

Endocannabinoid turnover in GtoPdb v.2025.3

Stephen P.H. Alexander¹, Patrick Doherty², Christopher J. Fowler³, Jürg Gertsch⁴ and Mario van der Stelt⁵

1. University of Nottingham, UK
2. King's College London, UK
3. University Hospital of Umeå, Sweden
4. University of Bern, Switzerland
5. Leiden University, The Netherlands

Abstract

The principle endocannabinoids are 2-acylglycerol esters, such as [2-arachidonoylglycerol](#) (2-AG), and *N*-acylethanolamines, such as [anandamide](#) (*N*-arachidonylethanolamine, AEA). The glycerol esters and ethanolamides are synthesised and hydrolysed by parallel, independent pathways. Mechanisms for release and re-uptake of endocannabinoids are unclear, although potent and selective inhibitors of facilitated diffusion of endocannabinoids across cell membranes have been developed [32]. [FABP5](#) ([Q01469](#)) has been suggested to act as a canonical intracellular endocannabinoid transporter *in vivo* [19]. For the generation of [2-arachidonoylglycerol](#), the key enzyme involved is diacylglycerol lipase (DAGL), whilst several routes for [anandamide](#) synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [79]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has been identified as a cytosolic enzyme, [PLA2G4E](#) ([Q3MJ16](#)) [70]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [6, 26, 81].

Contents

This is a citation summary for Endocannabinoid turnover 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 [13].

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

Endocannabinoid turnover

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=943>

N-Acylethanolamine turnover

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=273>

Enzymes

[NAPE-PLD](#)(*N*-Acylphosphatidylethanolamine-phospholipase D)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1398>

[FAAH](#)(Fatty acid amide hydrolase)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1400>

FAAH2(Fatty acid amide hydrolase-2)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1401>

NAAA(N-Acylethanolamine acid amidase)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1402>

2-Acylglycerol ester turnover

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=944>

Enzymes

DAGL α (diacylglycerol lipase α)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1396>

DAGL β (diacylglycerol lipase β)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1397>

MAGL(monoacylglycerol lipase)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1399>

ABHD2($\alpha\beta$ -Hydrolase 2)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=3147>

ABHD6($\alpha\beta$ -Hydrolase 6)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2919>

ABHD12($\alpha\beta$ -Hydrolase 12)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=3070>

References

1. Aaltonen N, Savinainen JR, Ribas CR, Rönkkö J, Kuusisto A, Korhonen J, Navia-Paldanius D, Häyrynen J, Takabe P and Käsänen H *et al.* (2013) Piperazine and piperidine triazole ureas as ultrapotent and highly selective inhibitors of monoacylglycerol lipase. *Chem Biol* **20**: 379-90 [PMID:23521796]
2. Aggarwal G, Zarrow JE, Mashhadi Z, Flynn CR, Vinson P, Weaver CD and Davies SS. (2020) Symmetrically substituted dichlorophenes inhibit N-acyl-phosphatidylethanolamine phospholipase D. *J Biol Chem* **295**: 7289-7300 [PMID:32284327]
3. Ahn K, Johnson DS, Fitzgerald LR, Liimatta M, Arendse A, Stevenson T, Lund ET, Nugent RA, Nomanbhoy TK and Alexander JP *et al.* (2007) Novel mechanistic class of fatty acid amide hydrolase inhibitors with remarkable selectivity. *Biochemistry* **46**: 13019-30 [PMID:17949010]
4. Ahn K, Johnson DS, Mileni M, Beidler D, Long JZ, McKinney MK, Weerapana E, Sadagopan N, Liimatta M and Smith SE *et al.* (2009) Discovery and characterization of a highly selective FAAH inhibitor that reduces inflammatory pain. *Chem Biol* **16**: 411-20 [PMID:19389627]
5. Ahn K, Smith SE, Liimatta MB, Beidler D, Sadagopan N, Dudley DT, Young T, Wren P, Zhang Y and Swaney S *et al.* (2011) Mechanistic and pharmacological characterization of PF-04457845: a highly potent and selective fatty acid amide hydrolase inhibitor that reduces inflammatory and noninflammatory pain. *J Pharmacol Exp Ther* **338**: 114-24 [PMID:21505060]
6. Alexander SP and Kendall DA. (2007) The complications of promiscuity: endocannabinoid action and metabolism. *Br J Pharmacol* **152**: 602-23 [PMID:17876303]
7. Bachovchin DA, Ji T, Li W, Simon GM, Blankman JL, Adibekian A, Hoover H, Niessen S and Cravatt BF. (2010) Superfamily-wide portrait of serine hydrolase inhibition achieved by library-versus-library screening. *Proc Natl Acad Sci USA* **107**: 20941-6 [PMID:21084632]
8. Baggelaar MP, Chameau PJ, Kantae V, Hummel J, Hsu KL, Janssen F, van der Wel T, Soethoudt M, Deng H and den Dulk H *et al.* (2015) Highly Selective, Reversible Inhibitor Identified by Comparative Chemoproteomics Modulates Diacylglycerol Lipase Activity in Neurons. *J Am Chem Soc* **137**: 8851-7 [PMID:26083464]
9. Baggelaar MP, Maccarrone M and van der Stelt M. (2018) 2-Arachidonoylglycerol: A signaling lipid with manifold actions in the brain. *Prog Lipid Res* **71**: 1-17 [PMID:29751000]
10. Bisogno T, Howell F, Williams G, Minassi A, Cascio MG, Ligresti A, Matias I, Schiano-Moriello A, Paul P and Williams EJ *et al.* (2003) Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. *J Cell Biol* **163**: 463-8 [PMID:14610053]
11. Blankman JL, Long JZ, Trauger SA, Siuzdak G and Cravatt BF. (2013) ABHD12 controls brain lysophosphatidylserine pathways that are deregulated in a murine model of the neurodegenerative disease PHARC. *Proc Natl Acad Sci USA* **110**: 1500-5 [PMID:23297193]
12. Blankman JL, Simon GM and Cravatt BF. (2007) A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. *Chem Biol* **14**: 1347-56 [PMID:18096503]
13. 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]
14. Bühler KM, Huertas E, Echeverry-Alzate V, Giné E, Moltó E, Montoliu L and López-Moreno JA. (2014) Risky alcohol consumption in young people is associated with the fatty acid amide hydrolase gene polymorphism C385A and affective rating of drug pictures. *Mol Genet Genomics*

