

Phosphatidylinositol-4,5-bisphosphate 3-kinase family in GtoPdb v.2025.1

Mohib Uddin¹

1. AstraZeneca, Sweden

Abstract

PI3K activation is one of the most important signal transduction pathways used to transmit signals from cell-surface receptors to regulate intracellular processes (cell growth, survival, proliferation and movement). PI3K catalytic (and regulatory) subunits play vital roles in normal cell function and in disease. Progress made in developing PI3K-targeted agents as potential therapeutics for treating cancer and other diseases is reviewed by Fruman *et al.* (2017) [44].

Contents

This is a citation summary for Phosphatidylinositol-4,5-bisphosphate 3-kinase family 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 [19].

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

Phosphatidylinositol-4,5-bisphosphate 3-kinase family

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=673>

Introduction to Phosphatidylinositol-4,5-bisphosphate 3-kinase family

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=673>

Enzymes

PI3K α (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2153>

PI3K β (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2154>

PI3K γ (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2156>

PI3K δ (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2155>

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. Ali AY, Wu X, Eissa N, Hou S, Ghia JE, Murooka TT, Banerji V, Johnston JB, Lin F and Gibson SB *et al.*. (2018) Distinct roles for phosphoinositide 3-kinases γ and δ in malignant B cell migration. *Leukemia* **32**: 1958-1969 [[PMID:29479062](#)]

3. Ali K, Soond DR, Piñeiro R, Hagemann T, Pearce W, Lim EL, Bouabe H, Scudamore CL, Hancox T and Maecker H *et al.*.. (2014) Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature* **510**: 407-11 [PMID:24919154]
4. Allen RA, Brookings DC, Powell MJ, Delgado J, Shuttleworth LK, Merriman M, Fahy IJ, Tewari R, Silva JP and Healy LJ *et al.*.. (2017) Seletalisib: Characterization of a Novel, Potent, and Selective Inhibitor of PI3Kδ. *J Pharmacol Exp Ther* **361**: 429-440 [PMID:28442583]
5. Angulo I, Vadas O, Garçon F, Banham-Hall E, Plagnol V, Leahy TR, Baxendale H, Coulter T, Curtis J and Wu C *et al.*.. (2013) Phosphoinositide 3-kinase δ gene mutation predisposes to respiratory infection and airway damage. *Science* **342**: 866-71 [PMID:24136356]
6. Apsel B, Blair JA, Gonzalez B, Nazif TM, Feldman ME, Aizenstein B, Hoffman R, Williams RL, Shokat KM and Knight ZA. (2008) Targeted polypharmacology: discovery of dual inhibitors of tyrosine and phosphoinositide kinases. *Nat Chem Biol* **4**: 691-9 [PMID:18849971]
7. Barda DA and Mader MM.. (2013) PI3 kinase/mTOR dual inhibitor. Patent number: US8440829 B2.
8. Barlaam B, Cosulich S, Delouvré B, Ellston R, Fitzek M, Germain H, Green S, Hancox U, Harris CS and Hudson K *et al.*.. (2015) Discovery of 1-(4-(5-(5-amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1,2,4-triazol-3-yl)piperidin-1-yl)-3-hydroxypropan-1-one (AZD8835): A potent and selective inhibitor of PI3Kα and PI3Kδ for the treatment of cancers. *Bioorg Med Chem Lett* **25**: 5155-62 [PMID:26475521]
9. Barton N, Convery M, Cooper AWJ, Down K, Hamblin JN, Inglis G, Peace S, Rowedder J, Rowland P and Taylor JA *et al.*.. (2018) Discovery of Potent, Efficient, and Selective Inhibitors of Phosphoinositide 3-Kinase δ through a Deconstruction and Regrowth Approach. *J Med Chem* **61**: 11061-11073 [PMID:30532965]
