

Cyclooxygenase in GtoPdb v.2023.1

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Abstract

Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icos-5,8,11,14-tetraenoate,hydrogen-donor : oxygen oxidoreductase) activity, catalyses the formation of PGG₂ from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH₂ from PGG₂. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indomethacin and paracetamol (acetaminophen). PGH₂ may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

Contents

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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. Auerbach SS and DrugMatrix® and ToxFX® Coordinator National Toxicology Program.. National Toxicology Program: Dept of Health and Human Services.
<https://ntp.niehs.nih.gov/drugmatrix/index.html>. Accessed on 02/05/2014.
 3. Bayly CI, Black WC, Léger S, Ouimet N, Ouellet M and Percival MD. (1999) Structure-based design of COX-2 selectivity into flurbiprofen. *Bioorg Med Chem Lett* **9**: 307-12 [PMID:10091674]
 4. Beswick P, Bingham S, Bountra C, Brown T, Browning K, Campbell I, Chessel I, Clayton N, Collins S and Corfield J *et al.* (2004) Identification of 2,3-diaryl-pyrazolo[1,5-b]pyridazines as potent and selective cyclooxygenase-2 inhibitors. *Bioorg Med Chem Lett* **14**: 5445-8 [PMID:15454242]
 5. Black WC, Brideau C, Chan CC, Charleson S, Cromlish W, Gordon R, Grimm EL, Hughes G, Leger S and Li CS *et al.* (2003) 3,4-Diaryl-5-hydroxyfuranones: highly selective inhibitors of cyclooxygenase-2 with aqueous solubility. *Bioorg Med Chem Lett* **13**: 1195-8 [PMID:12643942]
 6. Blobaum AL and Marnett LJ. (2007) Molecular determinants for the selective inhibition of cyclooxygenase-2 by lumiracoxib. *J Biol Chem* **282**: 16379-90 [PMID:17434872]
 7. Blobaum AL and Marnett LJ. (2007) Structural and functional basis of cyclooxygenase inhibition. *J Med Chem* **50**: 1425-41 [PMID:17341061]
 8. 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]
 9. Bézière N, Goossens L, Pommery J, Vezin H, Touati N, Hénichart JP and Pommery N. (2008) New NSAIDs-NO hybrid molecules with antiproliferative properties on human prostatic cancer cell lines. *Bioorg Med Chem Lett* **18**: 4655-7 [PMID:18667313]
 10. Chowdhury MA, Abdellatif KR, Dong Y, Das D, Yu G, Velázquez CA, Suresh MR and Knaus EE. (2009) Synthesis and biological evaluation of salicylic acid and N-acetyl-2-carboxybenzenesulfonamide regioisomers possessing a N-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore: dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity. *Bioorg Med Chem Lett* **19**: 6855-61 [PMID:19884005]
 11. Geisslinger G and Schaible HG. (1996) New insights into the site and mode of antinociceptive action of flurbiprofen enantiomers. *J Clin Pharmacol* **36**: 513-20 [PMID:8809636]
 12. Geusens P. (2009) Naproxincinod, a new cyclooxygenase-inhibiting nitric oxide donator (CINOD). *Expert Opin Biol Ther* **9**: 649-57 [PMID:19392579]
 13. Gierse JK, McDonald JJ, Hauser SD, Rangwala SH, Koboldt CM and Seibert K. (1996) A single amino acid difference between cyclooxygenase-1 (COX-1) and -2 (COX-2) reverses the selectivity of COX-2 specific inhibitors. *J Biol Chem* **271**: 15810-4 [PMID:8663121]
 14. Heinrich DM, Flanagan JU, Jamieson SM, Silva S, Rigoreau LJ, Trivier E, Raynham T, Turnbull AP and Denny WA. (2013) Synthesis and structure-activity relationships for 1-(4-(piperidin-1-ylsulfonyl)phenyl)pyrrolidin-2-ones as novel non-carboxylate inhibitors of the aldo-keto reductase enzyme AKR1C3. *Eur J Med Chem* **62**: 738-44 [PMID:23454516]
 15. Hieke M, Ness J, Steri R, Dittrich M, Greiner C, Werz O, Baumann K, Schubert-Zsilavecz M, Weggen S and Zettl H. (2010) Design, synthesis, and biological evaluation of a novel class of gamma-secretase modulators with PPARgamma activity. *J Med Chem* **53**: 4691-700 [PMID:20503989]
 16. Hieke M, Ness J, Steri R, Greiner C, Werz O, Schubert-Zsilavecz M, Weggen S and Zettl H. (2011) SAR studies of acidic dual γ -secretase/PPAR γ modulators. *Bioorg Med Chem* **19**: 5372-82 [PMID:21873070]
 17. Hinz B, Cheremina O and Brune K. (2008) Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J* **22**: 383-90 [PMID:17884974]
 18. Hoshino J, Park EJ, Kondratyuk TP, Marler L, Pezzuto JM, van Breemen RB, Mo S, Li Y and Cushman M. (2010) Selective synthesis and biological evaluation of sulfate-conjugated resveratrol metabolites. *J Med Chem* **53**: 5033-43 [PMID:20527891]
 19. Imanishi J, Morita Y, Yoshimi E, Kuroda K, Masunaga T, Yamagami K, Kuno M, Hamachi E, Aoki S and Takahashi F *et al.* (2011) Pharmacological profile of FK881(ASP6537), a novel potent and selective cyclooxygenase-1 inhibitor. *Biochem Pharmacol* **82**: 746-54 [PMID:21745460]
 20. Inagaki M, Tsuri T, Jyoyama H, Ono T, Yamada K, Kobayashi M, Hori Y, Arimura A, Yasui K and Ohno K *et al.* (2000) Novel antiarthritic agents with 1,2-isothiazolidine-1,1-dioxide (gamma-sultam) skeleton: cytokine suppressive dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase. *J Med Chem* **43**: 2040-8 [PMID:10821716]
 21. Janusz JM, Young PA, Scherz MW, Enzweiler K, Wu LI, Gan L, Pikul S, McDow-Dunham KL, Johnson CR