289: 279-89 [PMID:24407958]

15. Cajanus K, Holmström EJ, Wessman M, Anttila V, Kaunisto MA and Kalso E. (2016) Effect of endocannabinoid degradation on pain: role of FAAH polymorphisms in experimental and postoperative pain in women treated for breast cancer. *Pain* **157**: 361-9 [PMID:26808012]
16. Castellani B, Diamanti E, Pizzirani D, Tardia P, Maccesi M, Realini N, Magotti P, Garau G, Bakkum T and Rivara S *et al.*. (2017) Synthesis and characterization of the first inhibitor of N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD). *Chem Commun (Camb.)* **53**: 12814-12817 [PMID:29143042]
17. Chang JW, Niphakis MJ, Lum KM, Cognetta 3rd AB, Wang C, Matthews ML, Niessen S, Buczynski MW, Parsons LH and Cravatt BF. (2012) Highly selective inhibitors of monoacylglycerol lipase bearing a reactive group that is bioisosteric with endocannabinoid substrates. *Chem Biol* **19**: 579-88 [PMID:22542104]
18. Chiarugi S, Margheriti F, De Lorenzi V, Martino E, Margheritis EG, Moscardini A, Marotta R, Chaves-Sanjuan A, Del Seppia C and Federighi G *et al.*. (2025) NAPE-PLD is target of thiazide diuretics. *Cell Chem Biol* **32**: 449-462.e5 [PMID:39999832]
19. Chicca A, Nicolussi S, Bartholomäus R, Blunder M, Aparisi Rey A, Petrucci V, Reynoso-Moreno IDC, Viveros-Paredes JM, Dalghi Gens M and Lutz B *et al.*. (2017) Chemical probes to potently and selectively inhibit endocannabinoid cellular reuptake. *Proc Natl Acad Sci USA* **114**: E5006-E5015 [PMID:28584105]
20. Cisar JS, Weber OD, Clapper JR, Blankman JL, Henry CL, Simon GM, Alexander JP, Jones TK, Ezekowitz RAB and O'Neill GP *et al.*. (2018) Identification of ABX-1431, a Selective Inhibitor of Monoacylglycerol Lipase and Clinical Candidate for Treatment of Neurological Disorders. *J Med Chem* **61**: 9062-9084 [PMID:30067909]
21. Clapper JR, Henry CL, Niphakis MJ, Knize AM, Coppola AR, Simon GM, Ngo N, Herbst RA, Herbst DM and Reed AW *et al.*. (2018) Monoacylglycerol Lipase Inhibition in Human and Rodent Systems Supports Clinical Evaluation of Endocannabinoid Modulators. *J Pharmacol Exp Ther* **367**: 494-508 [PMID:30305428]
22. Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR and Lichtman AH. (2001) Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc Natl Acad Sci USA* **98**: 9371-6 [PMID:11470906]
23. Deng H, Kooijman S, van den Nieuwendijk AM, Ogasawara D, van der Wel T, van Dalen F, Baggelaar MP, Janssen FJ, van den Berg RJ and den Dulk H *et al.*. (2017) Triazole Ureas Act as Diacylglycerol Lipase Inhibitors and Prevent Fasting-Induced Refeeding. *J Med Chem* **60**: 428-440 [PMID:27992221]
24. Fiskerstrand T, H'mida-Ben Brahim D, Johansson S, M'zahem A, Haukanes BI, Drouot N, Zimmermann J, Cole AJ, Vedeler C and Bredrup C *et al.*. (2010) Mutations in ABHD12 cause the neurodegenerative disease PHARC: An inborn error of endocannabinoid metabolism. *Am J Hum Genet* **87**: 410-7 [PMID:20797687]
25. Fiskerstrand T, Knappskog P, Majewski J, Wanders RJ, Boman H and Bindoff LA. (2009) A novel Refsum-like disorder that maps to chromosome 20. *Neurology* **72**: 20-7 [PMID:19005174]
26. Fowler CJ. (2007) The contribution of cyclooxygenase-2 to endocannabinoid metabolism and action. *Br J Pharmacol* **152**: 594-601 [PMID:17618306]
27. Ghafouri N, Tiger G, Razdan RK, Mahadevan A, Pertwee RG, Martin BR and Fowler CJ. (2004) Inhibition of monoacylglycerol lipase and fatty acid amide hydrolase by analogues of 2-arachidonoylglycerol. *Br J Pharmacol* **143**: 774-84 [PMID:15492019]
28. Giang DK and Cravatt BF. (1997) Molecular characterization of human and mouse fatty acid amide hydrolases. *Proc Natl Acad Sci USA* **94**: 2238-42 [PMID:9122178]
29. Gorelik A, Gebai A, Illes K, Piomelli D and Nagar B. (2018) Molecular mechanism of activation of the immunoregulatory amidase NAAA. *Proc Natl Acad Sci USA* **115**: E10032-E10040 [PMID:30301806]
30. Granchi C, Rizzolio F, Bordoni V, Caligiuri I, Manera C, Macchia M, Minutolo F, Martinelli A, Giordano A and Tuccinardi T. (2016) 4-Aryliden-2-methyloxazol-5(4H)-one as a new scaffold for selective reversible MAGL inhibitors. *J Enzyme Inhib Med Chem* **31**: 137-46 [PMID:25669350]
31. Habib AM, Okorokov AL, Hill MN, Bras JT, Lee MC, Li S, Gossage SJ, van Drimmelen M, Morena M and Houlden H *et al.*. (2019) Microdeletion in a FAAH pseudogene identified in a patient with high anandamide concentrations and pain insensitivity. *Br J Anaesth* **123**: e249-e253 [PMID:30929760]
32. Haj-Dahmane S, Shen RY, Elmes MW, Studholme K, Kanjiya MP, Bogdan D, Thanos PK, Miyauchi JT, Tsirka SE and Deutsch DG *et al.*. (2018) Fatty-acid-binding protein 5 controls retrograde endocannabinoid signaling at central glutamate synapses. *Proc Natl Acad Sci USA* **115**: 3482-3487 [PMID:29531087]
33. Hammock B and Kodani S. (2017) Inhibitors for soluble epoxide hydrolase (seh) and fatty acid amide hydrolase (faah) Patent number: WO2017160861A1. Assignee: The Regents Of The University Of California. Priority date: 15/03/2016. Publication date: 21/09/2017.
34. Hoover HS, Blankman JL, Niessen S and Cravatt BF. (2008) Selectivity of inhibitors of endocannabinoid biosynthesis evaluated by activity-based protein profiling. *Bioorg Med Chem*

Lett **18**: 5838-41 [PMID:18657971]

