TARGET VALIDATION REPORT

RARG (Homo sapiens)

Target summery

Gene

Gene Symbol	RARG
Gene Name	Retinoic acid receptor gamma
Synonyms	RARC, NR1B3
Gene Family	Nuclear hormone receptors
Locus type	protein-coding gene
Chromosomal location	12q13.13
IDs	HGNC, NCBI, Ensembl, Vega

Protein

Protein Name	Retinoic acid receptor gamma
Synonyms	RAR-gamma, Nuclear receptor subfamily 1 group B member 3
Protein Classification	Transcription factor, Nuclear hormone receptor subfamily 1 group B member 3
IDs	UniProt, ChEMBL

Biological function

Molecular function	DNA-binding, Receptor
Biological process	Transcription, Transcription regulation
Ligand/substrate	all-trans retinoic acid, 9-cis retinoic acid
Cofactor	Zn(2+)
Cellular component	Nucleus (soluble protein)
Functional structure	Homodimer. Heterodimer with a RXR molecule (e.g. RXRG). Binds DNA preferentially as a RAR/RXR heterodimer.

Target summery

Pathways were the target protein is involved

Activation of anterior HOX genes in hindbrain development during early embryogenesis
Activation of HOX genes during differentiation
Developmental Biology
Endoderm Differentiation
Gene Expression
Generic Transcription Pathway
Mesodermal Commitment Pathway
Nuclear Receptor transcription pathway
Nuclear Receptors
Nuclear receptors in lipid metabolism and toxicity
Retinol metabolism
Signal Transduction
Signaling by Retinoic Acid
Vitamin A and Carotenoid Metabolism

Source: NCBI BioSystems

GENE EXPRESSION

Gene expression data

Gene products

Protein-coding transcripts	Length (aa)	Isoform
RARG-203	454	1 (canonical)
RARG-201	443	2
RARG-202	382	3
RARG-204	432	4
RARG-213	15	Protein fragment
RARG-215	32	Protein fragment
RARG-207	57	Protein fragment

Gene expression data

mRNA expression (1/2)

Human cancer cell lines are valuable tools for in vitro tests in the early stages of drug discovery. This is a list of cancer cell lines expressing the target gene.

Cell line	Origin	Category	Expression Level
CAPAN-2	Pancreas	Cancer cell line	High
MCF7	Pleural effusion	Cancer cell line	High
fHDF/TERT166	Foreskin	Immortalized human foreskin fibroblast cell line	High
HaCaT	Skin	Spontaneously immortalized cell line	High
WM-115	Skin	Cancer cell line	High
SiHa	Cervix	Cancer cell line	Medium
AN3-CA	Lymph node	Cancer cell line	Medium
hTCEpi	Cornea	Telomerase immortalized cell line	Medium
U-87 MG	Brain	Cancer cell line	Medium
T-47d	Mammary gland; derived from metastatic site: pleural effusion	Cancer cell line	Medium
BJ hTERT+	Foreskin	Telomerase immortalized cell line	Medium
PC-3	Bone marrow	Cancer cell line	Medium
ASC diff	Adipose tissue	Uncategorized	Medium
SK-BR-3	Breast adenocarcinoma	Cancer cell line	Medium
U-138 MG	Brain	Cancer cell line	Medium
ASC TERT1	Adipose tissue	Telomerase immortalized cell line	Medium
HBEC3-KT	Central lung bronchiole	Telomerase immortalized cell line	Medium
RT4	Urinary bladder	Cancer cell line	Medium

Source: Human Protein Atlas cell line data set. Technique: RNA-seq

Gene expression data

mRNA expression (2/2)

Human cancer cell lines are valuable tools for in vitro tests in the early stages of drug discovery. This is a list of cancer cell lines expressing the target gene.

Cell line	Origin	Category	Expression Level
hTEC/SVTERT24-B	Thyroid	Transformed cell line	Medium
BJ hTERT+ SV40 Large T+	Foreskin	Uncategorized	Medium
HSkMC	Trapezius and erector spinae muscles	Uncategorized	Medium
SK-MEL-30	Subcutis	Cancer cell line	Medium
SH-SY5Y	Bone marrow neuroblastoma cells	Homo sapiens cell line	Medium
BJ hTERT+ SV40 Large T+ RasG12V	Foreskin	Uncategorized	Medium
A549	Lung	Cancer cell line	Medium
U-2197	Subcutis	Cancer cell line	Medium

Source: Human Protein Atlas cell line data set. Technique: RNA-seq

Gene expression data

mRNA expression

Tissue	Expression level
skin 1	High
esophagus	High
urinary bladder	Medium
tonsil	Medium
thyroid gland	Medium
stomach 1	Medium
smooth muscle	Medium
seminal vesicle	Medium
prostate	Medium
placenta	Medium
parathyroid gland	Medium
ovary	Medium
lung	Medium
adipose tissue	Medium
adrenal gland	Medium
breast	Medium
cervix, uterine	Medium
endometrium 1	Medium
gallbladder	Medium
fallopian tube	Medium

