

Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs) in GtoPdb v.2021.3

Chen Yan¹

1. University of Rochester, USA

Abstract

3',5'-Cyclic nucleotide phosphodiesterases (PDEs, 3',5'-cyclic-nucleotide 5'-nucleotidohydrolase), [E.C. 3.1.4.17](#), catalyse the hydrolysis of a 3',5'-cyclic nucleotide (usually [cyclic AMP](#) or [cyclic GMP](#)). [isobutylmethylxanthine](#) is a nonselective inhibitor with an IC₅₀ value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2',3'-cyclic nucleotide 3'-phosphodiesterase ([E.C. 3.1.4.37](#) CNPase) activity is associated with myelin formation in the development of the CNS.

Contents

This is a citation summary for Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs) in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts. For further details see [\[12\]](#).

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=260>

Introduction to Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=260>

Enzymes

PDE1A(phosphodiesterase 1A)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1294>

PDE1B(phosphodiesterase 1B)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1295>

PDE1C(phosphodiesterase 1C)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1296>

PDE2A(phosphodiesterase 2A)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1297>

PDE3A(phosphodiesterase 3A)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1298>

PDE3B(phosphodiesterase 3B)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1299>

PDE4A(phosphodiesterase 4A)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1300>

PDE4B(phosphodiesterase 4B)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1301>

PDE4C(phosphodiesterase 4C)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1302>
PDE4D(phosphodiesterase 4D)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1303>
PDE5A(phosphodiesterase 5A)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1304>
PDE6A(phosphodiesterase 6A)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1312>
PDE6B(phosphodiesterase 6B)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1313>
PDE6C(phosphodiesterase 6C)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1314>
PDE6D(phosphodiesterase 6D)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1315>
PDE6G(phosphodiesterase 6G)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1316>
PDE6H(phosphodiesterase 6H)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1317>
PDE7A(phosphodiesterase 7A)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1305>
PDE7B(phosphodiesterase 7B)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1306>
PDE8A(phosphodiesterase 8A)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1307>
PDE8B(phosphodiesterase 8B)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1308>
PDE9A(phosphodiesterase 9A)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1309>
PDE10A(phosphodiesterase 10A)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1310>
PDE11A(phosphodiesterase 11A)
<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1311>

References

1. Adams JL, Smothers J, Srinivasan R and Hoos A. (2015) Big opportunities for small molecules in immuno-oncology. *Nat Rev Drug Discov* **14**: 603-22 [PMID:26228631]
2. Akama T, Baker SJ, Zhang YK, Hernandez V, Zhou H, Sanders V, Freund Y, Kimura R, Maples KR and Plattner JJ. (2009) Discovery and structure-activity study of a novel benzoxaborole anti-inflammatory agent (AN2728) for the potential topical treatment of psoriasis and atopic dermatitis. *Bioorg Med Chem Lett* **19**: 2129-32 [PMID:19303290]
3. Alaamery MA, Wyman AR, Ivey FD, Allain C, Demirbas D, Wang L, Ceyhan O and Hoffman CS. (2010) New classes of PDE7 inhibitors identified by a fission yeast-based HTS. *J Biomol Screen* **15**: 359-67 [PMID:20228279]
4. Albrecht W, Unger A, Bauer SM and Laufer SA. (2017) Discovery of N-{4-[5-(4-Fluorophenyl)-3-methyl-2-methylsulfanyl-3H-imidazol-4-yl]-pyridin-2-yl}-acetamide (CBS-3595), a Dual p38 α MAPK/PDE-4 Inhibitor with Activity against TNF α -Related Diseases. *J Med Chem* **60**: 5290-5305 [PMID:28613871]
5. Allcock RW, Blakli H, Jiang Z, Johnston KA, Morgan KM, Rosair GM, Iwase K, Kohno Y and Adams DR. (2011) Phosphodiesterase inhibitors. Part 1: Synthesis and structure-activity relationships of pyrazolopyridine-pyridazinone PDE inhibitors developed from ibudilast. *Bioorg Med Chem Lett* **21**: 3307-12 [PMID:21530250]
6. Aoki M, Kobayashi M, Ishikawa J, Saita Y, Terai Y, Takayama K, Miyata K and Yamada T. (2000) A novel phosphodiesterase type 4 inhibitor, YM976 (4-(3-chlorophenyl)-1,7-diethylpyrido[2,3-d]pyrimidin-2(1H)-one), with little emetogenic activity. *J Pharmacol Exp Ther* **295**: 255-60 [PMID:10991987]
7. Ashton MJ, Cook DC, Fenton G, Karlsson JA, Palfreyman MN, Raeburn D, Ratcliffe AJ, Souness JE, Thurairatnam S and Vicker N. (1994) Selective type IV phosphodiesterase inhibitors as antiasthmatic agents. The syntheses and biological activities of 3-(cyclopentyloxy)-4-methoxybenzamides and analogues. *J Med Chem* **37**: 1696-703 [PMID:8201604]
8. Basole CP, Nguyen RK, Lamothe K, Vang A, Clark R, Baillie GS, Epstein PM and Brocke S. (2017) PDE8 controls CD4⁺ T cell motility through the PDE8A-Raf-1 kinase signaling complex. *Cell Signal* **40**: 62-72 [PMID:28851628]
9. Boess FG, Hendrix M, van der Staay FJ, Erb C, Schreiber R, van Staveren W, de Vente J, Prickaerts J, Blokland A and Koenig G. (2004) Inhibition of phosphodiesterase 2 increases neuronal cGMP, synaptic plasticity and memory performance. *Neuropharmacology* **47**: 1081-92