10. Bergamini G, Bell K, Shimamura S, Werner T, Cansfield A, Müller K, Perrin J, Rau C, Ellard K and Hopf C *et al.*.. (2012) A selective inhibitor reveals PI3Kγ dependence of T(H)17 cell differentiation. *Nat Chem Biol* **8**: 576-82 [PMID:22544264]
11. Berger M, Wortmann L, Buchgraber P, Lücking U, Zitzmann-Kolbe S, Wengner AM, Bader B, Bömer U, Briem H and Eis K *et al.*.. (2021) BAY-8400: A Novel Potent and Selective DNA-PK Inhibitor which Shows Synergistic Efficacy in Combination with Targeted Alpha Therapies. *J Med Chem* **64**: 12723-12737 [PMID:34428039]
12. Berndt A, Miller S, Williams O, Le DD, Houseman BT, Pacold JI, Gorrec F, Hon WC, Liu Y and Rommel C *et al.*.. (2010) The p110 delta structure: mechanisms for selectivity and potency of new PI(3)K inhibitors. *Nat Chem Biol* **6**: 117-24 [PMID:20081827]
13. Biagetti M, Ronchi P, Fiorelli C and Bruno P. (2020) Isochromene derivatives as phosphoinositide 3-kinases inhibitors Patent number: WO2020200918A1.
14. Bonazzi S, Goold CP, Gray A, Thomsen NM, Nunez J, Karki RG, Gorde A, Biag JD, Malik HA and Sun Y *et al.*.. (2020) Discovery of a Brain-Penetrant ATP-Competitive Inhibitor of the Mechanistic Target of Rapamycin (mTOR) for CNS Disorders. *J Med Chem* **63**: 1068-1083 [PMID:31955578]
15. Borsari C, Rageot D, Dall'Asen A, Bohnacker T, Melone A, Sele AM, Jackson E, Langlois JB, Beaufils F and Hebeisen P *et al.*.. (2019) A Conformational Restriction Strategy for the Identification of a Highly Selective Pyrimido-pyrrolo-oxazine mTOR Inhibitor. *J Med Chem* **62**: 8609-8630 [PMID:31465220]
16. Braun M-G, Hanan E, Staben ST, Heald RA, Macleod C and Elliott R. (2017) Benzoxazepin oxazolidinone compounds and methods of use Patent number: US20170015678.
17. Brown SD and Matthews DJ. (2012) (alpha- substituted aralkylamino and heteroarylalkylamino) pyrimidinyl and 1,3,5 -triazinyl benzimidazoles, pharmaceutical compositions containing them, and these compounds for use in treating proliferative diseases Patent number: WO2012135160A1.
18. Buckbinder L, St Jean Jr DJ, Tieu T, Ladd B, Hilbert B, Wang W, Alltucker JT, Manimala S, Kryukov GV and Brooijmans N *et al.*.. (2023) STX-478, a Mutant-Selective, Allosteric PI3Kα Inhibitor Spares Metabolic Dysfunction and Improves Therapeutic Response in PI3Kα-Mutant Xenografts. *Cancer Discov* **13**: 2432-2447 [PMID:37623743]
19. 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]
20. Burger MT, Pecchi S, Wagman A, Ni ZJ, Knapp M, Hendrickson T, Atallah G, Pfister K, Zhang Y and Bartulis S *et al.*.. (2011) Identification of NVP-BKM120 as a Potent, Selective, Orally Bioavailable Class I PI3 Kinase Inhibitor for Treating Cancer. *ACS Med Chem Lett* **2**: 774-9 [PMID:24900266]
21. Camps M, Rückle T, Ji H, Ardissonne V, Rintelen F, Shaw J, Ferrandi C, Chabert C, Gillieron C and Françon B *et al.*.. (2005) Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis. *Nat Med* **11**: 936-43 [PMID:16127437]
22. Canaud G. (2017) BYL719 (ALPELISIB) FOR USE IN THE TREATMENT OF PIK3CA-RELATED OVERGROWTH SPECTRUM (PROS - CLOVES SYNDROME) Patent number: WO2017140828.
23. Cano C, Saravanan K, Bailey C, Bardos J, Curtin NJ, Frigerio M, Golding BT, Hardcastle IR, Hummersone MG and Meneer KA *et al.*.. (2013) 1-substituted (Dibenzo[b,d]thiophen-4-yl)-2-

