Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 2, Issue 11, November 2026
Website: usajournals.org
This work is Licensed under CC BY 4.0 a Creative Commons Attribution 4.0 International License.

REGULATORY MECHANISMS OF THE PDE4B ENZYME AND THEIR SIGNIFICANCE FOR THE DEVELOPMENT OF SELECTIVE ANTI-INFLAMMATORY DRUGS

Suyarova Gulandom Sirliboevna
Assistant, Department of Pharmacology
Tashkent State Medical University
Email: gulisuyarova60@mail.ru

Sattarova Dilrabo Numon qizi
Assistant, Department of Pharmacy and Pharmaceutical Technology
Zarmed University,

Jalilov Utkirbek Mamaraximovich
Department of Technology of Dosage Forms, Associate Professor (PhD)
Tashkent Pharmaceutical Institute

Tuxtasheva Visola Farmonova
Assistant (PhD), Department of Pharmacy and Pharmaceutical Technology
Zarmed University

Abstract
This article analyzes the molecular structure and regulatory mechanisms of the phosphodiesterase-4B (PDE4B) enzyme, as well as its role in inflammation. Experimental data concerning the C-terminal CR3 region and the selectivity of the inhibitor A-33 are reviewed. The need for further research to confirm the clinical advantages of PDE4B-targeted inhibitors is substantiated.

Keywords: phosphodiesterase-4B, cyclic adenosine monophosphate, selective inhibitors, inflammation, CR3, A-33.

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 2, Issue 11, November 2026
Website: usajournals.org
This work is Licensed under CC BY 4.0 a Creative Commons Attribution 4.0 International License.

PDE4B FERMENTINING REGULYATOR MEXANIZMLARI VA SELEKTIV YALLIG‘LANISHGA QARSHI DORI VOSITALARINI YARATISHDAGI AHAMIYATI

Suyarova Gulandom Sirliboyevna
Toshkent Davlat Tibbiyot universiteti
“Farmakalogiya kafedrasi” assistenti
Email: gulisuyarova60@mail.ru

Sattarova Dilrabo Numon qizi
Zarmed University, Farmatsiya va farmasevtik texnologiya kafedrasi assistenti,

Jalilov Utkirbek Mamaraximovich
Тошкент Фармацевтика институт Дори турлари технологияси кафедраси (PhD) доцент.

Tuxtasheva Visola Farmonova
Zarmed University, Farmatsiya va farmasevtik texnologiya kafedrasi (PhD) assistent,

Annotatsiya
Maqolada fosfodiesteraza-4B (PDE4B) fermentining molekulyar tuzilishi, regulyator mexanizmlari va yallig‘lanishdagi roli tahlil qilindi. C-terminal CR3 sohasi hamda A-33 ingibitorining selektivligi bo‘yicha eksperimental ma’lumotlar yoritildi. PDE4B ga yo‘naltirilgan ingibitorlarning klinik afzalliklarini tasdiqlash uchun qo‘shimcha tadqiqotlar zarurligi asoslandi.

Kalit so‘zlar: fosfodiesteraza-4B, siklik adenozinmonofosfat, selektiv ingibitorlar, yallig‘lanish, CR3, A-33.

Introduction

Inflammation plays an important role in the pathogenesis of many chronic diseases. The development of drugs that act on intracellular signal transduction mechanisms is a highly relevant direction of modern pharmacology. The

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 2, Issue 11, November 2026
Website: usajournals.org
This work is Licensed under CC BY 4.0 a Creative Commons Attribution 4.0 International License.

phosphodiesterase-4 family consists of the PDE4A, PDE4B, PDE4C and PDE4D subfamilies and hydrolyzes cyclic adenosine monophosphate (cAMP) [1]. PDE4B participates in the regulation of immune cell activity and of the production of inflammatory mediators.

Aim of the study

To analyze, on the basis of the scientific literature, the molecular structure and regulatory mechanisms of the PDE4B enzyme and its role in inflammation, and to assess the prospects for developing selective inhibitors.

Materials and methods

The article was prepared on the basis of a narrative analysis of selected scientific literature. The results of genetic, biochemical and structural studies were compared and analyzed. No new experimental data were obtained; no systematic review or meta-analysis was conducted.

Results and discussion

Molecular structure of the PDE4B enzyme

PDE4B regulates intracellular signal transduction by converting cyclic adenosine monophosphate into 5′-adenosine monophosphate. Inhibition of the enzyme reduces cAMP degradation and may enhance anti-inflammatory signaling pathways in certain immune cells. Because the catalytic domains of the PDE4 enzymes are highly similar to one another, achieving selectivity through the catalytic site alone is difficult.