- and Senanayake CB *et al.* (1998) New cyclooxygenase-2/5-lipoxygenase inhibitors. 2. 7-tert-butyl-2,3-dihydro-3,3-dimethylbenzofuran derivatives as gastrointestinal safe antiinflammatory and analgesic agents: variations of the dihydrobenzofuran ring. *J Med Chem* **41**: 1124-37 [PMID:9544212]
22. Kalgutkar AS, Rowlinson SW, Crews BC and Marnett LJ. (2002) Amide derivatives of meclofenamic acid as selective cyclooxygenase-2 inhibitors. *Bioorg Med Chem Lett* **12**: 521-4 [PMID:11844663]
23. Kassab SE, Khedr MA, Ali HI and Abdalla MM. (2017) Discovery of new indomethacin-based analogs with potentially selective cyclooxygenase-2 inhibition and observed diminishing to PGE2 activities. *Eur J Med Chem* **141**: 306-321 [PMID:29031075]
24. Kato M, Nishida S, Kitasato H, Sakata N and Kawai S. (2001) Cyclooxygenase-1 and cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs: investigation using human peripheral monocytes. *J Pharm Pharmacol* **53**: 1679-85 [PMID:11804398]
25. Kawai S, Nishida S, Kato M, Furumaya Y, Okamoto R, Koshino T and Mizushima Y. (1998) Comparison of cyclooxygenase-1 and -2 inhibitory activities of various nonsteroidal anti-inflammatory drugs using human platelets and synovial cells. *Eur J Pharmacol* **347**: 87-94 [PMID:9650852]
26. Kiefer JR, Pawlitz JL, Moreland KT, Stegeman RA, Hood WF, Gierse JK, Stevens AM, Goodwin DC, Rowlinson SW and Marnett LJ *et al.* (2000) Structural insights into the stereochemistry of the cyclooxygenase reaction. *Nature* **405**: 97-101 [PMID:10811226]
27. Kolasa T, Brooks CD, Rodrigues KE, Summers JB, Dellarria JF, Hulkower KI, Bouska J, Bell RL and Carter GW. (1997) Nonsteroidal anti-inflammatory drugs as scaffolds for the design of 5-lipoxygenase inhibitors. *J Med Chem* **40**: 819-24 [PMID:9057869]
28. Kramer JS, Woltersdorf S, Duflot T, Hiesinger K, Lillich FF, Knöll F, Wittmann SK, Klingler FM, Brunst S and Chaikud A *et al.* (2019) Discovery of the First in Vivo Active Inhibitors of the Soluble Epoxide Hydrolase Phosphatase Domain. *J Med Chem* **62**: 8443-8460 [PMID:31436984]
29. Kumar R, Saha N, Purohit P, Garg SK, Seth K, Meena VS, Dubey S, Dave K, Goyal R and Sharma SS *et al.* (2019) Cyclic enaminone as new chemotype for selective cyclooxygenase-2 inhibitory, anti-inflammatory, and analgesic activities. *Eur J Med Chem* **182**: 111601 [PMID:31445233]
30. Lazer ES, Miao CK, Cywin CL, Sorcek R, Wong HC, Meng Z, Potocki I, Hoermann M, Snow RJ and Tschantz MA *et al.* (1997) Effect of structural modification of enol-carboxamide-type nonsteroidal antiinflammatory drugs on COX-2/COX-1 selectivity. *J Med Chem* **40**: 980-9 [PMID:9083488]
31. Look GC, Schullek JR, Holmes CP, Chinn JP, Gordon EM and Gallop MA. (1996) The identification of cyclooxygenase-1 inhibitors from 4-thiazolidinone combinatorial libraries. *Bioorg Med Chem Lett* **6**: 707-712
32. 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]
33. Ochi T, Motoyama Y and Goto T. (2000) The analgesic effect profile of FR122047, a selective cyclooxygenase-1 inhibitor, in chemical nociceptive models. *Eur J Pharmacol* **391**: 49-54 [PMID:10720634]
34. Ottanà R, Carotti S, Maccari R, Landini I, Chiricosta G, Caciagli B, Vigorita MG and Mini E. (2005) In vitro antiproliferative activity against human colon cancer cell lines of representative 4-thiazolidinones. Part I. *Bioorg Med Chem Lett* **15**: 3930-3 [PMID:15993594]
35. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW and Miyashiro JM *et al.* (1997) Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benze nesulfonamide (SC-58635, celecoxib). *J Med Chem* **40**: 1347-65 [PMID:9135032]
36. Riendeau D, Percival MD, Brideau C, Charleson S, Dubé D, Ethier D, Falgueyret JP, Friesen RW, Gordon R and Greig G *et al.* (2001) Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Ther* **296**: 558-66 [PMID:11160644]
37. Riendeau D, Salem M, Styhler A, Ouellet M, Mancini JA and Li CS. (2004) Evaluation of loxoprofen and its alcohol metabolites for potency and selectivity of inhibition of cyclooxygenase-2. *Bioorg Med Chem Lett* **14**: 1201-3 [PMID:14980665]
38. Singh P, Kaur S, Kaur J, Singh G and Bhatti R. (2016) Rational Design of Small Peptides for Optimal Inhibition of Cyclooxygenase-2: Development of a Highly Effective Anti-Inflammatory Agent. *J Med Chem* **59**: 3920-34 [PMID:27019010]
39. Smith CJ, Zhang Y, Koboldt CM, Muhammad J, Zweifel BS, Shaffer A, Talley JJ, Masferrer JL, Seibert K