- [PMID:15555642]
10. Boyle CD, Xu R, Asberom T, Chackalamannil S, Clader JW, Greenlee WJ, Guzik H, Hu Y, Hu Z and Lankin CM *et al.*. (2005) Optimization of purine based PDE1/PDE5 inhibitors to a potent and selective PDE5 inhibitor for the treatment of male ED. *Bioorg Med Chem Lett* **15**: 2365-9 [PMID:15837326]
 11. Bridgewood C, Damiani G, Sharif K, Watad A, Bragazzi NL, Quartuccio L, Savic S and McGonagle D. (2020) Rationale for Evaluating PDE4 Inhibition for Mitigating against Severe Inflammation in COVID-19 Pneumonia and Beyond. *Isr Med Assoc J* **22**: 335-339 [PMID:32558435]
 12. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
 13. Ceyhan O, Birsoy K and Hoffman CS. (2012) Identification of biologically active PDE11-selective inhibitors using a yeast-based high-throughput screen. *Chem Biol* **19**: 155-63 [PMID:22284362]
 14. Clerin V, Gale J and Tamimi N.. (2014) Use of a tetrasubstituted pyrazolo[4,3-d]pyrimidine compound for treating diabetic nephropathy. Patent number: WO-2014064566-A1.
 15. Corbin JD, Turko IV, Beasley A and Francis SH. (2000) Phosphorylation of phosphodiesterase-5 by cyclic nucleotide-dependent protein kinase alters its catalytic and allosteric cGMP-binding activities. *Eur J Biochem* **267**: 2760-7 [PMID:10785399]
 16. Dalamaga M, Karampela I and Mantzoros CS. (2020) Commentary: Phosphodiesterase 4 inhibitors as potential adjunct treatment targeting the cytokine storm in COVID-19. *Metabolism* **109**: 154282 [PMID:32497535]
 17. Doh H, Shin CY, Son M, Ko JI, Yoo M, Kim SH and Kim WB. (2002) Mechanism of erectogenic effect of the selective phosphodiesterase type 5 inhibitor, DA-8159. *Arch Pharm Res* **25**: 873-8 [PMID:12510841]
 18. Edmondson SD, Mastracchio A, He J, Chung CC, Forrest MJ, Hofsess S, MacIntyre E, Metzger J, O'Connor N and Patel K *et al.*. (2003) Benzyl vinylogous amide substituted aryldihydropyridazinones and aryldimethylpyrazolones as potent and selective PDE3B inhibitors. *Bioorg Med Chem Lett* **13**: 3983-7 [PMID:14592490]
 19. Fawcett L, Baxendale R, Stacey P, McGrouther C, Harrow I, Soderling S, Hetman J, Beavo JA and Phillips SC. (2000) Molecular cloning and characterization of a distinct human phosphodiesterase gene family: PDE11A. *Proc Natl Acad Sci USA* **97**: 3702-7 [PMID:10725373]
 20. Fisher DA, Smith JF, Pillar JS, St Denis SH and Cheng JB. (1998) Isolation and characterization of PDE8A, a novel human cAMP-specific phosphodiesterase. *Biochem Biophys Res Commun* **246**: 570-7 [PMID:9618252]
 21. Fisher DA, Smith JF, Pillar JS, St Denis SH and Cheng JB. (1998) Isolation and characterization of PDE9A, a novel human cGMP-specific phosphodiesterase. *J Biol Chem* **273**: 15559-64 [PMID:9624146]
 22. Fujishige K, Kotera J, Michibata H, Yuasa K, Takebayashi S, Okumura K and Omori K. (1999) Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A). *J Biol Chem* **274**: 18438-45 [PMID:10373451]
 23. Gao J, Long L, Xu F, Feng L, Liu Y, Shi J and Gong Q. (2020) Icariside II, a phosphodiesterase 5 inhibitor, attenuates cerebral ischaemia/reperfusion injury by inhibiting glycogen synthase kinase-3 β -mediated activation of autophagy. *Br J Pharmacol* **177**: 1434-1452 [PMID:31658364]
 24. Gardner C, Robas N, Cawkill D and Fidock M. (2000) Cloning and characterization of the human and mouse PDE7B, a novel cAMP-specific cyclic nucleotide phosphodiesterase. *Biochem Biophys Res Commun* **272**: 186-92 [PMID:10872825]
 25. Gharat LA, Gopalan B and Khairatkar-Joshi N. (2006) Novel heterocyclic compounds useful for the treatment of inflammatory and allergic disorders. Patent number: WO2006064355A2.
 26. Giembycz MA. (2008) Can the anti-inflammatory potential of PDE4 inhibitors be realized: guarded optimism or wishful thinking? *Br J Pharmacol* **155**: 288-90 [PMID:18660832]
 27. Giembycz MA and Newton R. (2011) Harnessing the clinical efficacy of phosphodiesterase 4 inhibitors in inflammatory lung diseases: dual-selective phosphodiesterase inhibitors and novel combination therapies. *Handb Exp Pharmacol*: 415-46 [PMID:21695651]
 28. Guay D, Boulet L, Friesen RW, Girard M, Hamel P, Huang Z, Laliberté F, Laliberté S, Mancini JA and Muise E *et al.*. (2008) Optimization and structure-activity relationship of a series of 1-phenyl-1,8-naphthyridin-4-one-3-carboxamides: identification of MK-0873, a potent and effective PDE4 inhibitor. *Bioorg Med Chem Lett* **18**: 5554-8 [PMID:18835163]
 29. Gurney ME, Nugent RA, Mo X, Sindac JA, Hagen TJ, Fox 3rd D, O'Donnell JM, Zhang C, Xu Y and Zhang HT *et al.*. (2019) Design and Synthesis of Selective Phosphodiesterase 4D (PDE4D) Allosteric Inhibitors for the Treatment of Fragile X Syndrome and Other Brain Disorders. *J Med Chem* **62**: 4884-4901 [PMID:31013090]
 30. Hanifin JM, Ellis CN, Frieden IJ, Fölster-Holst R, Stein Gold LF, Secci A, Smith AJ, Zhao C, Kornyeveva E and Eichenfield LF. (2016) OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-