- morpholino-4H-chromen-4-ones endowed with dual DNA-PK/PI3-K inhibitory activity. *J Med Chem* **56**: 6386-401 [PMID:23855836]
- 24. Castro-Falcón G, Seiler GS, Demir Ö, Rathinaswamy MK, Hamelin D, Hoffmann RM, Makowski SL, Letzel AC, Field SJ and Burke JE *et al.*. (2018) Neolymphostin A Is a Covalent Phosphoinositide 3-Kinase (PI3K)/Mammalian Target of Rapamycin (mTOR) Dual Inhibitor That Employs an Unusual Electrophilic Vinylogous Ester. *J Med Chem* **61**: 10463-10472 [PMID:30380865]
 - 25. Certal V, Carry JC, Halley F, Virone-Oddos A, Thompson F, Filoche-Rommé B, El-Ahmad Y, Karlsson A, Charrier V and Delorme C *et al.*. (2014) Discovery and optimization of pyrimidone indoline amide PI3K β inhibitors for the treatment of phosphatase and tensin homologue (PTEN)-deficient cancers. *J Med Chem* **57**: 903-20 [PMID:24387221]
 - 26. Certal V, Halley F, Virone-Oddos A, Delorme C, Karlsson A, Rak A, Thompson F, Filoche-Rommé B, El-Ahmad Y and Carry JC *et al.*. (2012) Discovery and optimization of new benzimidazole- and benzoxazole-pyrimidone selective PI3K β inhibitors for the treatment of phosphatase and TENSin homologue (PTEN)-deficient cancers. *J Med Chem* **55**: 4788-805 [PMID:22524426]
 - 27. Cheng H, Li C, Bailey S, Baxi SM, Goulet L, Guo L, Hoffman J, Jiang Y, Johnson TO and Johnson TW *et al.*. (2013) Discovery of the Highly Potent PI3K/mTOR Dual Inhibitor PF-04979064 through Structure-Based Drug Design. *ACS Med Chem Lett* **4**: 91-7 [PMID:24900568]
 - 28. Cheng H, Orr STM, Bailey S, Brooun A, Chen P, Deal JG, Deng YL, Edwards MP, Gallego GM and Grodsky N *et al.*. (2021) Structure-Based Drug Design and Synthesis of PI3K α -Selective Inhibitor (PF-06843195). *J Med Chem* **64**: 644-661 [PMID:33356246]
 - 29. Cherian PT, Koikov LN, Wortman MD and Knittel JJ. (2009) Exploring the PI3K alpha and gamma binding sites with 2,6-disubstituted isonicotinic derivatives. *Bioorg Med Chem Lett* **19**: 2215-9 [PMID:19297156]
 - 30. Collier PN, Martinez-Botella G, Cornebise M, Cottrell KM, Doran JD, Griffith JP, Mahajan S, Maltais F, Moody CS and Huck EP *et al.*. (2015) Structural basis for isoform selectivity in a class of benzothiazole inhibitors of phosphoinositide 3-kinase γ . *J Med Chem* **58**: 517-21 [PMID:24754609]
 - 31. Cooke NG, Fernandes GDSP, Graveleau N, Hebach C, Hogenauer K, Hollingworth G, Smith AB, Soldermann N, Stowasser F and Strang R *et al.*. (2012) Tetrahydro-pyrido-pyrimidine derivatives Patent number: WO2012004299.
 - 32. Crank MC, Grossman JK, Moir S, Pittaluga S, Buckner CM, Kardava L, Agharahimi A, Meuwissen H, Stoddard J and Niemela J *et al.*. (2014) Mutations in PIK3CD can cause hyper IgM syndrome (HIGM) associated with increased cancer susceptibility. *J Clin Immunol* **34**: 272-6 [PMID:24610295]
 - 33. Cushing TD, Hao X, Shin Y, Andrews K, Brown M, Cardozo M, Chen Y, Duquette J, Fisher B and Gonzalez-Lopez de Turiso F *et al.*. (2015) Discovery and in vivo evaluation of (S)-N-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9H-purin-6-amine (AMG319) and related PI3K δ inhibitors for inflammation and autoimmune disease. *J Med Chem* **58**: 480-511 [PMID:25469863]
 - 34. D'Angelo ND, Kim TS, Andrews K, Booker SK, Caenepeel S, Chen K, D'Amico D, Freeman D, Jiang J and Liu L *et al.*. (2011) Discovery and optimization of a series of benzothiazole phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) dual inhibitors. *J Med Chem* **54**: 1789-811 [PMID:21332118]
 - 35. Davis MI, Hunt JP, Herrgard S, Ciceri P, Wodicka LM, Pallares G, Hocker M, Treiber DK and Zarrinkar PP. (2011) Comprehensive analysis of kinase inhibitor selectivity. *Nat Biotechnol* **29**: 1046-51 [PMID:22037378]
 - 36. Dittmann A, Werner T, Chung CW, Savitski MM, Fälth Savitski M, Grandi P, Hopf C, Lindon M, Neubauer G and Prinjha RK *et al.*. (2014) The commonly used PI3-kinase probe LY294002 is an inhibitor of BET bromodomains. *ACS Chem Biol* **9**: 495-502 [PMID:24533473]
 - 37. Down K, Amour A, Baldwin IR, Cooper AW, Deakin AM, Felton LM, Guntrip SB, Hardy C, Harrison ZA and Jones KL *et al.*. (2015) Optimization of Novel Indazoles as Highly Potent and Selective Inhibitors of Phosphoinositide 3-Kinase δ for the Treatment of Respiratory Disease. *J Med Chem* **58**: 7381-99 [PMID:26301626]
 - 38. Dulau Florea AE, Braylan RC, Schafernak KT, Williams KW, Daub J, Goyal RK, Puck JM, Rao VK, Pittaluga S and Holland SM *et al.*. (2017) Abnormal B-cell maturation in the bone marrow of patients with germline mutations in PIK3CD. *J Allergy Clin Immunol* **139**: 1032-1035.e6 [PMID:27697496]
 - 39. Evans CA, Liu T, Lescarbeau A, Nair SJ, Grenier L, Pradeilles JA, Glenadel Q, Tibbitts T, Rowley AM and DiNitto JP *et al.*. (2016) Discovery of a Selective Phosphoinositide-3-Kinase (PI3K) γ Inhibitor (IPI-549) as an Immuno-Oncology Clinical Candidate. *ACS Med Chem Lett* **7**: 862-7 [PMID:27660692]
 - 40. Fairhurst RA, Furet P, Imbach-Weese P, Stauffer F, Rueeger H, McCarthy C, Ripoche S, Oswald S, Arnaud B and Jary A *et al.*. (2022) Identification of NVP-CLR457 as an Orally Bioavailable Non-CNS-Penetrant pan-Class IA Phosphoinositol-3-Kinase Inhibitor. *J Med Chem* **65**: 8345-8379 [PMID:35500094]
 - 41. Fokas E, Prevo R, Pollard JR, Reaper PM, Charlton PA, Cornelissen B, Vallis KA, Hammond EM,

