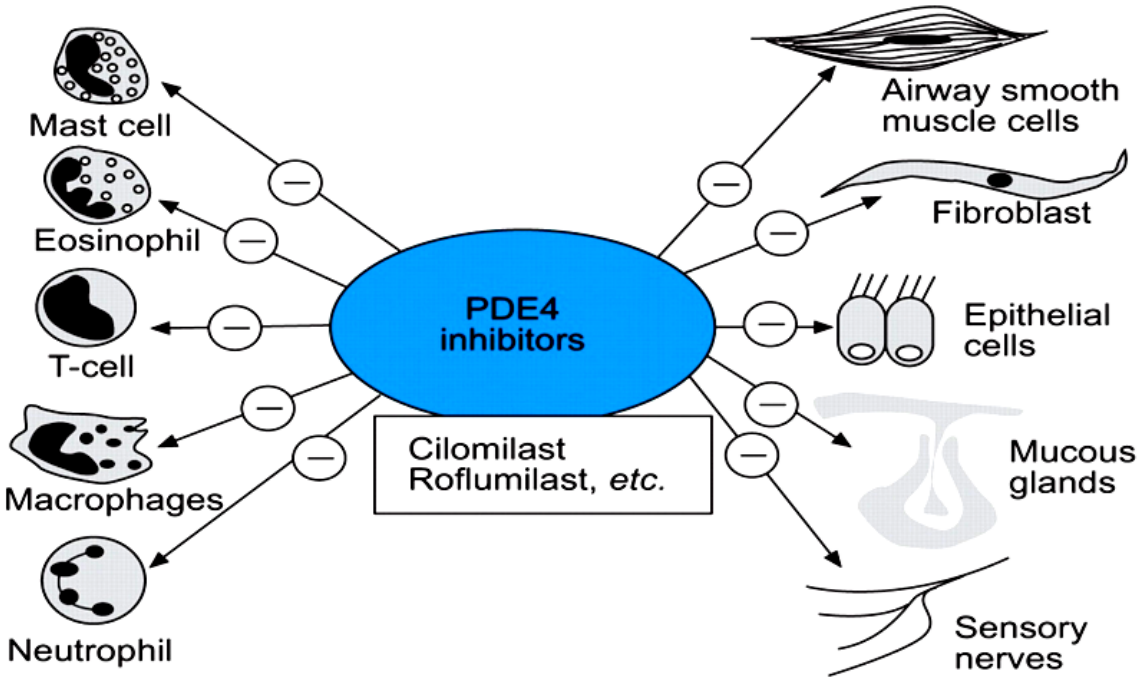


Fig. 7. Mechanism of phosphodiesterase-4.

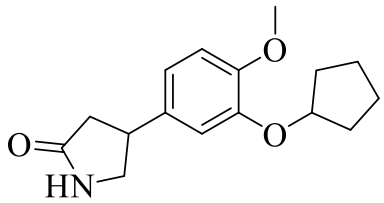


Fig. 8. Aminophthalic acid (aminobenzenedicarboxylic acid).

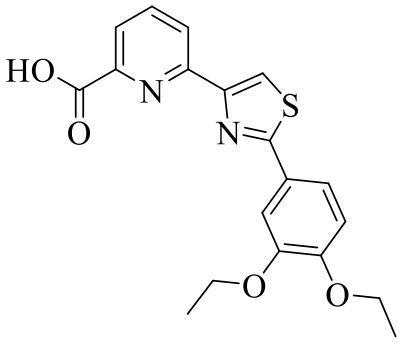


Fig. 9. Hydroxy-thiadiazolecarboxylic acid.