Tissue	Expression level
heart muscle	Low
appendix	Low
testis	Low
bone marrow	Low
spleen	Low
kidney	Low
small intestine	Low
cerebral cortex	Low
skeletal muscle	Low
salivary gland	Low
rectum	Low
colon	Low
duodenum	Low
lymph node	Low
epididymis	Low

Source: Human Protein Atlas. Technique: RNA-seq

Gene expression data

Protein expression (1/2)

Summary:

Ubiquitous nuclear expression

Details:

Tissue	Cell type (protein expression level)
endometrium	cells in endometrial stroma (high), glandular cells (high), glandular cells (medium), cells in endometrial stroma (medium)
epididymis	glandular cells (high)
esophagus	squamous epithelial cells (high)
gallbladder	glandular cells (high)
cervix, uterine	glandular cells (high), squamous epithelial cells (medium)
cerebral cortex	neuronal cells (high), endothelial cells (medium), glial cells (medium)
kidney	cells in glomeruli (high), cells in tubules (high)
cerebellum	Purkinje cells (high), cells in molecular layer (high), cells in granular layer (high)
prostate	glandular cells (high)
parathyroid gland	glandular cells (high)
pancreas	islets of Langerhans (high), exocrine glandular cells (high)
urinary bladder	urothelial cells (high)
seminal vesicle	glandular cells (medium)
salivary gland	glandular cells (medium)
skeletal muscle	myocytes (medium)
rectum	glandular cells (medium)
skin	fibroblasts (medium), keratinocytes (medium), Langerhans (medium), epidermal cells (medium), melanocytes (medium)
placenta	trophoblastic cells (medium)
vagina	squamous epithelial cells (medium)
tonsil	squamous epithelial cells (medium), non-germinal center cells (medium), germinal center cells (medium)
thyroid gland	glandular cells (medium)
testis	Leydig cells (medium), cells in seminiferous ducts (medium)

Source: Human Protein Atlas tissue data set. Technique: Immunohistochemistry (IHC)

Gene expression data

Protein expression (2/2)

Tissue	Cell type (protein expression level)
stomach	glandular cells (medium), glandular cells (medium)
spleen	cells in white pulp (medium), cells in red pulp (medium)
soft tissue	peripheral nerve (medium), peripheral nerve (medium), fibroblasts (medium), fibroblasts (low), adipocytes (low), chondrocytes (low)
smooth muscle	smooth muscle cells (medium)
small intestine	glandular cells (medium)
adrenal gland	glandular cells (medium)
appendix	glandular cells (medium), lymphoid tissue (medium)
bone marrow	hematopoietic cells (medium)
breast	glandular cells (medium), myoepithelial cells (medium), adipocytes (low)
bronchus	respiratory epithelial cells (medium)
caudate	neuronal cells (medium), glial cells (low)
colon	endothelial cells (medium), glandular cells (medium), peripheral nerve/ganglion (medium)
duodenum	glandular cells (medium)
ovary	ovarian stroma cells (medium)
oral mucosa	squamous epithelial cells (medium)
nasopharynx	respiratory epithelial cells (medium)
lymph node	non-germinal center cells (medium), germinal center cells (medium)
lung	pneumocytes (medium), macrophages (medium)
liver	hepatocytes (medium), bile duct cells (medium)
hippocampus	neuronal cells (medium), glial cells (medium)
heart muscle	myocytes (medium)
fallopian tube	glandular cells (medium)

Source: Human Protein Atlas tissue data set. Technique: Immunohistochemistry (IHC)

GENE-DISEASE ASSOCIATION

Gene-disease association

Mutations linked to disease

Mutation	Description and reference
S427L	dbSNP:rs2229774. A coding variant in RARG confers susceptibility to anthracycline-induced **cardiotoxicity** in childhood cancer. Nat Genet. 2015 Sep;47(9):1079-84
G430S	In a **breast cancer** sample; somatic mutation. The consensus coding sequences of human breast and colorectal cancers. Science. 2006 Oct 13;314(5797):268-74.

Source: UniProt

Cancer associations (1/3)

Publications

Oncogenic retinoic acid receptor γ knockdown reverses multi-drug resistance of human colorectal cancer via Wnt/β-catenin pathway.
Cell Cycle (2017) 10.1080/15384101.2017.1295180

The cytoplasmic nuclear receptor RARγ controls RIP1 initiated cell death when cIAP activity is inhibited.
Nat Commun (2017) 10.1038/s41467-017-00496-6

RARγ Downregulation Contributes to Colorectal Tumorigenesis and Metastasis by Derepressing the Hippo-Yap Pathway.
Cancer Res (2016) 10.1158/0008-5472.can-15-2882

Critical role of retinoid/rexinoid signaling in mediating transformation and therapeutic response of NUP98-RARG leukemia. (Qiu JJ et al. Leukemia (2015) 29: 1153-62)

A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer.
Nat Genet (2015) 10.1038/ng.3374

In vitro all-trans retinoic acid sensitivity of acute myeloid leukemia blasts with NUP98/RARG fusion gene.
Ann Hematol (2014) 10.1007/s00277-014-2073-5