- controlled study. *J Am Acad Dermatol* **75**: 297-305 [PMID:27189825]
31. Hayashi M, Matsushima K, Ohashi H, Tsunoda H, Murase S, Kawarada Y and Tanaka T. (1998) Molecular cloning and characterization of human PDE8B, a novel thyroid-specific isozyme of 3',5'-cyclic nucleotide phosphodiesterase. *Biochem Biophys Res Commun* **250**: 751-6 [PMID:9784418]
 32. Helal CJ, Arnold E, Boyden T, Chang C, Chappie TA, Fisher E, Hajos M, Harms JF, Hoffman WE and Humphrey JM *et al.*. (2018) Identification of a Potent, Highly Selective, and Brain Penetrant Phosphodiesterase 2A Inhibitor Clinical Candidate. *J Med Chem* **61**: 1001-1018 [PMID:29293004]
 33. Hoffmann R, Baillie GS, MacKenzie SJ, Yarwood SJ and Houslay MD. (1999) The MAP kinase ERK2 inhibits the cyclic AMP-specific phosphodiesterase HSPDE4D3 by phosphorylating it at Ser579. *EMBO J* **18**: 893-903 [PMID:10022832]
 34. Hoffmann R, Wilkinson IR, McCallum JF, Engels P and Houslay MD. (1998) cAMP-specific phosphodiesterase HSPDE4D3 mutants which mimic activation and changes in rolipram inhibition triggered by protein kinase A phosphorylation of Ser-54: generation of a molecular model. *Biochem J* **333** (Pt 1): 139-49 [PMID:9639573]
 35. Houslay MD and Adams DR. (2003) PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. *Biochem J* **370**: 1-18 [PMID:12444918]
 36. Huang Z, Dias R, Jones T, Liu S, Styhler A, Claveau D, Otu F, Ng K, Laliberte F and Zhang L *et al.*. (2007) L-454,560, a potent and selective PDE4 inhibitor with in vivo efficacy in animal models of asthma and cognition. *Biochem Pharmacol* **73**: 1971-81 [PMID:17428447]
 37. Hughes RO, Walker JK, Rogier DJ, Heasley SE, Bleviss-Bal RM, Benson AG, Jacobsen EJ, Cubbage JW, Fobian YM and Owen DR *et al.*. (2009) Optimization of the aminopyridopyrazinones class of PDE5 inhibitors: discovery of 3-[(trans-4-hydroxycyclohexyl)amino]-7-(6-methoxypyridin-3-yl)-1-(2-propoxyethyl)pyrido[3,4-b]pyrazin-2(1H)-one. *Bioorg Med Chem Lett* **19**: 5209-13 [PMID:19631533]
 38. Jones GH, Venuti MC, Alvarez R, Bruno JJ, Berks AH and Prince A. (1987) Inhibitors of cyclic AMP phosphodiesterase. 1. Analogues of cilostamide and anagrelide. *J Med Chem* **30**: 295-303 [PMID:3027338]
 39. Keshavarzian A, Mutlu E, Guzman JP, Forsyth C and Banan A. (2007) Phosphodiesterase 4 inhibitors and inflammatory bowel disease: emerging therapies in inflammatory bowel disease. *Expert Opin Investig Drugs* **16**: 1489-506 [PMID:17714033]