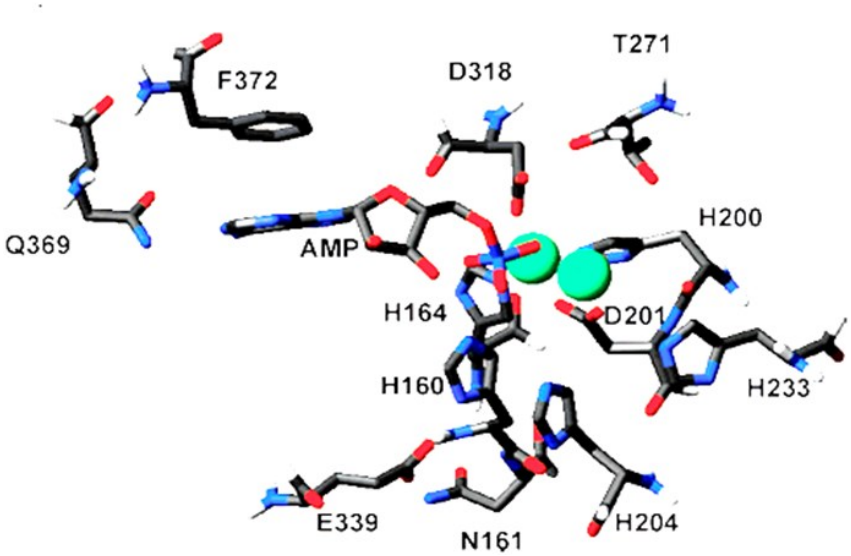


Fig. 10. Active site architecture of the enzyme showing AMP binding and coordinating residues.

catalytic pocket were predicted using programs like LigandFit and AutoDock/Vina, which identified important residues like Gln369 and Phe372 that are essential for hydrophobic stacking and hydrogen bonding. Nevertheless, the rigidity of crystal structures, insufficient solvent modeling, and the uneven relationship between docking scores and biological potency limit these in-silico methods (Mpamhanga et al., 2005). Therefore, docking is still a useful screening method, but it needs to be supported by experimental validation.

Xenarios et al. (2001) performed molecular docking studies and presented a model configuration for PDE4 substrate and PDE4-specific inhibitor (Rolipram) within the active site of the enzyme (**Fig. 15**.) .

Bonaccini et al. (2005) performed a comparative analysis on the alignment modes obtained with two (direct and indirect) approaches to compare the two virtual binding sites with the corresponding area of the actual 3D structure of the enzyme. The results obtained confirmed the ability of the FIGO procedure in 3D QSAR analysis (Gratteri et al., 2005).

Mpamhangaet al. (2005) evaluated the effectiveness of five scoring functions (PMF, JAIN, PLP2, LigScore2, and DockScore) through consideration of the success in enriching the top-ranked fractions of nine artificial databases, constructed by seeding 1980 inactive ligands (pIC50 < 5) with 20 randomly selected inhibitors (pIC50 > 6.5). The authors finally recommended LigandFit/DockScore for multiple docking into several versions of the protein.

Azam et al. (2013) explored the feasibility of four different docking approaches (AutoDock/Vina, GOLD, FRED, and FlexX) for the target ASMT (N-Acetylserotonin O-methyltransferase) to find out the lead compound. These results suggested that AutoDock/Vina

consistently outperformed other programs and was found to be relatively more useful in blind docking pose prediction (**Table 4**).

The literature on PDE4 inhibitors spans from early, poorly tolerated compounds like rolipram to clinically approved drugs such as roflumilast, and now to next-generation subtype-selective inhibitors under development. Computational and structural biology studies have complemented this evolution, providing the molecular basis for the rational design of safer and more effective agents.

4. Discussion

The developmental history of PDE4 inhibitors in COPD shows both scientific promise and clinical frustration in the development of anti -inflammatory drugs. A strong theoretical basis for PDE4 inhibition is provided by increasing intracellular cyclic adenosine monophosphate (cAMP) levels, which attenuate the release of inflammatory mediators, reduce neutrophilic activation, and promote bronchodilation (Hatzelmann et al., 2001; Torphy & Medicine, 1998). However, it has proven difficult to convert these molecular effects into long-term clinical advantages.