BCL-xL/MCL-1 inhibition and RARγ antagonism work cooperatively in human HL60 leukemia cells.
Exp Cell Res (2014) 10.1016/j.yexcr.2014.07.024

CDK1 interacts with RARγ and plays an important role in treatment response of acute myeloid leukemia.
Cell Cycle (2013) 10.4161/cc.24313

CDK1 links to RARγ in treatment response of cancer cells.
Cell Cycle (2013) 10.4161/cc.25069

Source: Europe PMC

Cancer associations (2/3)

Publications

Oncogenic activity of retinoic acid receptor γ is exhibited through activation of the Akt/NF-κB and Wnt/β-catenin pathways in cholangiocarcinoma. (Huang GL et al. Mol. Cell. Biol. (2013) 33: 3416-25)

Reversal by RARα agonist Am580 of c-Myc-induced imbalance in RARα/RARγ expression during MMTV-Myc tumorigenesis.
Breast Cancer Res (2012) 10.1186/bcr3247

A novel NUP98/RARG gene fusion in acute myeloid leukemia resembling acute promyelocytic leukemia.
Blood (2011) 10.1182/blood-2010-06-291658

Detection of variable levels of RARα and RARγ proteins in pluripotent and differentiating mouse embryonal carcinoma and mouse embryonic stem cells.
Cell Tissue Res (2011) 10.1007/s00441-011-1247-x

Gene expression profiling elucidates a specific role for RARgamma in the retinoic acid-induced differentiation of F9 teratocarcinoma stem cells.
Biochem Pharmacol (2008) 10.1016/j.bcp.2007.11.006

A microenvironment-induced myeloproliferative syndrome caused by retinoic acid receptor gamma deficiency.
Cell (2007) 10.1016/j.cell.2007.05.014

Antitumor activity of the retinoid-related molecules (E)-3-(4'-hydroxy-3'-adamantylbiphenyl-4-yl)acrylic acid (ST1926) and 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) in F9 teratocarcinoma: Role of retinoic acid receptor gamma and retinoid-independent pathways.
Mol Pharmacol (2006) 10.1124/mol.106.023614

Overexpression of RARgamma increases death of SH-SY5Y neuroblastoma cells in response to retinoic acid but not fenretinide.
Cell Death Differ (2006) 10.1038/sj.cdd.4401824

Ligation of RARgamma inhibits proliferation of phytohaemagglutinin-stimulated T-cells via down-regulating JAK3 protein levels.
Immunol Lett (2005) 10.1016/j.imlet.2004.10.018

RARgamma acts as a tumor suppressor in mouse keratinocytes.
Oncogene (2004) 10.1038/sj.onc.1207682

Retinoids cause apoptosis in pancreatic cancer cells via activation of RAR-gamma and altered expression of Bcl-2/Bax.
Br J Cancer (2002) 10.1038/sj.bjc.6600496

Coordinate regulation of RARgamma2, TBP, and TAFII135 by targeted proteolysis during retinoic acid-induced differentiation of F9 embryonal carcinoma cells.
BMC Mol Biol (2001) 10.1186/1471-2199-2-4

Source: Europe PMC

Cancer associations (3/3)

Publications

Expression of retinoic acid receptor gamma correlates with retinoic acid sensitivity and metabolism in head and neck squamous cell carcinoma cell lines.
Int J Cancer (2001) 10.1002/1097-0215(20010601)92:5<661::aid-ijc1251>3.0.co;2-o

The RARgamma selective agonist CD437 inhibits gastric cell growth through the mechanism of apoptosis.
Cancer Lett (1999) 10.1016/s0304-3835(98)00382-6

Retinoic acid receptor gamma1 expression determines retinoid sensitivity in pancreatic carcinoma cells.
Gastroenterology (1998) 10.1016/s0016-5085(98)70269-0

Retinoic acid receptor gamma1 (RARgamma1) levels control RARbeta2 expression in SK-N-BE2(c) neuroblastoma cells and regulate a differentiation-apoptosis switch.
Mol Cell Biol (1998) 10.1128/mcb.18.11.6482

Specific activation of retinoic acid receptors (RARs) and retinoid X receptors reveals a unique role for RARgamma in induction of differentiation and apoptosis of S91 melanoma cells.
J Biol Chem (1997) 10.1074/jbc.272.30.18990

Source: Europe PMC

Gene-disease association

Diseases associated to target

Disease
-

Source: Uniprot disease terms

Indication of drugs and clinical candidates

Disease	Associated drug
acne	Tretinoin and 3 others
neoplasm	Tretinoin and 1 others
acute myeloid leukemia	Tretinoin
lymphoma	Tretinoin
rosacea	Tretinoin and 1 others
multiple myeloma	Tretinoin
psoriasis	Tazarotene and 3 others
alzheimers disease	Isotretinoin
infection	Isotretinoin
hiv-1 infection	Isotretinoin
lung carcinoma	Isotretinoin
neuroblastoma	Isotretinoin
actinic keratosis	Isotretinoin
cutaneous lupus erythematosus	Alitretinoin
eczema	Alitretinoin
skin disease	Tazarotene and 1 others
carcinoma	Tazarotene

Source: analysis of MeshTerms of drugs linked to target

Gene-disease association

Gene expression in disease

Diseases in which the target gene expression is either **up-regulated** (positive Log2-fold change) or **down-regulated** (negative Log2-fold change) compared to the normal cell type.