 40. Kodimuthali A, Jabariss SS and Pal M. (2008) Recent advances on phosphodiesterase 4 inhibitors for the treatment of asthma and chronic obstructive pulmonary disease. *J Med Chem* **51**: 5471-89 [PMID:18686943]
 41. Korkmaz-Icöz S, Radovits T and Szabó G. (2018) Targeting phosphodiesterase 5 as a therapeutic option against myocardial ischaemia/reperfusion injury and for treating heart failure. *Br J Pharmacol* **175**: 223-231 [PMID:28213937]
 42. Loughney K, Martins TJ, Harris EA, Sadhu K, Hicks JB, Sonnenburg WK, Beavo JA and Ferguson K. (1996) Isolation and characterization of cDNAs corresponding to two human calcium, calmodulin-regulated, 3',5'-cyclic nucleotide phosphodiesterases. *J Biol Chem* **271**: 796-806 [PMID:8557689]
 43. Lunniss CJ, Cooper AW, Eldred CD, Kranz M, Lindvall M, Lucas FS, Neu M, Preston AG, Ranshaw LE and Redgrave AJ *et al.*. (2009) Quinolines as a novel structural class of potent and selective PDE4 inhibitors: optimisation for oral administration. *Bioorg Med Chem Lett* **19**: 1380-5 [PMID:19195882]
 44. Malamas MS, Ni Y, Erdei J, Stange H, Schindler R, Lankau HJ, Grunwald C, Fan KY, Parris K and Langen B *et al.*. (2011) Highly potent, selective, and orally active phosphodiesterase 10A inhibitors. *J Med Chem* **54**: 7621-38 [PMID:21988093]
 45. Martinez GR, Walker KA, Hirschfeld DR, Bruno JJ, Yang DS and Maloney PJ. (1992) 3,4-Dihydroquinolin-2(1H)-ones as combined inhibitors of thromboxane A2 synthase and cAMP phosphodiesterase. *J Med Chem* **35**: 620-8 [PMID:1311763]
 46. Maurice DH, Ke H, Ahmad F, Wang Y, Chung J and Manganiello VC. (2014) Advances in targeting cyclic nucleotide phosphodiesterases. *Nat Rev Drug Discov* **13**: 290-314 [PMID:24687066]
 47. Meanwell NA, Pearce BC, Roth HR, Smith EC, Wedding DL, Wright JJ, Buchanan JO, Baryla UM, Gamberdella M and Gillespie E *et al.*. (1992) Inhibitors of blood platelet cAMP phosphodiesterase. 2. Structure-activity relationships associated with 1,3-dihydro-2H-imidazo[4,5-b]quinolin-2-ones substituted with functionalized side chains. *J Med Chem* **35**: 2672-87 [PMID:1321910]
 48. Michaeli T, Bloom TJ, Martins T, Loughney K, Ferguson K, Riggs M, Rodgers L, Beavo JA and Wigler M. (1993) Isolation and characterization of a previously undetected human cAMP phosphodiesterase by complementation of cAMP phosphodiesterase-deficient *Saccharomyces cerevisiae*. *J Biol Chem* **268**: 12925-32 [PMID:8389765]
 49. Michie AM, Lobban M, Müller T, Harnett MM and Houslay MD. (1996) Rapid regulation of PDE-