- Olcina MM and Gillies McKenna W *et al.* (2012) Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. *Cell Death Dis* **3**: e441 [PMID:23222511]
42. Folkes AJ, Ahmadi K, Alderton WK, Alix S, Baker SJ, Box G, Chuckowree IS, Clarke PA, Depledge P and Eccles SA *et al.* (2008) The identification of 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine (GDC-0941) as a potent, selective, orally bioavailable inhibitor of class I PI3 kinase for the treatment of cancer. *J Med Chem* **51**: 5522-32 [PMID:18754654]
43. Fraser C, Carragher NO and Unciti-Broceta A. (2016) eCF309: a potent, selective and cell-permeable mTOR inhibitor *Medchemcomm* **7**: 471-477
44. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC and Abraham RT. (2017) The PI3K Pathway in Human Disease. *Cell* **170**: 605-635 [PMID:28802037]
45. Fu J, Wang Y, Sun Y, Wu G, Lu A, Zhang S, Goodnow RA, Gilmer T, Kastan M and Kirsch D. (2021) Dual atm and dna-pk inhibitors for use in anti-tumor therapy Patent number: WO2021022078A1.
46. Furet P, Guagnano V, Fairhurst RA, Imbach-Weese P, Bruce I, Knapp M, Fritsch C, Blasco F, Blanz J and Aichholz R *et al.* (2013) Discovery of NVP-BYL719 a potent and selective phosphatidylinositol-3 kinase alpha inhibitor selected for clinical evaluation. *Bioorg Med Chem Lett* **23**: 3741-8 [PMID:23726034]
47. Gaillard P, Jeanclaude-Etter I, Pomei V, Sebille E, Jeyaprakashnarayanan S and Muzerelle M. (2015) Tricyclic pyrazol amine derivatives Patent number: US9073940B2.
48. Gangadhara G, Dahl G, Bohnacker T, Rae R, Gunnarsson J, Blaho S, Öster L, Lindmark H, Karabelas K and Pemberton N *et al.* (2019) A class of highly selective inhibitors bind to an active state of PI3K γ . *Nat Chem Biol* **15**: 348-357 [PMID:30718815]
49. Goldberg FW, Finlay MRV, Ting AKT, Beattie D, Lamont GM, Fallan C, Wrigley GL, Schimpl M, Howard MR and Williamson B *et al.* (2020) The Discovery of 7-Methyl-2-[(7-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8H-purin-8-one (AZD7648), a Potent and Selective DNA-Dependent Protein Kinase (DNA-PK) Inhibitor. *J Med Chem* **63**: 3461-3471 [PMID:31851518]
50. Gopalsamy A, Bennett EM, Shi M, Zhang WG, Bard J and Yu K. (2012) Identification of pyrimidine derivatives as hSMG-1 inhibitors. *Bioorg Med Chem Lett* **22**: 6636-41 [PMID:23021994]
51. Griffin RJ, Fontana G, Golding BT, Guiard S, Hardcastle IR, Leahy JJ, Martin N, Richardson C, Rigoreau L and Stockley M *et al.* (2005) Selective benzopyranone and pyrimido[2,1-a]isoquinolin-4-one inhibitors of DNA-dependent protein kinase: synthesis, structure-activity studies, and radiosensitization of a human tumor cell line in vitro. *J Med Chem* **48**: 569-85 [PMID:15658870]
52. Hancox U, Cosulich S, Hanson L, Trigwell C, Lenaghan C, Ellston R, Dry H, Crafter C, Barlaam B and Fitzek M *et al.* (2015) Inhibition of PI3K β signaling with AZD8186 inhibits growth of PTEN-deficient breast and prostate tumors alone and in combination with docetaxel. *Mol Cancer Ther* **14**: 48-58 [PMID:25398829]
53. Harris SJ, Foster JG and Ward SG. (2009) PI3K isoforms as drug targets in inflammatory diseases: lessons from pharmacological and genetic strategies. *Curr Opin Investig Drugs* **10**: 1151-62 [PMID:19876783]
54. Hart S, Novotny-Diermayr V, Goh KC, Williams M, Tan YC, Ong LC, Cheong A, Ng BK, Amalini C and Madan B *et al.* (2013) VS-5584, a novel and highly selective PI3K/mTOR kinase inhibitor for the treatment of cancer. *Mol Cancer Ther* **12**: 151-61 [PMID:23270925]
55. Hawkins PT, Anderson KE, Davidson K and Stephens LR. (2006) Signalling through Class I PI3Ks in mammalian cells. *Biochem Soc Trans* **34**: 647-62 [PMID:17052169]
56. Hayakawa M, Kawaguchi K, Kaizawa H, Koizumi T, Ohishi T, Yamano M, Okada M, Ohta M, Tsukamoto S and Raynaud FI *et al.* (2007) Synthesis and biological evaluation of sulfonylhydrazone-substituted imidazo[1,2-a]pyridines as novel PI3 kinase p110alpha inhibitors. *Bioorg Med Chem* **15**: 5837-44 [PMID:17601739]
57. Heffron TP, Ndubaku CO, Salphati L, Alicke B, Cheong J, Drobnick J, Edgar K, Gould SE, Lee LB and Lesnick JD *et al.* (2016) Discovery of Clinical Development Candidate GDC-0084, a Brain Penetrant Inhibitor of PI3K and mTOR. *ACS Med Chem Lett* **7**: 351-6 [PMID:27096040]
58. Henley ZA, Amour A, Barton N, Bantscheff M, Bergamini G, Bertrand SM, Convery M, Down K, Dümpelfeld B and Edwards CD *et al.* (2020) Optimization of Orally Bioavailable PI3K δ Inhibitors and Identification of Vps34 as a Key Selectivity Target. *J Med Chem* **63**: 638-655 [PMID:31855425]
59. Hou Y, Zhang F, Min W, Yuan K, Kuang W, Wang X, Zhu Y, Sun C, Xia F and Wang Y *et al.* (2022) Discovery of Novel Phosphoinositide-3-Kinase α Inhibitors with High Selectivity, Excellent Bioavailability, and Long-Acting Efficacy for Gastric Cancer. *J Med Chem* **65**: 9873-9892 [PMID:35834807]
60. Hsieh AC, Liu Y, Edlind MP, Ingolia NT, Janes MR, Sher A, Shi EY, Stumpf CR, Christensen C and Bonham MJ *et al.* (2012) The translational landscape of mTOR signalling steers cancer