35. Hsu KL, Tsuboi K, Adibekian A, Pugh H, Masuda K and Cravatt BF. (2012) DAGL β inhibition perturbs a lipid network involved in macrophage inflammatory responses. *Nat Chem Biol* **8**: 999-1007 [PMID:23103940]
36. Ikeda S, Sugiyama H, Tokuhara H, Murakami M, Nakamura M, Oguro Y, Aida J, Morishita N, Sogabe S and Dougan DR *et al.*. (2021) Design and Synthesis of Novel Spiro Derivatives as Potent and Reversible Monoacylglycerol Lipase (MAGL) Inhibitors: Bioisosteric Transformation from 3-Oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl Moiety. *J Med Chem* **64**: 11014-11044 [PMID:34328319]
37. Jiang M, Huizenga MCW, Wirt JL, Paloczi J, Amedi A, van den Berg RJBHN, Benz J, Collin L, Deng H and Di X *et al.*. (2023) A monoacylglycerol lipase inhibitor showing therapeutic efficacy in mice without central side effects or dependence. *Nat Commun* **14**: 8039 [PMID:38052772]
38. Johnson DS, Stiff C, Lazerwith SE, Kesten SR, Fay LK, Morris M, Beidler D, Liimatta MB, Smith SE and Dudley DT *et al.*. (2011) Discovery of PF-04457845: A Highly Potent, Orally Bioavailable, and Selective Urea FAAH Inhibitor. *ACS Med Chem Lett* **2**: 91-96 [PMID:21666860]
39. Johnston M, Bhatt SR, Sikka S, Mercier RW, West JM, Makriyannis A, Gatley SJ and Duclos Jr RI. (2012) Assay and inhibition of diacylglycerol lipase activity. *Bioorg Med Chem Lett* **22**: 4585-92 [PMID:22738638]
40. Kamat SS, Camara K, Parsons WH, Chen DH, Dix MM, Bird TD, Howell AR and Cravatt BF. (2015) Immunomodulatory lysophosphatidylserines are regulated by ABHD16A and ABHD12 interplay. *Nat Chem Biol* **11**: 164-71 [PMID:25580854]
41. Karbarz MJ, Luo L, Chang L, Tham CS, Palmer JA, Wilson SJ, Wennerholm ML, Brown SM, Scott BP and Apodaca RL *et al.*. (2009) Biochemical and biological properties of 4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazine-1-carboxylic acid phenylamide, a mechanism-based inhibitor of fatty acid amide hydrolase. *Anesth Analg* **108**: 316-29 [PMID:19095868]
42. Keith JM, Apodaca R, Tichenor M, Xiao W, Jones W, Pierce J, Seierstad M, Palmer J, Webb M and Karbarz M *et al.*. (2012) Aryl Piperazinyl Ureas as Inhibitors of Fatty Acid Amide Hydrolase (FAAH) in Rat, Dog, and Primate. *ACS Med Chem Lett* **3**: 823-7 [PMID:24900385]
43. Keith JM, Apodaca R, Xiao W, Seierstad M, Pattabiraman K, Wu J, Webb M, Karbarz MJ, Brown S and Wilson S *et al.*. (2008) Thiadiazolopiperazinyl ureas as inhibitors of fatty acid amide hydrolase. *Bioorg Med Chem Lett* **18**: 4838-43 [PMID:18693015]
44. Keith JM and Liu J. (2011) Modulators of fatty acid amide hydrolase. Patent number: WO2011139951 A1. Assignee: Janssen Pharmaceutica Nv. Priority date: 03/05/2010. Publication date: 10/11/2011.
45. Kiss LE *et al.*. (2010) Pharmaceutical compounds. Patent number: WO2010074588 A2. Assignee: BIAL- PORTELA & C^a, S.A. Priority date: 24/12/2008. Publication date: 01/07/2010.
46. Kiss LE, Ferreira HS, Beliaev A, Torrao L and Bonafacio MJ Learmonth DA.. (2011) Design, synthesis, and structure-activity relationships of 1,3,4-oxadiazol-2(3H)-ones as novel FAAH inhibitors. *Medchemcomm* **2**: 889-894
47. Knight MA, Hernandez D, Diede SJ, Dauwerse HG, Rafferty I, van de Leemput J, Forrest SM, Gardner RJ, Storey E and van Ommen GJ *et al.*. (2008) A duplication at chromosome 11q12.2-11q12.3 is associated with spinocerebellar ataxia type 20. *Hum Mol Genet* **17**: 3847-53 [PMID:18801880]
48. Kodani SD, Wan D, Wagner KM, Hwang SH, Morisseau C and Hammock BD. (2018) Design and Potency of Dual Soluble Epoxide Hydrolase/Fatty Acid Amide Hydrolase Inhibitors. *ACS Omega* **3**: 14076-14086 [PMID:30411058]
49. Li W, Blankman JL and Cravatt BF. (2007) A functional proteomic strategy to discover inhibitors for uncharacterized hydrolases. *J Am Chem Soc* **129**: 9594-5 [PMID:17629278]
50. Li Y, Chen Q, Yang L, Li Y, Zhang Y, Qiu Y, Ren J and Lu C. (2017) Identification of highly potent N-acylethanolamine acid amidase (NAAA) inhibitors: Optimization of the terminal phenyl moiety of oxazolidone derivatives. *Eur J Med Chem* **139**: 214-221 [PMID:28802121]
51. Li Y, Zhou P, Chen H, Chen Q, Kuang X, Lu C, Ren J and Qiu Y. (2018) Inflammation-restricted anti-inflammatory activities of a N-acylethanolamine acid amidase (NAAA) inhibitor F215. *Pharmacol Res* **132**: 7-14 [PMID:29572189]
52. Lim ET, Raychaudhuri S, Sanders SJ, Stevens C, Sabo A, MacArthur DG, Neale BM, Kirby A, Ruderfer DM and Fromer M *et al.*. (2013) Rare complete knockouts in humans: population distribution and significant role in autism spectrum disorders. *Neuron* **77**: 235-42 [PMID:23352160]
53. Liu Q, Tonai T and Ueda N. (2002) Activation of N-acylethanolamine-releasing phospholipase D by polyamines. *Chem Phys Lipids* **115**: 77-84 [PMID:12047899]
54. Long JZ, Li W, Booker L, Burston JJ, Kinsey SG, Schlosburg JE, Pavón FJ, Serrano AM, Selley DE and Parsons LH *et al.*. (2009) Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. *Nat Chem Biol* **5**: 37-44 [PMID:19029917]
55. Long JZ, Nomura DK, Vann RE, Walentiny DM, Booker L, Jin X, Burston JJ, Sim-Selley LJ, Lichtman AH and Wiley JL *et al.*. (2009) Dual blockade of FAAH and MAGL identifies behavioral