- 2 and PDE-4 cyclic AMP phosphodiesterase activity following ligation of the T cell antigen receptor on thymocytes: analysis using the selective inhibitors erythro-9-(2-hydroxy-3-nonyl)-adenine (EHNA) and rolipram. *Cell Signal* **8**: 97-110 [PMID:8730511]
50. Mochida H, Takagi M, Inoue H, Noto T, Yano K, Fujishige K, Sasaki T, Yuasa K, Kotera J and Omori K *et al.*. (2002) Enzymological and pharmacological profile of T-0156, a potent and selective phosphodiesterase type 5 inhibitor. *Eur J Pharmacol* **456**: 91-8 [PMID:12450574]
 51. Mohamed HA, Girgis NM, Wilcken R, Bauer MR, Tinsley HN, Gary BD, Piazza GA, Boeckler FM and Abadi AH. (2011) Synthesis and molecular modeling of novel tetrahydro- β -carboline derivatives with phosphodiesterase 5 inhibitory and anticancer properties. *J Med Chem* **54**: 495-509 [PMID:21189023]
 52. Moslin R, Gardner D, Santella J, Zhang Y, Duncia JV, Liu C, Lin J, Tokarski JS, Strnad J and Pedicord D *et al.*. (2017) Identification of imidazo[1,2-*b*]pyridazine TYK2 pseudokinase ligands as potent and selective allosteric inhibitors of TYK2 signalling. *Medchemcomm* **8**: 700-712 [PMID:30108788]
 53. Mulhall AM, Droege CA, Ernst NE, Panos RJ and Zafar MA. (2015) Phosphodiesterase 4 inhibitors for the treatment of chronic obstructive pulmonary disease: a review of current and developing drugs. *Expert Opin Investig Drugs* **24**: 1597-611 [PMID:26419847]
 54. Okada M, Kato M, Sato N, Uno T, Kitagaki H, Haruta J, Hiyama H and Shibata T. (2007) Oxazole compound and pharmaceutical composition Patent number: WO2007058338.
 55. Perry MJ, O'Connell J, Walker C, Crabbe T, Baldock D, Russell A, Lumb S, Huang Z, Howat D and Allen R *et al.*. (1998) CDP840: a novel inhibitor of PDE-4. *Cell Biochem Biophys* **29**: 113-32 [PMID:9631241]
 56. Porteous DJ, Millar JK, Brandon NJ and Sawa A. (2011) DISC1 at 10: connecting psychiatric genetics and neuroscience. *Trends Mol Med* **17**: 699-706 [PMID:22015021]
 57. Rawson DJ, Ballard S, Barber C, Barker L, Beaumont K, Bunnage M, Cole S, Corless M, Denton S and Ellis D *et al.*. (2012) The discovery of UK-369003, a novel PDE5 inhibitor with the potential for oral bioavailability and dose-proportional pharmacokinetics. *Bioorg Med Chem* **20**: 498-509 [PMID:22100260]
 58. Salari-Sharif P and Abdollahi M. (2010) Phosphodiesterase 4 inhibitors in inflammatory bowel disease: a comprehensive review. *Curr Pharm Des* **16**: 3661-7 [PMID:21128899]
 59. Saldou N, Obernolte R, Huber A, Baecker PA, Wilhelm R, Alvarez R, Li B, Xia L, Callan O and Su C *et al.*. (1998) Comparison of recombinant human PDE4 isoforms: interaction with substrate and inhibitors. *Cell Signal* **10**: 427-40 [PMID:9720765]