Up-regulation

Disease	Cell type	Log2-fold change
Osteosarcoma	-	1.8
Atypical teratoid / rhabdoid tumor	-	1.3
Glioblastoma	-	1.3
Medulloblastoma, large-cell	-	1.2

Down-regulation

Disease	Cell type	Log2-fold change
Malignant mesothelioma	Epithelial cell	-1.8

Source: EMBL-EBI Expression Atlas

Gene-disease association

Conclusion and comments

The RARG gene plays an important role in the progression of several cancers. These observations makes RARG an interesting target to investigate for oncology.

DRUGGABILITY

Druggability

Approved drugs and clinical candidates

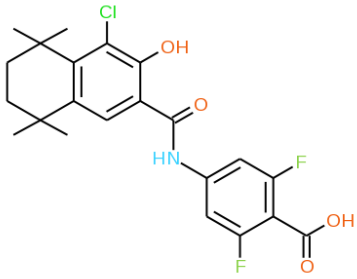
1	11	88
Targeting RARG	**Targeting members in sub-family** (NR1B subfamily)	**Targeting members in family** (nuclear receptor 1 Family)

Compounds targeting members in the NR1B subfamily

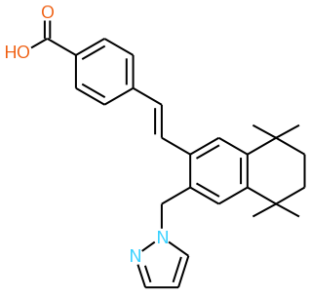
Name	Action Type	Max. clinical phase
Palovarotene	agonist (RARG)	2
NRX195183	agonist (RARA)	2
Tretinoin	agonist (Protein family: Retinoic acid receptor)	Approved
Isotretinoin	agonist (Protein family: Retinoic acid receptor)	Approved
Tazarotene	agonist (Protein family: Retinoic acid receptor)	Approved
Adapalene	agonist (Protein family: Retinoic acid receptor)	Approved
Acitretin	agonist (Protein family: Retinoic acid receptor)	Approved
Etretinate	agonist (Protein family: Retinoic acid receptor)	Withdrawn from the market
Alitretinoin	agonist (Protein family: Retinoic acid receptor)	Approved
IRX4310	agonist (Protein family: Retinoic acid receptor)	1
Mofarotene	modulator (Protein family: Retinoic acid receptor)	1

Known molecular structures shown on next page.

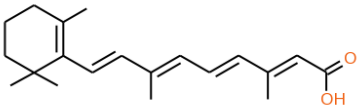
Approved drugs and clinical candidates



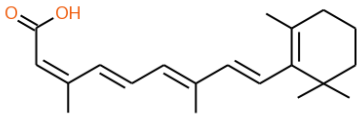
NRX195183



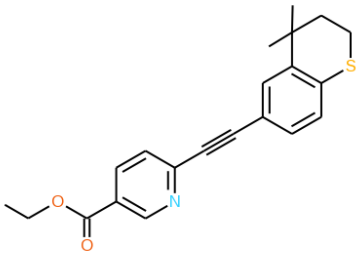
PALOVAROTENE



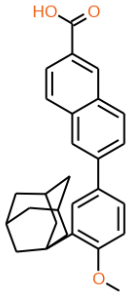
TRETINOIN



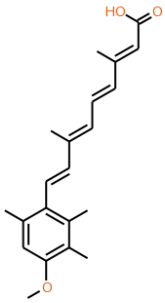
ISOTRETINOIN



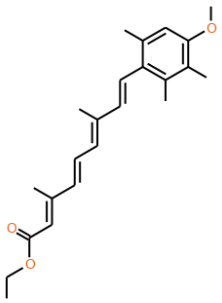
TAZAROTENE



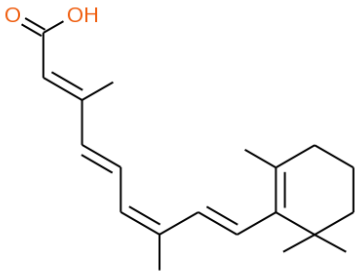
ADAPALENE



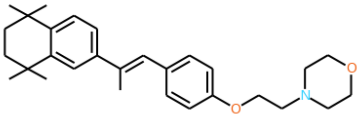
ACITRETIN



ETRETINATE



ALITRETINOIN



MOFAROTENE

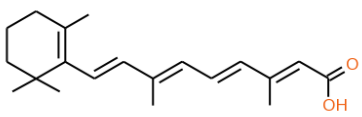
Other target inhibitors

56*

Targeting RARG

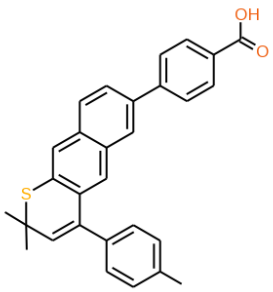
* Based on ChEMBL data (release chembl_23).
An active compounds is defined as having a residual activity <50% in the Millipore data set of kinase inhibitors or a pChEMBL value >6. pChEMBL is defined as the −log molar IC50, XC50, EC50, AC50, Ki, Kd, or potency (in M units). For example, an IC50 measurement of 1 µM would have a pChEMBL value of 6.
The data has also been filtered on the confidence score of the assigned target. Only activities with a score of 9, i.e. direct single protein target assigned, were kept.