- initiation and metastasis. *Nature* **485**: 55-61 [PMID:22367541]
61. Jackson SP, Schoenwaelder SM, Goncalves I, Nesbitt WS, Yap CL, Wright CE, Kenche V, Anderson KE, Dopheide SM and Yuan Y *et al.*. (2005) PI 3-kinase p110beta: a new target for antithrombotic therapy. *Nat Med* **11**: 507-14 [PMID:15834429]
 62. Jalota-Badhwar A, Bhatia DR, Boreddy S, Joshi A, Venkatraman M, Desai N, Chaudhari S, Bose J, Kolla LS and Deore V *et al.*. (2015) P7170: A Novel Molecule with Unique Profile of mTORC1/C2 and Activin Receptor-like Kinase 1 Inhibition Leading to Antitumor and Antiangiogenic Activity. *Mol Cancer Ther* **14**: 1095-106 [PMID:25700704]
 63. Kashiyama T, Oda K, Ikeda Y, Shiose Y, Hirota Y, Inaba K, Makii C, Kurikawa R, Miyasaka A and Koso T *et al.*. (2014) Antitumor activity and induction of TP53-dependent apoptosis toward ovarian clear cell adenocarcinoma by the dual PI3K/mTOR inhibitor DS-7423. *PLoS One* **9**: e87220 [PMID:24504419]
 64. Ketcham JM, Harwood SJ, Aranda R, Aloiau AN, Bobek BM, Briere DM, Burns AC, Caddell Haatveit K, Calinisan A and Clarine J *et al.*. (2024) Discovery of Pyridopyrimidinones that Selectively Inhibit the H1047R PI3K α Mutant Protein. *J Med Chem* **67**: 4936-4949 [PMID:38477582]
 65. Kim O, Jeong Y, Lee H, Hong SS and Hong S. (2011) Design and synthesis of imidazopyridine analogues as inhibitors of phosphoinositide 3-kinase signaling and angiogenesis. *J Med Chem* **54**: 2455-66 [PMID:21388141]
 66. King-Underwood J, Ito K, Murray PJ, Brookfield FA and Brown CJ. (2012) QUINAZOLIN-4 (3H) - ONE DERIVATIVES USED AS PI3 KINASE INHIBITORS Patent number: WO2012052753.
 67. Knight SD, Adams ND, Burgess JL, Chaudhari AM, Darcy MG, Donatelli CA, Luengo JI, Newlander KA, Parrish CA and Ridgers LH *et al.*. (2010) Discovery of GSK2126458, a Highly Potent Inhibitor of PI3K and the Mammalian Target of Rapamycin. *ACS Med Chem Lett* **1**: 39-43 [PMID:24900173]
 68. Knight ZA, Gonzalez B, Feldman ME, Zunder ER, Goldenberg DD, Williams O, Loewith R, Stokoe D, Balla A and Toth B *et al.*. (2006) A pharmacological map of the PI3-K family defines a role for p110alpha in insulin signaling. *Cell* **125**: 733-47 [PMID:16647110]
 69. Knight ZA and Shokat KM. (2005) Features of selective kinase inhibitors. *Chem Biol* **12**: 621-37 [PMID:15975507]
 70. Lannutti BJ, Meadows SA, Herman SE, Kashishian A, Steiner B, Johnson AJ, Byrd JC, Tyner JW, Loriaux MM and Deininger M *et al.*. (2011) CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. *Blood* **117**: 591-4 [PMID:20959606]
 71. Li Y-L, Metcalf BW and Combs AP. (2011) Pyrimidinones as PI3K inhibitors Patent number: WO2011008487.
 72. Li Y-L, Yao W, Combs AP, Yue EW, Mei S, Zhu W, Glenn J, Maduskuie TP Jr, Sparks RB and Douty B. (2013) Heterocycllamines as pi3k inhibitors Patent number: WO2013033569A1.
 73. Lin S, Jin J, Liu Y, Tian H, Zhang Y, Fu R, Zhang J, Wang M, Du T and Ji M *et al.*. (2019) Discovery of 4-Methylquinazoline Based PI3K Inhibitors for the Potential Treatment of Idiopathic Pulmonary Fibrosis. *J Med Chem* **62**: 8873-8879 [PMID:31335136]
 74. Liu F, Wang J, Yang X, Li B, Wu H, Qi S, Chen C, Liu X, Yu K and Wang W *et al.*. (2016) Discovery of a Highly Selective STK16 Kinase Inhibitor. *ACS Chem Biol* **11**: 1537-43 [PMID:27082499]
 75. Liu KK, Zhu J, Smith GL, Yin MJ, Bailey S, Chen JH, Hu Q, Huang Q, Li C and Li QJ *et al.*. (2011) Highly Selective and Potent Thiophenes as PI3K Inhibitors with Oral Antitumor Activity. *ACS Med Chem Lett* **2**: 809-13 [PMID:24900269]
 76. Liu N, Rowley BR, Bull CO, Schneider C, Haegebarth A, Schatz CA, Fracasso PR, Wilkie DP, Hentemann M and Wilhelm SM *et al.*. (2013) BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110 α and p110 δ activities in tumor cell lines and xenograft models. *Mol Cancer Ther* **12**: 2319-30 [PMID:24170767]
 77. Liu Q, Shi Q, Marcoux D, Batt DG, Cornelius L, Qin LY, Ruan Z, Neels J, Beaudoin-Bertrand M and Srivastava AS *et al.*. (2017) Identification of a Potent, Selective, and Efficacious Phosphatidylinositol 3-Kinase 6 (PI3K6) Inhibitor for the Treatment of Immunological Disorders. *J Med Chem* **60**: 5193-5208 [PMID:28541707]
 78. Liu Q, Wang J, Kang SA, Thoreen CC, Hur W, Ahmed T, Sabatini DM and Gray NS. (2011) Discovery of 9-(6-aminopyridin-3-yl)-1-(3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (Torin2) as a potent, selective, and orally available mammalian target of rapamycin (mTOR) inhibitor for treatment of cancer. *J Med Chem* **54**: 1473-80 [PMID:21322566]
 79. Lucas CL, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, Avery DT, Moens L, Cannons JL and Biancalana M *et al.*. (2014) Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110 δ result in T cell senescence and human immunodeficiency. *Nat Immunol* **15**: 88-97 [PMID:24165795]
 80. Luo Y, Xia Y, Wang W, Li Z, Jin Y, Gong Y, He T, Li Q, Li C and Yang J. (2018) Identification of a novel de novo gain-of-function mutation of PIK3CD in a patient with activated phosphoinositide 3-kinase 6 syndrome. *Clin Immunol* **197**: 60-67 [PMID:30138677]