processes regulated by endocannabinoid crosstalk in vivo. *Proc Natl Acad Sci USA* **106**: 20270-5 [PMID:19918051]

56. M NK, V B S C T, G K V, B CS, Guntupalli S and J S B. (2016) Molecular characterization of human ABHD2 as TAG lipase and ester hydrolase. *Biosci Rep* **36** [PMID:27247428]
57. Migliore M, Habrant D, Sasso O, Albani C, Bertozzi SM, Armirotti A, Piomelli D and Scarpelli R. (2016) Potent multitarget FAAH-COX inhibitors: Design and structure-activity relationship studies. *Eur J Med Chem* **109**: 216-37 [PMID:26774927]
58. Migliore M, Pontis S, Fuentes de Arriba AL, Realini N, Torrente E, Armirotti A, Romeo E, Di Martino S, Russo D and Pizzirani D *et al.*. (2016) Second-Generation Non-Covalent NAAA Inhibitors are Protective in a Model of Multiple Sclerosis. *Angew Chem Int Ed Engl* **55**: 11193-7 [PMID:27404798]
59. Miller MR, Mannowetz N, Iavarone AT, Safavi R, Gracheva EO, Smith JF, Hill RZ, Bautista DM, Kirichok Y and Lishko PV. (2016) Unconventional endocannabinoid signaling governs sperm activation via the sex hormone progesterone. *Science* **352**: 555-9 [PMID:26989199]
60. Mock ED, Mustafa M, Gunduz-Cinar O, Cinar R, Petrie GN, Kantae V, Di X, Ogasawara D, Varga ZV and Paloczi J *et al.*. (2020) Discovery of a NAPE-PLD inhibitor that modulates emotional behavior in mice. *Nat Chem Biol* **16**: 667-675 [PMID:32393901]
61. Moreno-Sanz G, Duranti A, Melzig L, Fiorelli C, Ruda GF, Colombano G, Mestichelli P, Sanchini S, Tontini A and Mor M *et al.*. (2013) Synthesis and structure-activity relationship studies of O-biphenyl-3-yl carbamates as peripherally restricted fatty acid amide hydrolase inhibitors. *J Med Chem* **56**: 5917-30 [PMID:23822179]
62. Navia-Paldanius D, Savinainen JR and Laitinen JT. (2012) Biochemical and pharmacological characterization of human α/β -hydrolase domain containing 6 (ABHD6) and 12 (ABHD12). *J Lipid Res* **53**: 2413-24 [PMID:22969151]
63. Niphakis MJ, Cognetta 3rd AB, Chang JW, Buczynski MW, Parsons LH, Byrne F, Burston JJ, Chapman V and Cravatt BF. (2013) Evaluation of NHS carbamates as a potent and selective class of endocannabinoid hydrolase inhibitors. *ACS Chem Neurosci* **4**: 1322-32 [PMID:23731016]
64. Niphakis MJ, Johnson DS, Ballard TE, Stiff C and Cravatt BF. (2012) O-hydroxyacetamide carbamates as a highly potent and selective class of endocannabinoid hydrolase inhibitors. *ACS Chem Neurosci* **3**: 418-26 [PMID:22860211]
65. Nishiguchi KM, Avila-Fernandez A, van Huet RA, Corton M, Pérez-Carro R, Martín-Garrido E, López-Molina MI, Blanco-Kelly F, Hoefsloot LH and van Zelst-Stams WA *et al.*. (2014) Exome sequencing extends the phenotypic spectrum for ABHD12 mutations: from syndromic to nonsyndromic retinal degeneration. *Ophthalmology* **121**: 1620-7 [PMID:24697911]