Top 3 binders



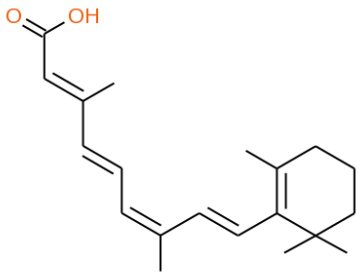
CHEMBL38: Ki= 0.040 nM

Name	Tretinoin
Clinical trial	Approved drug
Withdrawal	Not withdrawn



CHEMBL165629: IC50= 0.500 nM

Name	-
Clinical trial	0
Withdrawal	



CHEMBL705: Kd= 0.800 nM

Name	Alitretinoin
Clinical trial	Approved drug
Withdrawal	Not withdrawn

For the complete list, see ligand data.

Druggability

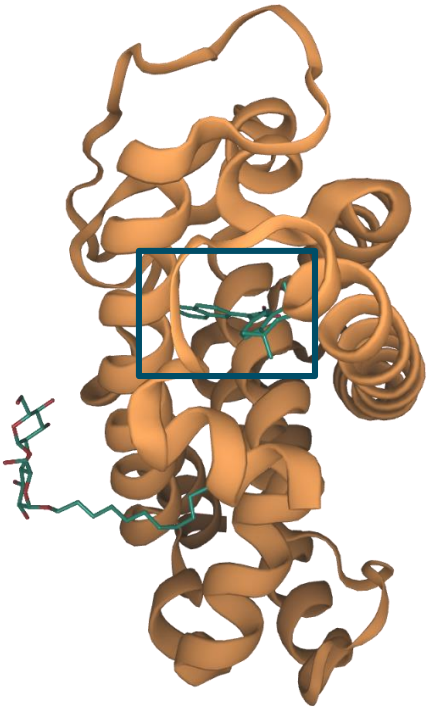
Druggable pockets

Predicted druggable pockets:

1. Ligand-binding site

Druggable pocket 1

Location	Ligand binding region
Druggability	Predicted as highly druggable
Ligands	8 confirmed binders (PDB structures)
Natural variations*	No variations in the binding site



Druggable pocket in RARG PDB structure (1exa)

*Naturally occurring sequence variations/mutations, including polymorphisms and disease-associated mutations.

Conclusion and comments

RARG has been shown to be inhibited by several small molecules. Several of these are compounds have already been approved as drugs (Tretinoin, Isotretinoin, Tazarotene, Adapalene, Acitretin, Alitretinoin), or is currently investigated (Palovarotene).

This data confirms that RARG is a druggable target.

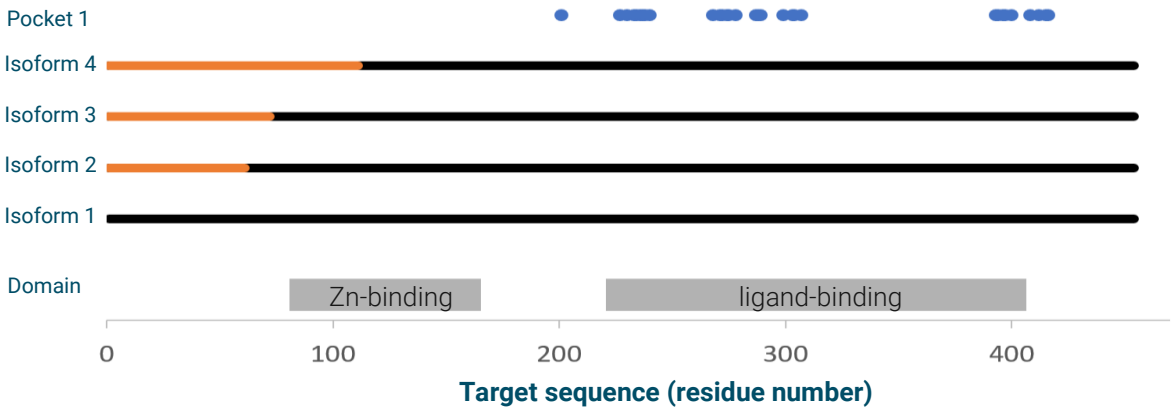
It should be noted that one drug targeting RARG has been withdrawn from the market because of a high risk of birth defects (Etretinate).

SELECTIVITY

Selectivity

Selectivity between isoforms

The variation between the four RARG isoforms is situated at the N-terminal of the sequence. This section is highlighted in orange in the graph beneath. The druggable pocket is situated in the ligand-binding domain and is not impacted by this sequence variation.



