

3A. Estrogen receptors in GtoPdb v.2025.3

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Abstract

Estrogen receptor (ER) activity regulates diverse physiological processes *via* transcriptional modulation of target genes [2]. The selection of target genes and the magnitude of the response, be it induction or repression, are determined by many factors, including the effect of the hormone ligand and DNA binding on ER structural conformation, and the local cellular regulatory environment. The cellular environment defines the specific complement of DNA enhancer and promoter elements present and the availability of coregulators to form functional transcription complexes. Together, these determinants control the resulting biological response.

Contents

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Database links

3A. Estrogen receptors

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=96>

Introduction to 3A. Estrogen receptors

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=96>

Receptors

Estrogen receptor- α

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=620>

Estrogen receptor- β

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=621>

References

1. Abdelmalek CM, Hu Z, Kronenberger T, Küblbeck J, Kinnen FJM, Hesse SS, Malik A, Kudolo M, Niess R and Gehringer M *et al.* (2022) Gefitinib-Tamoxifen Hybrid Ligands as Potent Agents against Triple-Negative Breast Cancer. *J Med Chem* **65**: 4616-4632 [PMID:35286086]
2. Alexander SPH, Cidlowski JA, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD and Pawson AJ *et al.* (2019) THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Nuclear hormone receptors. *Br J Pharmacol* **176** Suppl 1: S229-S246 [PMID:31710718]
3. Auerbach SS. DrugMatrix in vitro pharmacology data

<https://ntp.niehs.nih.gov/drugmatrix/index.html>. Accessed on 30/04/2019.

4. 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.
5. Barkhem T, Haldosén LA, Gustafsson JA and Nilsson S. (2002) pS2 Gene expression in HepG2 cells: complex regulation through crosstalk between the estrogen receptor alpha, an estrogen-responsive element, and the activator protein 1 response element. *Mol Pharmacol* **61**: 1273-83 [PMID:12021387]
6. Bastian JA, Cohen JD, Rubio A and Sall DJ. (2020) Selective estrogen receptor degraders Patent number: [WO2020014435A1](#). Assignee: Eli Lilly And Company. Priority date: 11/07/2019. Publication date: 16/01/2020.
7. 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]
8. Burke C. (2005) Endometrial cancer and tamoxifen. *Clin J Oncol Nurs* **9**: 247-9 [PMID:15853168]
9. Chao EY, Collins JL, Gaillard S, Miller AB, Wang L, Orband-Miller LA, Nolte RT, McDonnell DP, Willson TM and Zuercher WJ. (2006) Structure-guided synthesis of tamoxifen analogs with improved selectivity for the orphan ERRgamma. *Bioorg Med Chem Lett* **16**: 821-4 [PMID:16307879]
10. Chu S and Fuller PJ. (1997) Identification of a splice variant of the rat estrogen receptor beta gene. *Mol Cell Endocrinol* **132**: 195-9 [PMID:9324061]
11. Couse JF, Dixon D, Yates M, Moore AB, Ma L, Maas R and Korach KS. (2001) Estrogen receptor-alpha knockout mice exhibit resistance to the developmental effects of neonatal diethylstilbestrol exposure on the female reproductive tract. *Dev Biol* **238**: 224-38 [PMID:11784006]