66. Nuzzi A, Fiasella A, Ortega JA, Pagliuca C, Ponzano S, Pizzirani D, Bertozzi SM, Ottonello G, Tarozzo G and Reggiani A *et al.*. (2016) Potent α -amino- β -lactam carbamic acid ester as NAAA inhibitors. Synthesis and structure-activity relationship (SAR) studies. *Eur J Med Chem* **111**: 138-59 [PMID:26866968]
67. Ogasawara D, Deng H, Viader A, Baggelaar MP, Breman A, den Dulk H, van den Nieuwendijk AM, van den Nieuwendijk AM, Soethoudt M and van der Wel T *et al.*. (2016) Rapid and profound rewiring of brain lipid signaling networks by acute diacylglycerol lipase inhibition. *Proc Natl Acad Sci USA* **113**: 26-33 [PMID:26668358]
68. Ogasawara D, Ichu TA, Jing H, Hulce JJ, Reed A, Ulanovskaya OA and Cravatt BF. (2019) Discovery and Optimization of Selective and in Vivo Active Inhibitors of the Lysophosphatidylserine Lipase α/β -Hydrolase Domain-Containing 12 (ABHD12). *J Med Chem* **62**: 1643-1656 [PMID:30720278]
69. Ogasawara D, Ichu TA, Vartabedian VF, Benthuyssen J, Jing H, Reed A, Ulanovskaya OA, Hulce JJ, Roberts A and Brown S *et al.*. (2018) Selective blockade of the lyso-PS lipase ABHD12 stimulates immune responses in vivo. *Nat Chem Biol* **14**: 1099-1108 [PMID:30420694]
70. Ogura Y, Parsons WH, Kamat SS and Cravatt BF. (2016) A calcium-dependent acyltransferase that produces N-acyl phosphatidylethanolamines. *Nat Chem Biol* **12**: 669-71 [PMID:27399000]
71. Parkkari T, Haavikko R, Laitinen T, Navia-Paldanius D, Rytilahti R, Vaara M, Lehtonen M, Alakurtti S, Yli-Kauhaluoma J and Nevalainen T *et al.*. (2014) Discovery of triterpenoids as reversible inhibitors of α/β -hydrolase domain containing 12 (ABHD12). *PLoS ONE* **9**: e98286 [PMID:24879289]
72. Petersen A, Benz J, Grether U, Hornsperger B, Kocer B, Kuhn B, Richter H, Tsuchiya S, Qui Y and Chen R. (2019) Octahydropyrido[1,2- α]pyrazines as magl inhibitors Patent number: WO2019134985A1. Assignee: Hoffmann-La Roche. Priority date: 08/01/2018. Publication date: 11/07/2019.
73. Petersen G and Hansen HS. (1999) N-acylphosphatidylethanolamine-hydrolysing phospholipase D lacks the ability to transphosphatidylate. *FEBS Lett* **455**: 41-4 [PMID:10428468]
74. Petrosino S, Campolo M, Impellizzeri D, Paterniti I, Allarà M, Gugliandolo E, D'Amico R, Siracusa R, Cordaro M and Esposito E *et al.*. (2017) 2-Pentadecyl-2-Oxazoline, the Oxazoline of Pea, Modulates Carrageenan-Induced Acute Inflammation. *Front Pharmacol* **8**: 308 [PMID:28611664]