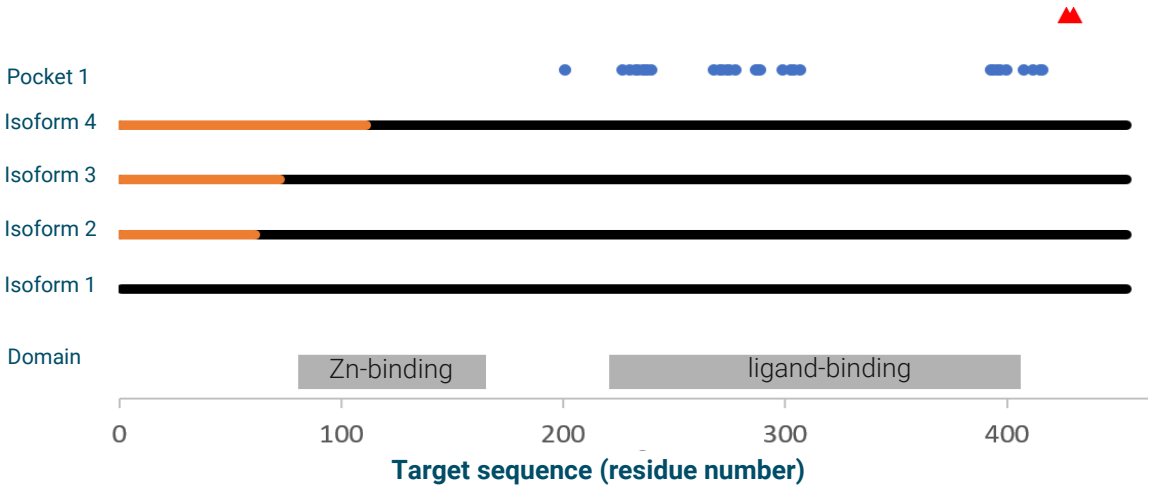
Selectivity

Selectivity versus mutations in the target gene

A mutation in the target gene can result in the substitution of a residue on the protein itself. If this residue is placed within the druggable pocket, it can give rise to selectivity issues and even resistance to the drug.

Bellow is a list of sequence variations and mutations, including polymorphisms and disease-associated mutations that modify the protein sequence. The mutations are indicated by red triangles in the graph underneath.

Mutation	Reference
S427L	dbSNP
G430S	Somatic mutation in a breast cancer sample PubMed



Source: Uniprot (February 20, 2018)

Selectivity versus other targets

Analysis of ChEMBL data

The ChEMBL database contains 176 compounds that are reported to inhibit RARG. RARG is the principle target of 50 of these compounds, i.e. their inhibition of RARG is stronger then for the other targets reported in ChEMBL. These 50 inhibitors are active on 0-9 other targets.
In total, the 176 RARG-inhibiting compounds, inhibit* 27 other targets.

These targets are listed beneath. For the complete list of all inhibitors, targets and activities, please consult **SI1.xlsx**

Protein class	Off targets
Transcription factor	
nuclear receptor nr1	RARA, RARB, RORC, RORA, RORB, PPARG
nuclear receptor nr2	RXRA, RXRG, RXRB
Other	HIF1A
Enzyme	
protein kinase	MAPK1
cytochrome p450	CYP2C19, CYP2D6, CYP26B1, CYP26A1
Other	GCK, MTOR, BLM, HSD17B10
Epigenetic regulator	
Reader	SMN1
Membrane receptor	
Family A G protein-coupled receptor	TSHR, ADORA3, HTR2B
Ion channel	
ligand-gated ion channel	GLRA1
Unclassified	
other	RAB9A, NPC1, LMNA

*Based on ChEMBL data (release chembl_23).
An active compounds is defined as having a pChEMBL value >5 or a residual activity <50% in the Millipore data set of kinase inhibitors.
pChEMBL is defined as the −log molar IC50, XC50, EC50, AC50, Ki, Kd, or potency (in M units). For example, an IC50 measurement of 1nM would have a pChEMBL value of 9.

Selectivity versus other targets

Analysis of sequence and structural data (pocket specific analysis)

The druggable pocket in RARG (described here) was used as query to search for similar pockets in our database of structures and sequences.

Bellow is a list of the most similar pockets identified through this analysis.

Protein class	Off targets	Pocket
Transcription factor		
nuclear receptor nr1	RARB	Ligand-binding pocket
	RARA	Ligand-binding pocket
nuclear receptor nr2	RXRA	Ligand-binding pocket
Auxiliary transport protein		
fatty acid binding protein	CRABP1	Retinoic acid binding region
	CRABP2	Retinoic acid binding region
Enzyme		
cytochrome p450	CYP2C8	Catalytic site
ldehyde dehydrogenase	ALDH1A3	Active site
Secreted protein		
other	TTR	Thyroid hormones binding site
	RBP4	Binding site

Selectivity versus animal orthologs (for in vivo assays)