Although early first-generation PDE4 inhibitors, like rolipram and its analogues, demonstrated proof-of-concept for cAMP-mediated anti-inflammatory action, their limited therapeutic indices and poor tolerability severely limited their potential. Despite strong preclinical efficacy, their non-selective inhibition of PDE4 isoforms especially PDE4D in the central nervous system caused severe nausea, vomiting, and gastric disturbances, effectively stopping clinical advancement (Barnette et al., 1998; Blauvelt et al., 2023; Crocetti et al., 2022; Giembycz et al., 1992; Montana & Dyke, 2002; Torphy & Medicine, 1998). These restrictions highlighted the need for peripheral restriction and isoform selectivity, which fueled the development of later generations of PDE4 inhibitors. Second-generation medications like cilomilast (SB-207499) and roflumilast (Daxas®) were created to increase the therapeutic ratio (Giembycz, 2001; Xu et al., 2000). In Phase III trials, cilomilast showed improved gastrointestinal tolerability but no discernible clinical benefit (Barnette et al., 1998). On the other hand, because of a slight improvement in lung function and a decrease in the frequency of exacerbations, roflumilast was approved for severe COPD with chronic bronchitis (Katharine, 2009; Blackburn-Munro, 2004; McIntyre et al., 2004). However, side effects like gastrointestinal distress, sleeplessness, and weight loss still prevent it from being widely used (Katharine , 2009; Hara-Yokoyama, 2013). These findings show that despite the robust mechanistic foundation of PDE4 inhibition, patient tolerability and disease heterogeneity continue to be significant obstacles to clinical success.

Recent research have concentrated on dual-target mechanisms, inhaled formulations, and next-generation PDE4 inhibitors with enhanced selectivity. Phase III ENHANCE trials have shown promising results for compounds such as ensifentrine (dual PDE3/4 inhibitor) and CHF6001 (inhaled PDE4 inhibitor), which exhibit local anti-inflammatory activity and synergistic bronchodilation with minimal systemic exposure (Calzetta et al., 2020; De Savi et al., 2014; Ferguson et al., 2018). These developments point to a slow but significant move toward precision-oriented, phenotype-specific COPD treatment.

Similar to this, docking and computational methods have revealed conserved residues like Gln369 involved in inhibitor binding, providing important structural insights into PDE4 catalytic pockets (Dym et al., 2002; Gratteri et al., 2005; Mpamhanga et al., 2005; Xu et al., 2000). Nevertheless, these computational approaches are constrained by reliance on crystal structures that are readily available, rigid-body assumptions that overlook protein flexibility, and the inadequate conversion of in-silico affinity scores to in-vivo pharmacodynamics (Azam et al., 2013; Gratteri et al., 2005; Mpamhanga et al., 2005). Therefore, even though molecular docking has been crucial for developing hypotheses and prioritizing scaffolds, it is still a supplement to experimental validation rather than its replacement.

Despite these developments, a number of enduring issues continue to shape the PDE4 inhibitor therapeutic landscape. First, "one-size-fits-all" strategies are ineffective due to the multifactorial and heterogeneous nature of COPD, which has a variety of inflammatory endotypes (neutrophilic, eosinophilic, or mixed) (Barnes, 2019; Barnes & Immunology, 2016). Second, the absence of trustworthy biomarkers to identify PDE4-responsive patients dilutes clinical efficacy signals. Third, there is still a dearth of long-term safety information for inhaled PDE4 inhibitors, especially with regard to local tolerance and systemic absorption. Lastly, the inherent limitations of PDE4 inhibition in disease modification are unlikely to be overcome by incremental potency gains alone.