12. Cvoro A, Tatomer D, Tee MK, Zogovic T, Harris HA and Leitman DC. (2008) Selective estrogen receptor-beta agonists repress transcription of proinflammatory genes. *J Immunol* **180**: 630-6 [PMID:18097065]
13. Dahlman-Wright K, Cavailles V, Fuqua SA, Jordan VC, Katzenellenbogen JA, Korach KS, Maggi A, Muramatsu M, Parker MG and Gustafsson JA. (2006) International Union of Pharmacology. LXIV. Estrogen receptors. *Pharmacol Rev* **58**: 773-81 [PMID:17132854]
14. de Koning J, Lambalk CB, Helmerhorst FM and Helder MN. (2001) Is GnRH self-priming an obligatory feature of the reproductive cycle? *Hum Reprod* **16**: 209-14 [PMID:11157808]
15. Delfosse V, Grimaldi M, Pons JL, Boulahtouf A, le Maire A, Cavailles V, Labesse G, Bourguet W and Balaguer P. (2012) Structural and mechanistic insights into bisphenols action provide guidelines for risk assessment and discovery of bisphenol A substitutes. *Proc Natl Acad Sci USA* **109**: 14930-5 [PMID:22927406]
16. Devin-Leclerc J, Meng X, Delahaye F, Leclerc P, Baulieu EE and Catelli MG. (1998) Interaction and dissociation by ligands of estrogen receptor and Hsp90: the antiestrogen RU 58668 induces a protein synthesis-dependent clustering of the receptor in the cytoplasm. *Mol Endocrinol* **12**: 842-54 [PMID:9626660]
17. El-Ahmad Y, Tabart M, Halley F, Certal V, Thompson F, Filoche-Rommé B, Gruss-Leleu F, Muller C, Brollo M and Fabien L *et al.*. (2020) Discovery of 6-(2,4-Dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (SAR439859), a Potent and Selective Estrogen Receptor Degradar (SERD) for the Treatment of Estrogen-Receptor-Positive Breast Cancer. *J Med Chem* **63**: 512-528 [PMID:31721572]
18. Escande A, Servant N, Rabenoelina F, Auzou G, Kloosterboer H, Cavailles V, Balaguer P and Maudelonde T. (2009) Regulation of activities of steroid hormone receptors by tibolone and its primary metabolites. *J Steroid Biochem Mol Biol* **116**: 8-14 [PMID:19464167]
19. Flouriot G, Brand H, Denger S, Metivier R, Kos M, Reid G, Sonntag-Buck V and Gannon F. (2000) Identification of a new isoform of the human estrogen receptor-alpha (hER-alpha) that is encoded by distinct transcripts and that is able to repress hER-alpha activation function 1. *EMBO J* **19**: 4688-700 [PMID:10970861]
20. Fuqua SA, Wiltchke C, Zhang QX, Borg A, Castles CG, Friedrichs WE, Hopp T, Hilsenbeck S, Mohsin S, O'Connell P and Allred DC. (2000) A hypersensitive estrogen receptor-alpha mutation in premalignant breast lesions. *Cancer Res* **60**: 4026-9 [PMID:10945602]
21. Germain P, Staels B, Dacquet C, Spedding M and Laudet V. (2006) Overview of nomenclature of nuclear receptors. *Pharmacol Rev* **58**: 685-704 [PMID:17132848]
22. Greene GL, Gilna P, Waterfield M, Baker A, Hort Y and Shine J. (1986) Sequence and expression of human estrogen receptor complementary DNA. *Science* **231**: 1150-4 [PMID:3753802]
23. Hall DA, Beresford IJ, Browning C and Giles H. (1999) Signalling by CXC-chemokine receptors 1 and 2 expressed in CHO cells: a comparison of calcium mobilization, inhibition of adenylyl cyclase and stimulation of GTPgammaS binding induced by IL-8 and GROalpha. *Br J Pharmacol* **126**: 810-8 [PMID:10188995]
24. Hall JM and Korach KS. (2002) Analysis of the molecular mechanisms of human estrogen