The long isoforms contain the regulatory regions UCR1 and UCR2. Phosphorylation of UCR1 by protein kinase A participates in the regulation of enzyme activity through a feedback mechanism. The C-terminal CR3 region, in turn, affects the conformation of the enzyme and the binding of certain inhibitors [1, 3]. Because intracellular cAMP signals are formed within discrete microdomains, inhibition measured with the isolated enzyme does not fully reflect selective effects within the cell.

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 2, Issue 11, November 2026
Website: usajournals.org
This work is Licensed under CC BY 4.0 a Creative Commons Attribution 4.0 International License.

The role of PDE4B in inflammatory processes

In the study by Jin and Conti, secretion of tumor necrosis factor alpha in response to lipopolysaccharide was reduced by approximately 90 percent in the blood leukocytes of PDE4B-deficient mice. No such effect was observed in PDE4D-deficient animals under the same conditions [2]. This finding demonstrates the important role of PDE4B in this innate immune response.

The generalized mechanism is as follows: inhibition of PDE4B → reduced degradation of cAMP → enhanced cAMP signaling → decreased secretion of certain pro-inflammatory mediators. However, genetic deletion is not equivalent to transient pharmacological inhibition of the enzyme. Further investigation is required before these results can be extrapolated to human disease.

Molecular mechanism of selective inhibitors

Fox and co-authors demonstrated the role of the CR3 region in the selectivity of the inhibitor A-33. Leucine at position 674 in PDE4B1 and the corresponding glutamine at position 594 in PDE4D7 affect inhibitor binding. Reciprocal substitution of these amino acids markedly altered inhibitor activity [3]. A-33 binds to the catalytic site and stabilizes the CR3 helix in a closed conformation. The long isoforms used in the assays carried a phosphomimetic mutation in UCR1 [3].

Table 1. Effect of the inhibitor A-33 on enzyme variants

Enzyme variant	IC_{50}, nM
PDE4B1	32
PDE4D7	1569
PDE4B1 (L674Q)	2035
PDE4D7 (Q594L)	21

The PDE4D7/PDE4B1 IC_{50} ratio for A-33 is approximately 49. This reflects biochemical selectivity under specific experimental conditions rather than a clinical advantage. The result cannot be generalized to all PDE4B isoforms and inhibitors.

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 2, Issue 11, November 2026
Website: usajournals.org
This work is Licensed under CC BY 4.0 a Creative Commons Attribution 4.0 International License.

Pharmacological prospects

Some systemic PDE4 inhibitors may cause adverse effects such as nausea and diarrhea. Reducing adverse effects while preserving efficacy through selective action on PDE4B is a promising hypothesis. Confirming it will require standardized assays using full-length variants of the PDE4A–D enzymes, assessment of target engagement in human immune cells, and determination of free drug concentrations and pharmacokinetic properties. In clinical studies, efficacy and safety should be compared with those of existing PDE4 inhibitors. In their 2026 review (published online in 2025), Zhang and co-authors classified PDE4B inhibitors [4]. The principal focus of the present article, by contrast, is to distinguish the evidence for molecular selectivity from the evidence for clinical advantage.

Conclusion

PDE4B is an important molecular target in the regulation of inflammatory mediator secretion. Structural differences in the CR3 region make it possible to develop selective inhibitors. The findings concerning A-33 demonstrate the molecular basis of this strategy; however, an advantage in clinical efficacy and safety still needs to be confirmed by further research.

References

1. Maurice D.H. et al. Advances in targeting cyclic nucleotide phosphodiesterases. Nature Reviews Drug Discovery. 2014;13:290–314. doi:10.1038/nrd4228.
1. Jin S.L.C., Conti M. Induction of the cyclic nucleotide phosphodiesterase PDE4B is essential for LPS-activated TNF-alpha responses. PNAS. 2002;99(11):7628–7633. doi:10.1073/pnas.122041599.
2. Fox D. 3rd, Burgin A.B., Gurney M.E. Structural basis for the design of selective phosphodiesterase 4B inhibitors. Cellular Signalling. 2014;26(3):657–663. doi:10.1016/j.cellsig.2013.12.003.
3. Zhang J., Zhai J., Liu H., Liu H., Sun B., Gao J., Sang F. Phosphodiesterase 4B (PDE4B) inhibitors and their applications in recent years (2014 to early 2025). Molecular Diversity. 2026;30(1):179–195. doi:10.1007/s11030-025-11242-2.