 60. Sasaki T, Kotera J, Yuasa K and Omori K. (2000) Identification of human PDE7B, a cAMP-specific phosphodiesterase. *Biochem Biophys Res Commun* **271**: 575-83 [PMID:10814504]
 61. Schafer PH, Parton A, Capone L, Cedzik D, Brady H, Evans JF, Man HW, Muller GW, Stirling DI and Chopra R. (2014) Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal* **26**: 2016-29 [PMID:24882690]
 62. Sircar I, Steffen RP, Bobowski G, Burke SE, Newton RS, Weishaar RE, Bristol JA and Evans DB. (1989) Cardiotonic agents. 9. Synthesis and biological evaluation of a series of (E)-4,5-dihydro-6-[2-[4-(1H-imidazol-1-yl)phenyl]ethenyl]-3 (2H)-pyridazinones: a novel class of compounds with positive inotropic, antithrombotic, and vasodilatory activities for the treatment of congestive heart failure. *J Med Chem* **32**: 342-50 [PMID:2536438]
 63. Smith SJ, Cieslinski LB, Newton R, Donnelly LE, Fenwick PS, Nicholson AG, Barnes PJ, Barnette MS and Giembycz MA. (2004) Discovery of BRL 50481 [3-(N,N-dimethylsulfonamido)-4-methyl-nitrobenzene], a selective inhibitor of phosphodiesterase 7: in vitro studies in human monocytes, lung macrophages, and CD8+ T-lymphocytes. *Mol Pharmacol* **66**: 1679-89 [PMID:15371556]
 64. Sudo T, Tachibana K, Toga K, Tochizawa S, Inoue Y, Kimura Y and Hidaka H. (2000) Potent effects of novel anti-platelet aggregatory cilostamide analogues on recombinant cyclic nucleotide phosphodiesterase isozyme activity. *Biochem Pharmacol* **59**: 347-56 [PMID:10644042]
 65. Torphy TJ and Undem BJ. (1991) Phosphodiesterase inhibitors: new opportunities for the treatment of asthma. *Thorax* **46**: 512-23 [PMID:1877039]
 66. Tsai YF, Chu TC, Chang WY, Wu YC, Chang FR, Yang SC, Wu TY, Hsu YM, Chen CY and Chang SH *et al.*. (2017) 6-Hydroxy-5,7-dimethoxy-flavone suppresses the neutrophil respiratory burst via selective PDE4 inhibition to ameliorate acute lung injury. *Free Radic Biol Med* **106**: 379-392 [PMID:28263828]
 67. Turko IV, Ballard SA, Francis SH and Corbin JD. (1999) Inhibition of cyclic GMP-binding cyclic GMP-specific phosphodiesterase (Type 5) by sildenafil and related compounds. *Mol Pharmacol* **56**: 124-30 [PMID:10385692]
 68. Vemulapalli S, Watkins RW, Chintala M, Davis H, Ahn HS, Fawzi A, Tulshian D, Chiu P, Chatterjee M and Lin CC *et al.*. (1996) Antiplatelet and antiproliferative effects of SCH 51866, a novel type 1 and type 5 phosphodiesterase inhibitor. *J Cardiovasc Pharmacol* **28**: 862-9 [PMID:8961086]
 69. Venhuis BJ, Zomer G, Hamzink M, Meiring HD, Aubin Y and de Kaste D. (2011) The identification of a nitrosated prodrug of the PDE-5 inhibitor aildenafil in a dietary supplement: a