In order to improve therapeutic relevance, lung-retentive formulations, isoform-selective PDE4B inhibitors, and biomarker-guided patient stratification are essential next steps (Brüssow, 2025; Matera et al., 2020). PDE4 inhibitors may improve anti-inflammatory synergy when combined with long-acting bronchodilators, corticosteroids, or biologics, and advances in computational modeling and structure-based drug design may make it easier to create molecules that are -inflammatory drugs for COPD that are clinically limited but mechanistically well-established. The mechanistic validity of cAMP elevation was confirmed by early studies using first-generation compounds like rolipram, which showed strong suppression of TNF-α and IL-8 release in airway inflammation models. However, intolerable nausea and vomiting caused by PDE4D inhibition in the central nervous system hampered clinical progress. Improved isoform selectivity and tolerability were attained by second-generation medications, such as cilomilast (SB-207499) and roflumilast (Daxas®). In Phase III trials, roflumilast produced statistically significant improvements in FEV_1 (40–80 mL increase) and decreased exacerbation frequency by 17–23% in patients with COPD associated with chronic bronchitis. More recently, dual-target and inhaled PDE inhibitors like ensifentrine and CHF6001 have shown encouraging results in preliminary clinical trials, exhibiting strong local anti-inflammatory activity, enhanced lung function, and few systemic side effects. Critical residues like Gln369 within the catalytic site of PDE4B and PDE4D were further identified by crystallographic and computational investigations, directing structure-based optimization toward isoform-selective compounds. Despite these developments, there are still a number of significant research gaps, including the lack of large-scale, long-term clinical trials verifying sustained efficacy and safety; the lack of accurate biomarkers to predict therapeutic response; the scarcity of long-term data on inhaled PDE4 inhibitors; and the insufficient investigation of synergistic combinations with corticosteroids, biologics, or dual PDE3/4 inhibitors. PDE4 inhibitors could become precision-based, disease-modifying treatments for COPD if these drawbacks are addressed through biomarker-guided clinical trials, mechanistic research, and computationally driven drug design.

specific to certain subtypes and tissues. In the end, the creation of PDE4 inhibitors for COPD exemplifies a more general reality in respiratory medication: clinical impact is not always ensured by biological plausibility. PDE4-targeted therapy's future hinges on balancing practical efficacy with solid mechanistic justification, with a focus on tolerability, accuracy, and customization. PDE4 inhibitors can only progress from adjuncts to truly disease-modifying treatments for COPD by filling in these translational gaps. Recent research have concentrated on dual-target mechanisms, inhaled formulations, and next-generation PDE4 inhibitors with enhanced selectivity.

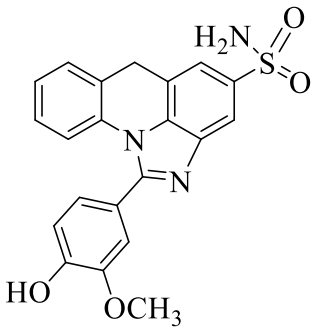
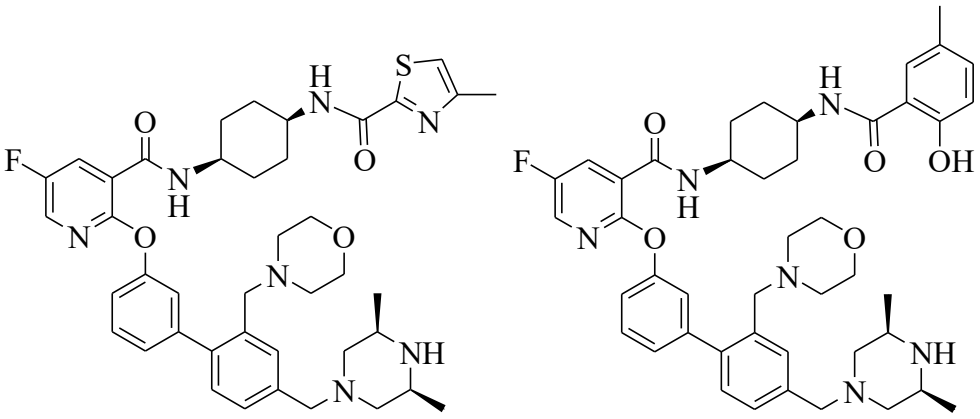


Fig. 11. Hydroxy-methoxy-1,2,3-triazole sulfonamide derivative.



a b

Fig. 12. (a), Fluoropyridinyl-triazolyl-thiadiazole urea derivative **(b),** Fluoropyridinyl-triazolyl-carboxamide urea derivative.