75. Piomelli D, Scalvini L, Fotio Y, Lodola A, Spadoni G, Tarzia G and Mor M. (2020) N-Acylethanolamine Acid Amidase (NAAA): Structure, Function, and Inhibition. *J Med Chem* **63**: 7475-7490 [PMID:32191459]
76. Ribeiro A, Pontis S, Mengatto L, Armirotti A, Chiurchiù V, Capurro V, Fiasella A, Nuzzi A, Romeo E and Moreno-Sanz G *et al.*. (2015) A Potent Systemically Active N-Acylethanolamine Acid Amidase Inhibitor that Suppresses Inflammation and Human Macrophage Activation. *ACS Chem Biol* **10**: 1838-46 [PMID:25874594]
77. Roughley S, Walls S, Hart T, Parsons R, Brough P, Graham C and Macias A. (2009) Azetidine derivatives. Patent number: WO2009109743 A1. Assignee: Vernalis (R&D) Ltd.. Priority date: 04/03/2008. Publication date: 11/09/2009.
78. Savinainen JR, Saario SM and Laitinen JT. (2012) The serine hydrolases MAGL, ABHD6 and ABHD12 as guardians of 2-arachidonoylglycerol signalling through cannabinoid receptors. *Acta Physiol (Oxf)* **204**: 267-76 [PMID:21418147]
79. Simon GM and Cravatt BF. (2010) Characterization of mice lacking candidate N-acyl ethanolamine biosynthetic enzymes provides evidence for multiple pathways that contribute to endocannabinoid production in vivo. *Mol Biosyst* **6**: 1411-8 [PMID:20393650]
80. Sirrs S, van Karnebeek CD, Peng X, Shyr C, Tarailo-Graovac M, Mandal R, Testa D, Dubin D, Carbonetti G and Glynn SE *et al.*. (2015) Defects in fatty acid amide hydrolase 2 in a male with neurologic and psychiatric symptoms. *Orphanet J Rare Dis* **10**: 38 [PMID:25885783]
81. Snider NT, Walker VJ and Hollenberg PF. (2010) Oxidation of the endogenous cannabinoid arachidonoyl ethanolamide by the cytochrome P450 monooxygenases: physiological and pharmacological implications. *Pharmacol Rev* **62**: 136-54 [PMID:20133390]
82. Solorzano C, Zhu C, Battista N, Astarita G, Lodola A, Rivara S, Mor M, Russo R, Maccarrone M and Antonietti F *et al.*. (2009) Selective N-acylethanolamine-hydrolyzing acid amidase inhibition reveals a key role for endogenous palmitoylethanolamide in inflammation. *Proc Natl Acad Sci USA* **106**: 20966-71 [PMID:19926854]
83. Spadoni G, Bedini A, Furiassi L, Mari M, Mor M, Scalvini L, Lodola A, Ghidini A, Lucini V and Dugnani S *et al.*. (2018) Identification of Bivalent Ligands with Melatonin Receptor Agonist and Fatty Acid Amide Hydrolase (FAAH) Inhibitory Activity That Exhibit Ocular Hypotensive Effect in the Rabbit. *J Med Chem* **61**: 7902-7916 [PMID:30126274]
84. Tanaka M, Moran S, Wen J, Affram K, Chen T, Symes AJ and Zhang Y. (2017) WWL70 attenuates PGE2 production derived from 2-arachidonoylglycerol in microglia by ABHD6-independent mechanism. *J Neuroinflammation* **14**: 7 [PMID:28086912]