Sequence variability within druggable pocket 1

Species	Seq. overlap (%)	Sequence identity (%)	Mutations
Mus musculus (Mouse)	100	100	-
Rattus norvegicus (Rat)	100	100	-
Cavia porcellus (Guinea pig)	100	100	-
Canis lupus familiaris (Dog)	100	100	-
Felis catus (Cat)	100	100	-
Ovis aries (Sheep)	100	100	-
Macaca mulatta (Rhesus macaque)	100	100	-
Pan troglodytes (Chimpanzee)	100	100	-
Sus scrofa (Pig)	100	100	-
Mesocricetus auratus (Golden hamster)	100	100	-
Oryctolagus cuniculus (Rabbit)	100	84	M272V, R274Q, I275A, R278G, T287A
Danio rerio (Zebrafish)	100	97	A234S

No RARG ortholog sequence identified for

Gallus gallus (Chicken)

Source: ENSEMBL

Selectivity

Conclusion and comments

The sequence difference between the four isoforms does not alter the druggable pockets identified on the ligand-binding domain. Drugs targeting this pocket are therefore likely to have a very similar affinity for the four isoforms.

There are no currently known sequence variation or mutation situated within in the druggable pocket. However, in order to minimize the risk of drug resistance caused by a mutation in the binding site, we recommend that you continuously verify updates on sequence variation for your target.

Several of the RARG-inhibiting compounds reported in ChEMBL also inhibit other targets (a total of 27 different targets). These potential off-targets should be considered in the design of a drug candidate.

The structural similarity search revealed 9 targets having a pocket similar to the druggable pocket identified on RARG. In all of these off-targets, the structural data can be exploited to guide the design of more selective drug candidates.

The druggable pocket in the human RARG was compared to the pockets in animal orthologs. The pockets were found to be identical in the RARG orthologs of mouse, rat, guinea pig, dog, cat, sheep, rhesus macaque, chimpanzee, pig, and golden hamster. There are several factors to be considered when choosing an in vivo model but based on the pocket similarity, these are all suitable models

TARGET VALIDATION MODELS

Target validation methods

Gene intervention: cell-based models

Latest publications

Publication: The cytoplasmic nuclear receptor RARγ controls RIP1 initiated cell death when cIAP activity is inhibited.
Nat Commun (2017) 10.1038/s41467-017-00496-6
Technique: shRNA
Outcome: RARγ is required for cell death initiated by RIP1

Publication: Oncogenic retinoic acid receptor γ knockdown reverses multi-drug resistance of human colorectal cancer via Wnt/β-catenin pathway.
Cell Cycle (2017) 10.1080/15384101.2017.1295180
Technique: -
Outcome: RARγ knockdown increased the sensitivity of colorectal cancer (CRC) cells to chemotherapeutics through downregulation of multi-drug resistance 1(MDR1).

Publication: Retinoic Acid Receptor γ Regulates B and T Lymphopoiesis via Nestin-Expressing Cells in the Bone Marrow and Thymic Microenvironments.
J Immunol (2016) 10.4049/jimmunol.1501246
Technique: Rarγ conditionally deleted
Outcome: RARγ is a regulator of B and T lymphopoiesis via Nes-expressing cells in the BM and thymic microenvironments, respectively.

Publication: RARγ-induced E-cadherin downregulation promotes hepatocellular carcinoma invasion and metastasis.
J Exp Clin Cancer Res (2016)
Technique: shRNA
Outcome: RARγ could promote HCC invasion and metastasis by regulating E-cadherin reduction, and implicate new strategies to aggressively treat HCC through targeting RARγ/E-cadherin signaling axis.

Source: Europe PMC

Target validation methods

Gene intervention: animal models

Latest publications

Publication: RARγ is a negative regulator of osteoclastogenesis.
J Steroid Biochem Mol Biol (2015) 10.1016/j.jsbmb.2015.03.005
Technique: RARγ null mice
Outcome: RARγ null mice had significantly less trabecular bone at 8 weeks of age compared to wildtype littermates. Further histomorphometric analysis revealed a significantly greater osteoclast surface in bones from 8-week-old RARγ null male mice. Collectively, our data indicates a physiological role for RARγ as a negative regulator of osteoclastogenesis in vivo and in vitro, and reveals distinct influences of RARα and RARγ in bone structure regulation.

Publication: Retinoic Acid Receptor γ Regulates B and T Lymphopoiesis via Nestin-Expressing Cells in the Bone Marrow and Thymic Microenvironments.
Technique: RARγ null mice - Cardiotoxin-Induced Muscle Injury Model and Critical Defect Muscle Injury Model
Outcome: muscle repair was remarkably delayed in RARγ-null mice in both critical defect and cardiotoxin injury models.

Source: Europe PMC

Target validation methods

Pharmacological intervention: cell-based models

Latest publications

Publication: RARα and RARγ reciprocally control K5+ progenitor cell expansion in developing salivary glands.
Organogenesis (2017) 10.1080/15476278.2017.1358336
Technique: inhibitors and agonists
Outcome: RARγ is necessary but not sufficient to positively maintain K5+ cells, as agonism of RARγ alone failed to significantly expand the population.