81. Maira SM, Stauffer F, Brueggen J, Furet P, Schnell C, Fritsch C, Brachmann S, Chène P, De Pover A and Schoemaker K *et al.*. (2008) Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. *Mol Cancer Ther* **7**: 1851-63 [[PMID:18606717](#)]
82. Markman B, Tabernero J, Krop I, Shapiro GI, Siu L, Chen LC, Mita M, Melendez Cuero M, Stutvoet S and Birle D *et al.*. (2012) Phase I safety, pharmacokinetic, and pharmacodynamic study of the oral phosphatidylinositol-3-kinase and mTOR inhibitor BGT226 in patients with advanced solid tumors. *Ann Oncol* **23**: 2399-408 [[PMID:22357447](#)]
83. Methot JL, Zhou H, Kattar SD, McGowan MA, Wilson K, Garcia Y, Deng Y, Altman M, Fradera X and Lesburg C *et al.*. (2019) Structure Overhaul Affords a Potent Purine PI3Kδ Inhibitor with Improved Tolerability. *J Med Chem* **62**: 4370-4382 [[PMID:30986068](#)]
84. Mårdh CK, Root J, Uddin M, Stenvall K, Malmgren A, Karabelas K and Thomas M. (2017) Targets of Neutrophil Influx and Weaponry: Therapeutic Opportunities for Chronic Obstructive Airway Disease. *J Immunol Res* **2017**: 5273201 [[PMID:28596972](#)]
85. Nacht M, Qiao L, Sheets MP, St Martin T, Labenski M, Mazdiyasni H, Karp R, Zhu Z, Chaturvedi P and Bhavsar D *et al.*. (2013) Discovery of a Potent and Isoform-Selective Targeted Covalent Inhibitor of the Lipid Kinase PI3K α . *J Med Chem* **56**: 712-21 [[PMID:23360348](#)]
86. Ndubaku CO, Heffron TP, Staben ST, Baumgardner M, Blaquiere N, Bradley E, Bull R, Do S, Dotson J and Dudley D *et al.*. (2013) Discovery of 2-[3-[2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl]-1H-pyrazol-1-yl]-2-methylpropanamide (GDC-0032): a β -sparing phosphoinositide 3-kinase inhibitor with high unbound exposure and robust in vivo antitumor activity. *J Med Chem* **56**: 4597-610 [[PMID:23662903](#)]
87. Nylander S, Kull B, Björkman JA, Ulvinge JC, Oakes N, Emanuelsson BM, Andersson M, Skärby T, Inghardt T and Fjellström O *et al.*. (2012) Human target validation of phosphoinositide 3-kinase (PI3K) β : effects on platelets and insulin sensitivity, using AZD6482 a novel PI3K β inhibitor. *J Thromb Haemost* **10**: 2127-36 [[PMID:22906130](#)]
88. Ohwada J, Ebiike H, Kawada H, Tsukazaki M, Nakamura M, Miyazaki T, Morikami K, Yoshinari K, Yoshida M and Kondoh O *et al.*. (2011) Discovery and biological activity of a novel class I PI3K inhibitor, CH5132799. *Bioorg Med Chem Lett* **21**: 1767-72 [[PMID:21316229](#)]
89. Palanki MS, Dneprovskaya E, Doukas J, Fine RM, Hood J, Kang X, Lohse D, Martin M, Noronha G and Soll RM *et al.*. (2007) Discovery of 3,3'-(2,4-diaminopteridine-6,7-diy)diphenol as an isozyme-selective inhibitor of PI3K for the treatment of ischemia reperfusion injury associated with myocardial infarction. *J Med Chem* **50**: 4279-94 [[PMID:17685602](#)]
90. Pemberton N, Mogemark M, Arlbrandt S, Bold P, Cox RJ, Gardelli C, Holden NS, Karabelas K, Karlsson J and Lever S *et al.*. (2018) Discovery of Highly Isoform Selective Orally Bioavailable Phosphoinositide 3-Kinase (PI3K)- γ Inhibitors. *J Med Chem* **61**: 5435-5441 [[PMID:29852070](#)]
91. Perry M, Karabelas K, Mogemark M, Bold P, Tyrchan C, Nikitidid A, Petersen J and Borjesson U. (2018) 5-[2-(pyridin-2-ylamino)-1,3-thiazol-5-yl]-2,3-dihydro-1 h-isoindol-1 -one derivatives and their use as dual inhibitors of phosphatidylinositol 3-kinase delta & gamma Patent number: WO2018055040A1.
92. Perry MWD, Björhall K, Bonn B, Carlsson J, Chen Y, Eriksson A, Fredlund L, Hao H, Holden NS and Karabelas K *et al.*. (2017) Design and Synthesis of Soluble and Cell-Permeable PI3K δ Inhibitors for Long-Acting Inhaled Administration. *J Med Chem* **60**: 5057-5071 [[PMID:28520415](#)]
93. Pomet V, Klicic J, Covini D, Church DD, Shaw JP, Roulin K, Burgat-Charvillon F, Valognes D, Camps M and Chabert C *et al.*. (2006) Furan-2-ylmethylenethiazolidinediones as novel, potent, and selective inhibitors of phosphoinositide 3-kinase gamma. *J Med Chem* **49**: 3857-71 [[PMID:16789742](#)]
94. Qian C, Lai CJ, Bao R, Wang DG, Wang J, Xu GX, Atoyan R, Qu H, Yin L and Samson M *et al.*. (2012) Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. *Clin Cancer Res* **18**: 4104-13 [[PMID:22693356](#)]
95. Rae W, Gao Y, Ward D, Mattocks CJ, Eren E and Williams AP. (2017) A novel germline gain-of-function variant in PIK3CD. *Clin Immunol* **181**: 29-31 [[PMID:28578023](#)]
96. Rageot D, Bohnacker T, Melone A, Langlois JB, Borsari C, Hillmann P, Sele AM, Beaufils F, Zvelebil M and Hebeisen P *et al.*. (2018) Discovery and Preclinical Characterization of 5-[4,6-Bis({3-oxa-8-azabicyclo[3.2.1]octan-8-yl})-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine (PQR620), a Highly Potent and Selective mTORC1/2 Inhibitor for Cancer and Neurological Disorders. *J Med Chem* **61**: 10084-10105 [[PMID:30359003](#)]
97. Raynaud FI, Eccles SA, Patel S, Alix S, Box G, Chuckowree I, Folkes A, Gowan S, De Haven Brandon A and Di Stefano F *et al.*. (2009) Biological properties of potent inhibitors of class I phosphatidylinositol 3-kinases: from PI-103 through PI-540, PI-620 to the oral agent GDC-0941. *Mol Cancer Ther* **8**: 1725-38 [[PMID:19584227](#)]
98. Ren P, Liu Y, Li L, Chan K, Wilson TE and Campbell SF.. (2013) Heterocyclic compounds and uses thereof. Patent number: US20130035324 A1.
99. Sadhu C, Masinovsky B, Dick K, Sowell CG and Staunton DE. (2003) Essential role of