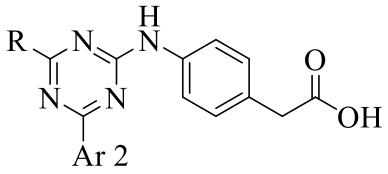


Fig.13. 1, 2, 4-Triazole-3-carboxamide-4-carboxylic acid derivative.

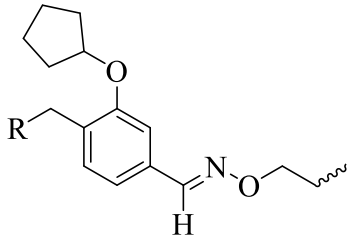


Fig.14. 2-Pyrrolidone (γ-lactam).

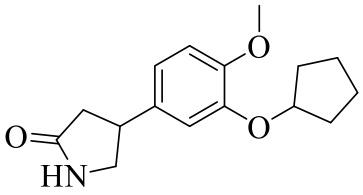


Fig. 15. N-(4-hydroxyphenyl) acetamide.

Table 4. Chronological overview of major advances in phosphodiesterase-4 inhibitor research.

Author(s), Year	Key Contribution	Strategy / Scaffold	Category
Wei et al., 1998	Synthesized non-emetic indan-1,3-dione inhibitors	Indan-dione scaffold	First-generation
Hulme et al., 1998	Indole N-oxide PDE4 inhibitors (TNF-α inhibition)	Indole N-oxide	First-generation
Napoletano et al., 2000	Phthalazine analogues of piclimilast with reduced side effects	Phthalazine scaffold	First-generation
Giembycz et al., 2001	Review of cilomilast (2nd-generation PDE4 inhibitor)	Hydroxynicotinic acid	Second-generation
Alexander et al., 2002	Triarylethane PDE4 inhibitors (CDP840)	Triarylethane scaffold	First-generation
Burnouf et al., 2002	SAR of advanced PDE4 clinical candidates	Structural series	Second-generation
Kim et al., 2003	Catechol hydrazines with improved rolipram binding	Catechol hydrazines	First-generation
Hassell et al., 2000	Crystal structure of PDE4B2B catalytic domain	Structural mechanism	Second-generation
Ochiai et al., 2004	Hydrophilic analogues to reduce CNS side effects	Piperidine derivatives	Second-generation
McIntyre et al., 2004	Tetomilast inhibits superoxide production	Thiadiazolecarboxylic acid	Second-generation
Vignola et al., 2004	Review of selective PDE4 inhibitors in COPD	Clinical advance	Second-generation
Manallack et al., 2005	PDE crystal structures and ligand mapping	Structural biology	Second-generation
Banner et al., 2009	Combined PDE3/PDE4 inhibition synergy	Dual inhibition	Next-generation
Reddy et al., 2013	Imidazophenoxazine-4-sulfonamides synthesis	Triazole sulfonamides	Next-generation
Savi et al., 2014	Free-Wilson model guided synthesis (compounds 12a, 12b)	Fluoropyridinyl-triazole derivatives	Next-generation
Hagen et al., 2014	Triazine core selective for PDE4B vs PDE4D	Triazine derivatives	Next-generation
Jansen et al., 2016	PDEStrIAn database for PDE–ligand interaction	Structure-based design	Next-generation
Brullo et al., 2015	Fluorinated PDE4D inhibitors with better pharmacokinetics	Catechol derivatives	Next-generation
Xenarios et al., 2002	Docking study with rolipram in the PDE4 active site	Computational docking	Docking/ computational
Bonaccini et al., 2005	FIGO docking validation procedure	Virtual binding alignment	Docking/ computational
Mpamhanga et al., 2005	Evaluation of multiple docking scoring functions	LigandFit/DockScore	Docking/ computational
Azam et al., 2013	Comparison of four docking routines (Vina best)	Docking benchmarking	Docking/ computational