- receptors alpha and beta reveals differential specificity in target promoter regulation by xenoestrogens. *J Biol Chem* **277**: 44455-61 [PMID:12200415]
25. Hall JM and McDonnell DP. (2005) Coregulators in nuclear estrogen receptor action: from concept to therapeutic targeting. *Mol Interv* **5**: 343-57 [PMID:16394250]
 26. Henke BR, Drewry DH, Jones SA, Stewart EL, Weaver SL and Wiethe RW. (2001) 2-Amino-4,6-diarylpyridines as novel ligands for the estrogen receptor. *Bioorg Med Chem Lett* **11**: 1939-42 [PMID:11459665]
 27. Hu J, Hu B, Wang M, Xu F, Miao B, Yang CY, Wang M, Liu Z, Hayes DF and Chinnaswamy K *et al.*. (2019) Discovery of ERD-308 as a Highly Potent Proteolysis Targeting Chimera (PROTAC) Degradator of Estrogen Receptor (ER). *J Med Chem* **62**: 1420-1442 [PMID:30990042]
 28. Hughes ZA, Liu F, Platt BJ, Dwyer JM, Pulicicchio CM, Zhang G, Schechter LE, Rosenzweig-Lipson S and Day M. (2008) WAY-200070, a selective agonist of estrogen receptor beta as a potential novel anxiolytic/antidepressant agent. *Neuropharmacology* **54**: 1136-42 [PMID:18423777]
 29. Jain N, Kanojia RM, Xu J, Jian-Zhong G, Pacia E, Lai MT, Du F, Musto A, Allan G and Hahn D *et al.*. (2006) Novel chromene-derived selective estrogen receptor modulators useful for alleviating hot flushes and vaginal dryness. *J Med Chem* **49**: 3056-9 [PMID:16722623]
 30. Kim SS, Kwack SJ, Lee RD, Lim KJ, Rhee GS, Seok JH, Kim BH, Won YH, Lee GS, Jeung EB, Lee BM and Park KL. (2005) Assessment of estrogenic and androgenic activities of tetramethrin in vitro and in vivo assays. *J Toxicol Environ Health Part A* **68**: 2277-89 [PMID:16326440]
 31. Koike S, Sakai M and Muramatsu M. (1987) Molecular cloning and characterization of rat estrogen receptor cDNA. *Nucleic Acids Res* **15**: 2499-513 [PMID:3031601]
 32. Kraichely DM, Sun J, Katzenellenbogen JA and Katzenellenbogen BS. (2000) Conformational changes and coactivator recruitment by novel ligands for estrogen receptor-alpha and estrogen receptor-beta: correlations with biological character and distinct differences among SRC coactivator family members. *Endocrinology* **141**: 3534-45 [PMID:11014206]
 33. Kuiper GG, Carlsson B, Grandien K, Enmark E, Häggblad J, Nilsson S and Gustafsson JA. (1997) Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology* **138**: 863-70 [PMID:9048584]
 34. Kuiper GG, Enmark E, Peltö-Huikko M, Nilsson S and Gustafsson JA. (1996) Cloning of a novel receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci USA* **93**: 5925-30 [PMID:8650195]
 35. Lewis JS and Jordan VC. (2005) Selective estrogen receptor modulators (SERMs): mechanisms of anticarcinogenesis and drug resistance. *Mutat Res* **591**: 247-63 [PMID:16083919]
 36. Liang J, Zbieg JR, Blake RA, Chang JH, Daly S, DiPasquale AG, Friedman LS, Gelzleichter T, Gill M and Giltner JM *et al.*. (2021) GDC-9545 (Giredestrant): A Potent and Orally Bioavailable Selective Estrogen Receptor Antagonist and Degradator with an Exceptional Preclinical Profile for ER+ Breast Cancer. *J Med Chem* **64**: 11841-11856 [PMID:34251202]
 37. Lv W, Liu J, Lu D, Flockhart DA and Cushman M. (2013) Synthesis of mixed (E,Z)-, (E)-, and (Z)-norendoxifen with dual aromatase inhibitory and estrogen receptor modulatory activities. *J Med Chem* **56**: 4611-8 [PMID:23731360]
 38. Malamas MS, Manas ES, McDevitt RE, Gunawan I, Xu ZB, Collini MD, Miller CP, Dinh T, Henderson RA and Keith JC *et al.*. (2004) Design and synthesis of aryl diphenolic azoles as potent and selective estrogen receptor-beta ligands. *J Med Chem* **47**: 5021-40 [PMID:15456246]
 39. Maruyama K, Nakamura M, Tomoshige S, Sugita K, Makishima M, Hashimoto Y and Ishikawa M. (2013) Structure-activity relationships of bisphenol A analogs at estrogen receptors (ERs): discovery of an ER α -selective antagonist. *Bioorg Med Chem Lett* **23**: 4031-6 [PMID:23768907]
 40. McFarland K, Price DL, Davis CN, Ma JN, Bonhaus DW, Burstein ES and Olsson R. (2013) AC-186, a selective nonsteroidal estrogen receptor β agonist, shows gender specific neuroprotection in a Parkinson's disease rat model. *ACS Chem Neurosci* **4**: 1249-55 [PMID:23898966]
 41. Mersereau JE, Levy N, Staub RE, Baggett S, Zogovic T, Zogric T, Chow S, Ricke WA, Tagliaferri M and Cohen I *et al.*. (2008) Liquiritigenin is a plant-derived highly selective estrogen receptor beta agonist. *Mol Cell Endocrinol* **283**: 49-57 [PMID:18177995]
 42. Meyers MJ, Sun J, Carlson KE, Katzenellenbogen BS and Katzenellenbogen JA. (1999) Estrogen receptor subtype-selective ligands: asymmetric synthesis and biological evaluation of cis- and trans-5,11-dialkyl- 5,6,11, 12-tetrahydrochrysenes. *J Med Chem* **42**: 2456-68 [PMID:10395487]
 43. Meyers MJ, Sun J, Carlson KE, Marriner GA, Katzenellenbogen BS and Katzenellenbogen JA. (2001) Estrogen receptor-beta potency-selective ligands: structure-activity relationship studies of diarylpropionitriles and their acetylene and polar analogues. *J Med Chem* **44**: 4230-51 [PMID:11708925]
 44. Miller CP, Collini MD, Tran BD, Harris HA, Kharode YP, Marzolf JT, Moran RA, Henderson RA, Bender RH and Unwalla RJ *et al.*. (2001) Design, synthesis, and preclinical characterization of novel, highly selective indole estrogens. *J Med Chem* **44**: 1654-7 [PMID:11356100]
 45. Minutolo F, Bertini S, Granchi C, Marchitelli T, Protà G, Rapposelli S, Tuccinardi T, Martinelli A, Gunther JR and Carlson KE *et al.*. (2009) Structural evolutions of salicylaldoximes as selective