- phosphoinositide 3-kinase delta in neutrophil directional movement. *J Immunol* **170**: 2647-54 [PMID:12594293]
100. Shugg RP, Thomson A, Tanabe N, Kashishian A, Steiner BH, Puri KD, Pereverzev A, Lannutti BJ, Jirik FR and Dixon SJ *et al.*.. (2013) Effects of isoform-selective phosphatidylinositol 3-kinase inhibitors on osteoclasts: actions on cytoskeletal organization, survival, and resorption. *J Biol Chem* **288**: 35346-57 [PMID:24133210]
101. Su W-G, Dai G, Zhang W and Deng W. (2016) Novel imidazopyridazine compounds and their use Patent number: WO2016045591A1.
102. Sutherlin DP, Bao L, Berry M, Castanedo G, Chuckowree I, Dotson J, Folks A, Friedman L, Goldsmith R and Gunzner J *et al.*.. (2011) Discovery of a potent, selective, and orally available class I phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) kinase inhibitor (GDC-0980) for the treatment of cancer. *J Med Chem* **54**: 7579-87 [PMID:21981714]
103. Taddei DMA, Onions ST, Smith AJ, Copmans AH and Broeckx RLM. (2016) Phosphoinositide 3-kinase inhibitors Patent number: US9227977B2.
104. Takeda AJ, Zhang Y, Dornan GL, Siempelkamp BD, Jenkins ML, Matthews HF, McElwee JJ, Bi W, Seeborg FO and Su HC *et al.*.. (2017) Novel PIK3CD mutations affecting N-terminal residues of p110 δ cause activated PI3K δ syndrome (APDS) in humans. *J Allergy Clin Immunol* **140**: 1152-1156.e10 [PMID:28414062]
105. Tang Y, Zheng F, Bao X, Zheng Y, Hu X, Lou S, Zhao H and Cui S. (2023) Discovery of Highly Selective and Orally Bioavailable PI3K δ Inhibitors with Anti-Inflammatory Activity for Treatment of Acute Lung Injury. *J Med Chem* **66**: 11905-11926 [PMID:37606563]
106. Tsujita Y, Mitsui-Sekinaka K, Imai K, Yeh TW, Mitsuiki N, Asano T, Ohnishi H, Kato Z, Sekinaka Y and Zaha K *et al.*.. (2016) Phosphatase and tensin homolog (PTEN) mutation can cause activated phosphatidylinositol 3-kinase δ syndrome-like immunodeficiency. *J Allergy Clin Immunol* **138**: 1672-1680.e10 [PMID:27426521]
107. Uddin M, Lau LC, Seumois G, Vijayanand P, Staples KJ, Bagmane D, Cornelius V, Dorinsky P, Davies DE and Djukanović R. (2013) EGF-induced bronchial epithelial cells drive neutrophil chemotactic and anti-apoptotic activity in asthma. *PLoS ONE* **8**: e72502 [PMID:24039773]
108. Vadas O, Burke JE, Zhang X, Berndt A and Williams RL. (2011) Structural basis for activation and inhibition of class I phosphoinositide 3-kinases. *Sci Signal* **4**: re2 [PMID:22009150]
109. Vakkalanka SKVS, Bhavar PK, Viswanadha S and Babu G. (2017) Dual selective PI3 delta and gamma kinase inhibitors Patent number: US9790224B2.
110. Vakkalanka SKVS, Muthuppalaniappan M and Nagarathnam D.. (2014) Novel selective pi3k delta inhibitors. Patent number: US20140011819 A1.
111. Vanhaesebroeck B, Welham MJ, Kotani K, Stein R, Warne PH, Zvelebil MJ, Higashi K, Volinia S, Downward J and Waterfield MD. (1997) P110delta, a novel phosphoinositide 3-kinase in leukocytes. *Proc Natl Acad Sci USA* **94**: 4330-5 [PMID:9113989]
112. Varkaris A, Pazolli E, Gunaydin H, Wang Q, Pierce L, Boezio AA, Bulku A, DiPietro L, Fridrich C and Frost A *et al.*.. (2024) Discovery and Clinical Proof-of-Concept of RLY-2608, a First-in-Class Mutant-Selective Allosteric PI3K α Inhibitor That Decouples Antitumor Activity from Hyperinsulinemia. *Cancer Discov* **14**: 240-257 [PMID:37916956]
113. Venkatesan AM, Dehnhardt CM, Delos Santos E, Chen Z, Dos Santos O, Ayral-Kaloustian S, Khafizova G, Brooijmans N, Mallon R and Hollander I *et al.*.. (2010) Bis(morpholino-1,3,5-triazine) derivatives: potent adenosine 5'-triphosphate competitive phosphatidylinositol-3-kinase/mammalian target of rapamycin inhibitors: discovery of compound 26 (PKI-587), a highly efficacious dual inhibitor. *J Med Chem* **53**: 2636-45 [PMID:20166697]
114. Venot Q, Blanc T, Rabia SH, Berteloot L, Ladraa S, Duong JP, Blanc E, Johnson SC, Hoguin C and Boccara O *et al.*.. (2018) Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* **558**: 540-546 [PMID:29899452]
115. Walker EH, Pacold ME, Perisic O, Stephens L, Hawkins PT, Wymann MP and Williams RL. (2000) Structural determinants of phosphoinositide 3-kinase inhibition by wortmannin, LY294002, quercetin, myricetin, and staurosporine. *Mol Cell* **6**: 909-19 [PMID:11090628]
116. Wentink M, Dalm V, Lankester AC, van Schouwenburg PA, Schölvinck L, Kalina T, Zachova R, Sediva A, Lambeck A and Pico-Knijnenburg I *et al.*.. (2017) Genetic defects in PI3K δ affect B-cell differentiation and maturation leading to hypogammaglobulineamia and recurrent infections. *Clin Immunol* **176**: 77-86 [PMID:28104464]
117. Winkler DG, Faia KL, DiNitto JP, Ali JA, White KF, Brophy EE, Pink MM, Proctor JL, Lussier J and Martin CM *et al.*.. (2013) PI3K- δ and PI3K- γ inhibition by IPI-145 abrogates immune responses and suppresses activity in autoimmune and inflammatory disease models. *Chem Biol* **20**: 1364-74 [PMID:24211136]
118. Wodicka LM, Ciceri P, Davis MI, Hunt JP, Floyd M, Salerno S, Hua XH, Ford JM, Armstrong RC and Zarrinkar PP *et al.*.. (2010) Activation state-dependent binding of small molecule kinase inhibitors: structural insights from biochemistry. *Chem Biol* **17**: 1241-9 [PMID:21095574]
119. Wu C, Yu T and Chen S. (2015) Pyridino[1,2-a]pyrimidone analogue used as pi3k inhibitor Patent number: WO2015192760A1.
120. Wu P and Hu Y.. (2012) Small molecules targeting phosphoinositide 3-kinases. *Medchemcomm*