85. Thorel MF, Krichevsky M and Lévy-Frébault VV. (1990) Numerical taxonomy of mycobactin-dependent mycobacteria, emended description of *Mycobacterium avium*, and description of *Mycobacterium avium* subsp. *avium* subsp. nov., *Mycobacterium avium* subsp. *paratuberculosis* subsp. nov., and *Mycobacterium avium* subsp. *silvaticum* subsp. nov. *Int J Syst Bacteriol* **40**: 254-60 [PMID:2397193]
86. Tingaud-Sequeira A, Raldúa D, Lavie J, Mathieu G, Bordier M, Knoll-Gellida A, Rambeau P, Couprie I, André M and Malm E *et al.*. (2017) Functional validation of ABHD12 mutations in the neurodegenerative disease PHARC. *Neurobiol Dis* **98**: 36-51 [PMID:27890673]
87. Tsuboi K, Hilligsmann C, Vandevorde S, Lambert DM and Ueda N. (2004) N-cyclohexanecarbonylpentadecylamine: a selective inhibitor of the acid amidase hydrolysing N-acylethanolamines, as a tool to distinguish acid amidase from fatty acid amide hydrolase. *Biochem J* **379**: 99-106 [PMID:14686878]
88. Tsuboi K, Ikematsu N, Uyama T, Deutsch DG, Tokumura A and Ueda N. (2013) Biosynthetic pathways of bioactive N-acylethanolamines in brain. *CNS Neurol Disord Drug Targets* **12**: 7-16 [PMID:23394527]
89. Tuo W, Leleu-Chavain N, Spencer J, Sansook S, Millet R and Chavatte P. (2017) Therapeutic Potential of Fatty Acid Amide Hydrolase, Monoacylglycerol Lipase, and N-Acylethanolamine Acid Amidase Inhibitors. *J Med Chem* **60**: 4-46 [PMID:27766867]
90. Ueda N, Yamanaka K and Yamamoto S. (2001) Purification and characterization of an acid amidase selective for N-palmitoylethanolamine, a putative endogenous anti-inflammatory substance. *J Biol Chem* **276**: 35552-7 [PMID:11463796]
91. van Esbroeck ACM, Janssen APA, Cognetta 3rd AB, Ogasawara D, Shpak G, van der Kroeg M, Kantae V, Baggelaar MP, de Vrij FMS and Deng H *et al.*. (2017) Activity-based protein profiling reveals off-target proteins of the FAAH inhibitor BIA 10-2474. *Science* **356**: 1084-1087 [PMID:28596366]
92. van Esbroeck ACM, Kantae V, Di X, van der Wel T, den Dulk H, Stevens AF, Singh S, Bakker AT, Florea BI and Stella N *et al.*. (2019) Identification of α,β -Hydrolase Domain Containing Protein 6 as a Diacylglycerol Lipase in Neuro-2a Cells. *Front Mol Neurosci* **12**: 286 [PMID:31849602]
93. Wan M, Cravatt BF, Ring HZ, Zhang X and Francke U. (1998) Conserved chromosomal location and genomic structure of human and mouse fatty-acid amide hydrolase genes and evaluation of clasper as a candidate neurological mutation. *Genomics* **54**: 408-14 [PMID:9878243]
94. Watabiki T, Tsuji N, Kiso T, Ozawa T, Narazaki F and Kakimoto S. (2017) In vitro and in vivo pharmacological characterization of ASP8477: A novel highly selective fatty acid amide