- Viagra with a pop. *J Pharm Biomed Anal* **54**: 735-41 [PMID:21145686]
70. Venuti MC, Jones GH, Alvarez R and Bruno JJ. (1987) Inhibitors of cyclic AMP phosphodiesterase. 2. Structural variations of N-cyclohexyl-N-methyl-4-[(1,2,3,5-tetrahydro-2-oxoimidazo[2,1-b]quinazolin-7-yl)-oxy]butyramide (RS-82856). *J Med Chem* **30**: 303-18 [PMID:3027339]
 71. Verhoest PR, Chapin DS, Corman M, Fonseca K, Harms JF, Hou X, Marr ES, Menniti FS, Nelson F and O'Connor R *et al.*. (2009) Discovery of a novel class of phosphodiesterase 10A inhibitors and identification of clinical candidate 2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxy]methyl-quinoline (PF-2545920) for the treatment of schizophrenia. *J Med Chem* **52**: 5188-96 [PMID:19630403]
 72. Wang G, Liu Z, Chen T, Wang Z, Yang H, Zheng M, Ren J, Tian G, Yang X and Li L *et al.*. (2012) Design, synthesis, and pharmacological evaluation of monocyclic pyrimidinones as novel inhibitors of PDE5. *J Med Chem* **55**: 10540-50 [PMID:23137303]
 73. Wang P, Myers JG, Wu P, Cheewatrakoolpong B, Egan RW and Billah MM. (1997) Expression, purification, and characterization of human cAMP-specific phosphodiesterase (PDE4) subtypes A, B, C, and D. *Biochem Biophys Res Commun* **234**: 320-4 [PMID:9177268]
 74. Wang P, Wu P, Ohleth KM, Egan RW and Billah MM. (1999) Phosphodiesterase 4B2 is the predominant phosphodiesterase species and undergoes differential regulation of gene expression in human monocytes and neutrophils. *Mol Pharmacol* **56**: 170-4 [PMID:10385698]
 75. Wilson LS and Brandon NJ. (2015) Emerging biology of PDE10A. *Curr Pharm Des* **21**: 378-88 [PMID:25159072]
 76. Wu Y, Tian YJ, Le ML, Zhang SR, Zhang C, Huang MX, Jiang MY, Zhang B and Luo HB. (2020) Discovery of Novel Selective and Orally Bioavailable Phosphodiesterase-1 Inhibitors for the Efficient Treatment of Idiopathic Pulmonary Fibrosis. *J Med Chem* **63**: 7867-7879 [PMID:32603117]
 77. Yang SW, Smotrski J, McElroy WT, Tan Z, Ho G, Tulshian D, Greenlee WJ, Guzzi M, Zhang X and Mullins D *et al.*. (2012) Discovery of orally active pyrazoloquinolines as potent PDE10 inhibitors for the management of schizophrenia. *Bioorg Med Chem Lett* **22**: 235-9 [PMID:22142545]
 78. You T, Cheng Y, Zhong J, Bi B, Zeng B, Zheng W, Wang H and Xu J. (2017) Roflupram, a Phosphodiesterase 4 Inhibitor, Suppresses Inflammasome Activation through Autophagy in Microglial Cells. *ACS Chem Neurosci* **8**: 2381-2392 [PMID:28605578]
 79. Zhang X, Dong G, Li H, Chen W, Li J, Feng C, Gu Z, Zhu F, Zhang R and Li M *et al.*. (2019) Structure-Aided Identification and Optimization of Tetrahydro-isoquinolines as Novel PDE4 Inhibitors Leading to Discovery of an Effective Antipsoriasis Agent. *J Med Chem* **62**: 5579-5593 [PMID:31099559]