3: 1337-1355

121. Xiang HY, Wang X, Chen YH, Zhang X, Tan C, Wang Y, Su Y, Gao ZW, Chen XY and Xiong B *et al.*. (2021) Identification of methyl (5-((4-(methylsulfonyl)piperazin-1-yl)methyl)-4-morpholinopyrrolo[2,1-f][1,2,4]triazin-2-yl)-4-(trifluoromethyl)pyridin-2-yl)carbamate (CYH33) as an orally bioavailable, highly potent, PI3K alpha inhibitor for the treatment of advanced solid tumors. *Eur J Med Chem* **209**: 112913 [[PMID:33109399](#)]
122. Xie C, He Y, Zhen M, Wang Y, Xu Y and Lou L. (2017) Puquitinib, a novel orally available PI3K δ inhibitor, exhibits potent antitumor efficacy against acute myeloid leukemia. *Cancer Sci* **108**: 1476-1484 [[PMID:28418085](#)]
123. Xu Z and Lou Y. (2017) Fused heterocyclic compound, preparation method therefor, pharmaceutical composition, and uses thereof Patent number: US20160244432A1.
124. Yaguchi S, Fukui Y, Koshimizu I, Yoshimi H, Matsuno T, Gouda H, Hirono S, Yamazaki K and Yamori T. (2006) Antitumor activity of ZSTK474, a new phosphatidylinositol 3-kinase inhibitor. *J Natl Cancer Inst* **98**: 545-56 [[PMID:16622124](#)]
125. Yang J, Shamji A, Matchacheep S and Schreiber SL. (2007) Identification of a small-molecule inhibitor of class Ia PI3Ks with cell-based screening. *Chem Biol* **14**: 371-7 [[PMID:17462572](#)]
126. Yoon YN, Lee E, Kwon YJ, Gim JA, Kim TJ and Kim JS. (2022) PI3K δ/γ inhibitor BR101801 extrinsically potentiates effector CD8 $^{+}$ T cell-dependent antitumor immunity and abscopal effect after local irradiation. *J Immunother Cancer* **10**: e003762 [[PMID:35288465](#)]
127. Yu Y, Han Y, Zhang F, Gao Z, Zhu T, Dong S and Ma M. (2020) Design, Synthesis, and Biological Evaluation of Imidazo[1,2-a]pyridine Derivatives as Novel PI3K/mTOR Dual Inhibitors. *J Med Chem* **63**: 3028-3046 [[PMID:32069401](#)]
128. Zhan X and Su L. (2021) Three fused ring derivative-containing salt or crystal form and pharmaceutical composition thereof Patent number: WO2021104146A1.