- agonists for estrogen receptor beta. *J Med Chem* **52**: 858-67 [PMID:19128016]
46. Ning M, Zhou C, Weng J, Zhang S, Chen D, Yang C, Wang H, Ren J, Zhou L and Jin C *et al.*. (2007) Biological activities of a novel selective oestrogen receptor modulator derived from raloxifene (Y134). *Br J Pharmacol* **150**: 19-28 [PMID:17115070]
 47. Ogawa S, Inoue S, Watanabe T, Hiroi H, Orimo A, Hosoi T, Ouchi Y and Muramatsu M. (1998) The complete primary structure of human estrogen receptor beta (hER beta) and its heterodimerization with ER alpha in vivo and in vitro. *Biochem Biophys Res Commun* **243**: 122-6 [PMID:9473491]
 48. Ogawa S, Inoue S, Watanabe T, Orimo A, Hosoi T, Ouchi Y and Muramatsu M. (1998) Molecular cloning and characterization of human estrogen receptor betax: a potential inhibitor of estrogen action in human. *Nucleic Acids Res* **26**: 3505-12 [PMID:9671811]
 49. Petz LN, Ziegler YS, Schultz JR, Kim H, Kemper JK and Nardulli AM. (2004) Differential regulation of the human progesterone receptor gene through an estrogen response element half site and Sp1 sites. *J Steroid Biochem Mol Biol* **88**: 113-22 [PMID:15084343]
 50. Renaud J, Bischoff SF, Buhl T, Floersheim P, Fournier B, Geiser M, Halleux C, Kallen J, Keller H and Ramage P. (2005) Selective estrogen receptor modulators with conformationally restricted side chains. Synthesis and structure-activity relationship of ERalpha-selective tetrahydroisoquinoline ligands. *J Med Chem* **48**: 364-79 [PMID:15658851]
 51. Rosenfeld CS, Roberts RM and Lubahn DB. (2001) Estrogen receptor- and aromatase-deficient mice provide insight into the roles of estrogen within the ovary and uterus. *Mol Reprod Dev* **59**: 336-46 [PMID:11424220]
 52. Safe S. (2001) Transcriptional activation of genes by 17 beta-estradiol through estrogen receptor-Sp1 interactions. *Vitam Horm* **62**: 231-52 [PMID:11345900]
 53. Schmidt JM, Mercure J, Tremblay GB, Pagé M, Kalbakji A, Feher M, Dunn-Dufault R, Peter MG and Redden PR. (2003) De novo design, synthesis, and evaluation of novel nonsteroidal phenanthrene ligands for the estrogen receptor. *J Med Chem* **46**: 1408-18 [PMID:12672240]
 54. Scott JS, Moss TA, Balazs A, Barlaam B, Breed J, Carbajo RJ, Chiarparin E, Davey PRJ, Delpuech O and Fawell S *et al.*. (2020) Discovery of AZD9833, a Potent and Orally Bioavailable Selective Estrogen Receptor Degradation and Antagonist. *J Med Chem* **63**: 14530-14559 [PMID:32910656]
 55. Shiau AK, Barstad D, Loria PM, Cheng L, Kushner PJ, Agard DA and Greene GL. (1998) The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. *Cell* **95**: 927-37 [PMID:9875847]
 56. Shiau AK, Barstad D, Radek JT, Meyers MJ, Nettles KW, Katzenellenbogen BS, Katzenellenbogen JA, Agard DA and Greene GL. (2002) Structural characterization of a subtype-selective ligand reveals a novel mode of estrogen receptor antagonism. *Nat Struct Biol* **9**: 359-64 [PMID:11953755]
 57. Simpson E, Jones M, Misso M, Hewitt K, Hill R, Maffei L, Carani C and Boon WC. (2005) Estrogen, a fundamental player in energy homeostasis. *J Steroid Biochem Mol Biol* **95**: 3-8 [PMID:16054355]
 58. Stauffer SR, Coletta CJ, Tedesco R, Nishiguchi G, Carlson K, Sun J, Katzenellenbogen BS and Katzenellenbogen JA. (2000) Pyrazole ligands: structure-affinity/activity relationships and estrogen receptor-alpha-selective agonists. *J Med Chem* **43**: 4934-47 [PMID:11150164]
 59. Sun J, Huang YR, Harrington WR, Sheng S, Katzenellenbogen JA and Katzenellenbogen BS. (2002) Antagonists selective for estrogen receptor alpha. *Endocrinology* **143**: 941-7 [PMID:11861516]
 60. Sun J, Meyers MJ, Fink BE, Rajendran R, Katzenellenbogen JA and Katzenellenbogen BS. (1999) Novel ligands that function as selective estrogens or antiestrogens for estrogen receptor-alpha or estrogen receptor-beta. *Endocrinology* **140**: 800-4 [PMID:9927308]
 61. Swaneck GE and Fishman J. (1988) Covalent binding of the endogenous estrogen 16 alpha-hydroxyestrone to estradiol receptor in human breast cancer cells: characterization and intranuclear localization. *Proc Natl Acad Sci U S A* **85**: 7831-5 [PMID:3186693]
 62. Teyssier C, Belguise K, Galtier F and Chalbos D. (2001) Characterization of the physical interaction between estrogen receptor alpha and JUN proteins. *J Biol Chem* **276**: 36361-9 [PMID:11477071]
 63. Tremblay GB, Tremblay A, Copeland NG, Gilbert DJ, Jenkins NA, Labrie F and Giguère V. (1997) Cloning, chromosomal localization, and functional analysis of the murine estrogen receptor beta. *Mol Endocrinol* **11**: 353-65 [PMID:9058381]
 64. Tria GS, Abrams T, Baird J, Burks HE, Firestone B, Gaither LA, Hamann LG, He G, Kirby CA and Kim S *et al.*. (2018) Discovery of LSZ102, a Potent, Orally Bioavailable Selective Estrogen Receptor Degradation (SERD) for the Treatment of Estrogen Receptor Positive Breast Cancer. *J Med Chem* **61**: 2837-2864 [PMID:29562737]
 65. Unkila M, Kari S, Yarkin E and Lammintausta R. (2013) Vaginal effects of ospemifene in the ovariectomized rat preclinical model of menopause. *J Steroid Biochem Mol Biol* **138**: 107-15 [PMID:23665515]
 66. Walker VR and Korach KS. (2004) Estrogen receptor knockout mice as a model for endocrine

