

Type XII RTKs: TIE family of angiopoietin receptors in GtoPdb v.2025.3

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Abstract

The TIE family were initially associated with formation of blood vessels (angiogenesis). Endogenous ligands are [angiopoietin-1](#), [angiopoietin-2](#), and [angiopoietin-4](#). [angiopoietin-2](#) appears to act as an endogenous antagonist of angiopoietin-1 function, thus blocking TIE2-mediated signalling. Due to roles in blood vessel formation, monoclonal antibodies are being developed against the ligand Ang2 ([cyamemazine](#)⁵⁷) or a bispecific antibody against VEGF and Ang2 ([faricimab](#)) for the treatment of ocular diseases.

Contents

This is a citation summary for Type XII RTKs: TIE family of angiopoietin receptors 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 [\[4\]](#).

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

Type XII RTKs: TIE family of angiopoietin receptors

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=330>

Receptors

[TIE1\(tyrosine kinase with immunoglobulin like and EGF like domains 1\)](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1841>

[TIE2\(TEK receptor tyrosine kinase\)](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1842>

References

1. Albert DH, Tapang P, Magoc TJ, Pease LJ, Reuter DR, Wei RQ, Li J, Guo J, Bousquet PF and Ghoreishi-Haack NS *et al.* (2006) Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. *Mol Cancer Ther* **5**: 995-1006 [[PMID:16648571](#)]
2. Anastassiadis T, Deacon SW, Devarajan K, Ma H and Peterson JR. (2011) Comprehensive assay of kinase catalytic activity reveals features of kinase inhibitor selectivity. *Nat Biotechnol* **29**: 1039-45 [[PMID:22037377](#)]
3. Bachegowda L, Morrone K, Winski SL, Mantzaris I, Bartenstein M, Ramachandra N, Giricz O, Sukrithan V, Nwankwo G and Shahnaz S *et al.* (2016) Pexmetinib: A Novel Dual Inhibitor of Tie2 and p38 MAPK with Efficacy in Preclinical Models of Myelodysplastic Syndromes and Acute

Myeloid Leukemia. *Cancer Res* **76**: 4841-4849 [PMID:27287719]

4. 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]
5. Chan S, Zhang Y, Wang J, Yu Q, Peng X, Zou J, Zhou L, Tan L, Duan Y and Zhou Y *et al.* (2022) Discovery of 3-Aminopyrazole Derivatives as New Potent and Orally Bioavailable AXL Inhibitors *Journal of Medicinal Chemistry*
6. 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]
7. Flynn DL, Kaufman MD and Smith BD. (2016) Inhibition of tumor cell interactions with the microenvironment resulting in a reduction in tumor growth and disease progression Patent number: WO2016061231. Assignee: Deciphera Pharmaceuticals, Llc. Priority date: 14/10/2014. Publication date: 21/04/2016.
8. Gao Y, Davies SP, Augustin M, Woodward A, Patel UA, Kovelman R and Harvey KJ. (2013) A broad activity screen in support of a chemogenomic map for kinase signalling research and drug discovery. *Biochem J* **451**: 313-28 [PMID:23398362]
9. Hodous BL, Geuns-Meyer SD, Hughes PE, Albrecht BK, Bellon S, Caenepeel S, Cee VJ, Chaffee SC, Emery M and Fretland J *et al.* (2007) Synthesis, structural analysis, and SAR studies of triazine derivatives as potent, selective Tie-2 inhibitors. *Bioorg Med Chem Lett* **17**: 2886-9 [PMID:17350837]
10. Hopkins BT, Bame E, Bajrami B, Black C, Bohnert T, Boisselle C, Burdette D, Burns JC, Delva L and Donaldson D *et al.* (2022) Discovery and Preclinical Characterization of BIIB091, a Reversible, Selective BTK Inhibitor for the Treatment of Multiple Sclerosis. *J Med Chem* **65**: 1206-1224 [PMID:34734694]
11. Hudkins RL, Becknell NC, Zulli AL, Underiner TL, Angeles TS, Aimone LD, Albom MS, Chang H, Miknyoczki SJ and Hunter K *et al.* (2012) Synthesis and biological profile of the pan-vascular endothelial growth factor receptor/tyrosine kinase with immunoglobulin and epidermal growth factor-like homology domains 2 (VEGF-R/TIE-2) inhibitor 11-(2-methylpropyl)-12,13-dihydro-2-methyl-8-(pyrimidin-2-ylamino)-4H-indazolo[5,4-a]pyrrolo[3,4-c]carbazol-4-one (CEP-11981): a novel oncology therapeutic agent. *J Med Chem* **55**: 903-13 [PMID:22148921]
12. Kim M, Allen B, Korhonen EA, Nitschké M, Yang HW, Baluk P, Saharinen P, Alitalo K, Daly C and Thurston G *et al.* (2016) Opposing actions of angiopoietin-2 on Tie2 signaling and FOXO1 activation. *J Clin Invest* **126**: 3511-25 [PMID:27548529]
13. Milkiewicz KL, Aimone LD, Albom MS, Angeles TS, Chang H, Grobelny JV, Husten J, Losardo C, Miknyoczki S and Murthy S *et al.* (2011) Improvement in oral bioavailability of 2,4-diaminopyrimidine c-Met inhibitors by incorporation of a 3-amidobenzazepin-2-one group. *Bioorg Med Chem* **19**: 6274-84 [PMID:21967808]
14. Semones M, Feng Y, Johnson N, Adams JL, Winkler J and Hansbury M. (2007) Pyridinylimidazole inhibitors of Tie2 kinase. *Bioorg Med Chem Lett* **17**: 4756-60 [PMID:17618114]
15. Shewchuk LM, Hassell AM, Ellis B, Holmes WD, Davis R, Horne EL, Kadwell SH, McKee DD and Moore JT. (2000) Structure of the Tie2 RTK domain: self-inhibition by the nucleotide binding loop, activation loop, and C-terminal tail. *Structure* **8**: 1105-13 [PMID:11080633]
16. Thomas M, Huang WS, Wen D, Zhu X, Wang Y, Metcalf CA, Liu S, Chen I, Romero J and Zou D *et al.* (2011) Discovery of 5-(arenethynyl) hetero-monocyclic derivatives as potent inhibitors of BCR-ABL including the T315I gatekeeper mutant. *Bioorg Med Chem Lett* **21**: 3743-8 [PMID:21561767]
17. Wang Z, Zhang Y, Pinkas DM, Fox AE, Luo J, Huang H, Cui S, Xiang Q, Xu T and Xun Q *et al.* (2018) Design, Synthesis, and Biological Evaluation of 3-(Imidazo[1,2-a]pyrazin-3-ylethynyl)-4-isopropyl- N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide as a Dual Inhibitor of Discoidin Domain Receptors 1 and 2. *J Med Chem* **61**: 7977-7990 [PMID:30075624]
18. 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]
19. Yan SB, Peek VL, Ajamie R, Buchanan SG, Graff JR, Heidler SA, Hui YH, Huss KL, Konicek BW and Manro JR *et al.* (2013) LY2801653 is an orally bioavailable multi-kinase inhibitor with potent activity against MET, MST1R, and other oncoproteins, and displays anti-tumor activities in mouse xenograft models. *Invest New Drugs* **31**: 833-44 [PMID:23275061]
20. You WK, Sennino B, Williamson CW, Falcón B, Hashizume H, Yao LC, Aftab DT and McDonald DM. (2011) VEGF and c-Met blockade amplify angiogenesis inhibition in pancreatic islet cancer. *Cancer Res* **71**: 4758-68 [PMID:21613405]