- and Isakson PC. (1998) Pharmacological analysis of cyclooxygenase-1 in inflammation. *Proc Natl Acad Sci USA* **95**: 13313-8 [PMID:9789085]
40. Takahashi T and Miyazawa M. (2012) N-Caffeoyl serotonin as selective COX-2 inhibitor. *Bioorg Med Chem Lett* **22**: 2494-6 [PMID:22386242]
 41. Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, Perkins WE, Rogers RS, Shaffer AF and Zhang YY *et al.*. (2000) 4-[5-Methyl-3-phenylisoxazol-4-yl]- benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. *J Med Chem* **43**: 775-7 [PMID:10715145]
 42. Uddin MJ, Xu S, Crews BC, Ghebreselasie K, Banerjee S and Marnett LJ. (2020) Harmaline Analogs as Substrate-Selective Cyclooxygenase-2 Inhibitors *ACS Med Chem Lett*
 43. Viegas A, Manso J, Corvo MC, Marques MM and Cabrita EJ. (2011) Binding of ibuprofen, ketorolac, and diclofenac to COX-1 and COX-2 studied by saturation transfer difference NMR. *J Med Chem* **54**: 8555-62 [PMID:22091869]
 44. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA and Vane JR. (1999) Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci USA* **96**: 7563-8 [PMID:10377455]
 45. Wilkerson WW, Copeland RA, Covington M and Trzaskos JM. (1995) Antiinflammatory 4,5-diarylpyrroles. 2. Activity as a function of cyclooxygenase-2 inhibition. *J Med Chem* **38**: 3895-901 [PMID:7562922]
 46. Zhang Z, Ghosh A, Connolly PJ, King P, Wilde T, Wang J, Dong Y, Li X, Liao D and Chen H *et al.*. (2021) Gut-Restricted Selective Cyclooxygenase-2 (COX-2) Inhibitors for Chemoprevention of Colorectal Cancer. *J Med Chem* **64**: 11570-11596 [PMID:34279934]
 47. Zhou H, Liu W, Su Y, Wei Z, Liu J, Kolluri SK, Wu H, Cao Y, Chen J and Wu Y *et al.*. (2010) NSAID sulindac and its analog bind RXRalpha and inhibit RXRalpha-dependent AKT signaling. *Cancer Cell* **17**: 560-73 [PMID:20541701]
 48. Zou J, Jin D, Chen W, Wang J, Liu Q, Zhu X and Zhao W. (2005) Selective cyclooxygenase-2 inhibitors from Calophyllum membranaceum. *J Nat Prod* **68**: 1514-8 [PMID:16252917]