5. Conclusion

Phosphodiesterase-4 (PDE4) inhibitors continue to be a class of anti inflammatory drugs for COPD that are clinically limited but mechanistically well-established. The mechanistic validity of cAMP elevation was confirmed by early studies using first-generation compounds like rolipram, which showed strong suppression of TNF -α and IL-8 release in airway inflammation models. However, intolerable nausea and vomiting caused by PDE4D inhibition in the central nervous system hampered clinical progress. Improved

isoform selectivity and tolerability were attained by second-generation medications, such as cilomilast (SB-207499) and roflumilast (Daxas®). In Phase III trials, roflumilast produced statistically significant improvements in FEV_1 (40–80 mL increase) and decreased exacerbation frequency by 17–23% in patients with COPD associated with chronic bronchitis. More recently, dual-target and inhaled PDE inhibitors like ensifentrine and CHF6001 have shown encouraging results in preliminary clinical trials, exhibiting strong local anti-inflammatory activity, enhanced lung function, and few systemic side effects. Critical residues like Gln369 within the catalytic site of PDE4B and PDE4D were further identified by crystallographic and computational investigations, directing structure-based optimization toward isoform-selective compounds. Despite these developments, there are still a number of significant research gaps, including the lack of large-scale, long-term clinical trials verifying sustained efficacy and safety; the lack of accurate biomarkers to predict therapeutic response; the scarcity of long-term data on inhaled PDE4 inhibitors; and the insufficient investigation of synergistic combinations with corticosteroids, biologics, or dual PDE3/4 inhibitors. PDE4 inhibitors could become precision-based, disease-modifying treatments for COPD if these drawbacks are addressed through biomarker-guided clinical trials, isoform-targeted mechanistic research, and computationally driven drug design.

List of Abbreviations

Abbreviation	Full Form
AD	Alzheimer's Disease
AMP	Adenosine Monophosphate
ATP	Adenosine Triphosphate
BLF	Bronchoalveolar Lavage Fluid
cAMP	Cyclic Adenosine Monophosphate
cGMP	Cyclic Guanosine Monophosphate
CD	Cluster of Differentiation
COPD	Chronic Obstructive Pulmonary Disease
CNS	Central Nervous System
DNA	Deoxyribonucleic Acid
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GBD	Global Burden of Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HPDE4	High-Affinity Rolipram-Binding Phosphodiesterase-4
ICS	Inhaled Corticosteroids
IFN-γ	Interferon-Gamma
IL	Interleukin
LABA	Long-Acting $Beta_2$-Adrenergic Agonist
LAMA	Long-Acting Muscarinic Antagonist
LAM	Long-Acting Muscarinic
LPS	Lipopolysaccharide
LPDE4	Low-Affinity Rolipram-Binding Phosphodiesterase-4
LMICs	Low- and Middle-Income Countries
LTB_4	Leukotriene B_4
MCP-1	Monocyte Chemoattractant Protein-1
mRNA	Messenger Ribonucleic Acid
PAS	Per-Arnt-Sim Domain
PDE	Phosphodiesterase
PDE4	Phosphodiesterase-4
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SAR	Structure–Activity Relationship
SPSS	Statistical Package for the Social Sciences
TNF-α	Tumor Necrosis Factor-Alpha
UCR	Upstream Conserved Region
UC	Ulcerative Colitis
WHO	World Health Organization

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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