- hydrolase inhibitor. *Eur J Pharmacol* **815**: 42-48 [PMID:29017758]
95. Wei BQ, Mikkelsen TS, McKinney MK, Lander ES and Cravatt BF. (2006) A second fatty acid amide hydrolase with variable distribution among placental mammals. *J Biol Chem* **281**: 36569-78 [PMID:17015445]
96. Whibley AC, Plagnol V, Tarpey PS, Abidi F, Fullston T, Choma MK, Boucher CA, Shepherd L, Willatt L and Parkin G *et al.*. (2010) Fine-scale survey of X chromosome copy number variants and indels underlying intellectual disability. *Am J Hum Genet* **87**: 173-88 [PMID:20655035]
97. Wyatt RM, Fraser I, Welty N, Lord B, Wennerholm M, Sutton S, Ameriks MK, Dugovic C, Yun S and White A *et al.*. (2020) Pharmacologic Characterization of JNJ-42226314, [1-(4-Fluorophenyl)indol-5-yl]-[3-[4-(thiazole-2-carbonyl)piperazin-1-yl]azetidin-1-yl]methanone, a Reversible, Selective, and Potent Monoacylglycerol Lipase Inhibitor. *J Pharmacol Exp Ther* **372**: 339-353 [PMID:31818916]
98. Xie S, Borazjani A, Hatfield MJ, Edwards CC, Potter PM and Ross MK. (2010) Inactivation of lipid glyceryl ester metabolism in human THP1 monocytes/macrophages by activated organophosphorus insecticides: role of carboxylesterases 1 and 2. *Chem Res Toxicol* **23**: 1890-904 [PMID:21049984]
99. Xiong F, Ding X, Zhang H, Luo X, Chen K, Jiang H, Luo C and Xu H. (2021) Discovery of novel reversible monoacylglycerol lipase inhibitors via docking-based virtual screening. *Bioorg Med Chem Lett* **41**: 127986 [PMID:33766770]
100. Zhi Z, Zhang W, Yao J, Shang Y, Hao Q, Liu Z, Ren Y, Li J, Zhang G and Wang J. (2020) Discovery of Aryl Formyl Piperidine Derivatives as Potent, Reversible, and Selective Monoacylglycerol Lipase Inhibitors. *J Med Chem* **63**: 5783-5796 [PMID:32429662]