- research. *ILAR J* **45**: 455-61 [[PMID:15454684](#)]
67. Wang F, Porter W, Xing W, Archer TK and Safe S. (1997) Identification of a functional imperfect estrogen-responsive element in the 5'-promoter region of the human cathepsin D gene. *Biochemistry* **36**: 7793-801 [[PMID:9201922](#)]
68. Waters EM, Mitterling K, Spencer JL, Mazid S, McEwen BS and Milner TA. (2009) Estrogen receptor alpha and beta specific agonists regulate expression of synaptic proteins in rat hippocampus. *Brain Res* **1290**: 1-11 [[PMID:19596275](#)]
69. White R, Lees JA, Needham M, Ham J and Parker M. (1987) Structural organization and expression of the mouse estrogen receptor. *Mol Endocrinol* **1**: 735-44 [[PMID:2484714](#)]
70. Zhang G, Huang PQ, Bunker KD, Hegde SG, Ma J, Lee CC, Samatar AA, Unni A, Al-Amin M and Kakarla R. (2025) Discovery of an Orally Bioavailable and Brain Penetrant Selective Estrogen Receptor Degradar. *J Med Chem* **68**: 11990-12003 [[PMID:40393772](#)]
71. Zhou HB, Sheng S, Compton DR, Kim Y, Joachimiak A, Sharma S, Carlson KE, Katzenellenbogen BS, Nettles KW and Greene GL *et al.*. (2007) Structure-guided optimization of estrogen receptor binding affinity and antagonist potency of pyrazolopyrimidines with basic side chains. *J Med Chem* **50**: 399-403 [[PMID:17228884](#)]