Publication: Suppression by an RAR-γ Agonist of Collagen Degradation Mediated by Corneal Fibroblasts.
Invest Ophthalmol Vis Sci (2017) 10.1167/iovs.15-18701
Technique: Primary rabbit corneal fibroblasts embedded in a three-dimensional collagen gel were incubated with or without all-trans retinoic acid (ATRA), the RAR-α agonist Am580, the RAR-β agonist AC55649, or the RAR-γ agonist R667.
Outcome: RARα and RARγ reciprocally control K5+ progenitor cell expansion in developing salivary glands.
The RAR-γ agonist R667 suppressed MMP production and thereby inhibited collagen degradation by corneal fibroblasts exposed to the proinflammatory cytokine IL-1β. These effects of R667 may be mediated by the NF-κB signaling pathway.

Publication: Effects of retinoic acid receptor-γ on the Aspergillus fumigatus induced innate immunity response in human corneal epithelial cells.
Int J Ophthalmol (2016) 10.18240/ijo.2016.12.02
Technique: BMS961 (RARγ agonist)
Outcome: BMS961 can inhibit the expression of Dectin-1, TNF-α and IL-6, and play an anti-inflammatory role in innate immune responses against A. fumigatus.

Source: Europe PMC

Target validation methods

Pharmacological intervention: animal models

Latest publications

Publication: RARγ is a negative regulator of osteoclastogenesis.
J Steroid Biochem Mol Biol (2015) 10.1016/j.jsbmb.2015.03.005
Technique: Oral administration of 5 mg/kg/day all-trans retinoic acid (ATRA) for 10 days in mice
Outcome: ATRA protected against bone loss induced by granulocyte colony-stimulating factor (G-CSF) by inhibiting the pro-osteoclastogenic action of G-CSF. Collectively, our data indicates a physiological role for RARγ as a negative regulator of osteoclastogenesis in vivo and in vitro, and reveals distinct influences of RARα and RARγ in bone structure regulation.

Publication: Retinoic Acid Receptor γ Regulates B and T Lymphopoiesis via Nestin-Expressing Cells in the Bone Marrow and Thymic Microenvironments.
Technique: We generated a critical defect in the tibialis anterior muscle of 7-week-old mice with a cautery, treated them with RARγ agonist or vehicle corn oil, and examined the effects of RARγ agonist on muscle repair.
Outcome: The fibrous or adipose area was smaller in RARγ agonist-treated mice than in the control.

Source: Europe PMC

ASSAY DATA

Cell-based assays (1/2)

Target-specific assays

Agonist activity at Gal4 DNA binding domain-tagged human RARgamma ligand binding domain expressed in HEK293 cells assessed as activation of receptor-mediated transcriptional activity by luciferase reporter gene assay, and 1 other assay(s)
Discovery of biaryl carboxylamides as potent ROR inverse agonists.
Bioorg. Med. Chem. Lett. (2015) 10.1016/j.bmcl.2015.05.026

Antagonist activity against RARgamma ligand binding domain (unknown origin) expressed in human MCF7 cells assessed as inhibition of ATRA-induced receptor transactivation at 10 uM after 18 hrs by luciferase reporter gene based mammalian one-hybrid assay
Identification of a New RXR Antagonist Targeting the Coregulator-Binding Site.
ACS Med. Chem. Lett. (2014) 10.1021/ml5000405

Transactivation of Gal4-fused RARgamma (unknown origin) expressed in African green monkey COS1 cells at 100 nM by luciferase reporter gene assay relative to DMSO-treated control
Design, synthesis and evaluation of retinoids with novel bulky hydrophobic partial structures.
Bioorg. Med. Chem. (2013) 10.1016/j.bmc.2013.04.053

Activity at human RARgamma ligand binding domain expressed in COS7 cells co-transfected with Gal4-DBD assessed as transcriptional activation after 16 hrs by Gal4 response element-driven luciferase reporter gene assay, and 3 other assay(s)
Novel non-carboxylic acid retinoids: 1,2,4-oxadiazol-5-one derivatives.
Bioorg. Med. Chem. Lett. (2009) 10.1016/j.bmcl.2008.11.040

Antagonist activity at human RARgamma expressed in african green monkey CV1 cells assessed as all-trans-retinoic acid-stimulated Gal4 transactivation activity by luciferase reporter gene assay, and 1 other assay(s)
Inhibition of IkappaB kinase-beta and anticancer activities of novel chalcone adamantyl arotinoids.
J. Med. Chem. (2008) 10.1021/jm800285f

Agonist activity at human RARgamma expressed in human HeLa cells assessed as relative luminescence units at >=10 uM by luciferase assay relative to control
New retinoid chemotypes: 9-cis-retinoic acid analogs with hydrophobic rings derived from terpenes as selective RAR agonists.
Bioorg. Med. Chem. (2008) https://doi.org/10.1016/j.bmc.2008.09.069

Antagonism of retinoic acid receptor gamma in ATRA treated CV-1 cells co-expressing CRBP-I-tk-CAT reporter at 10e-6 M, and 1 other assay(s)
Determinants of retinoid X receptor transcriptional antagonism.
J. Med. Chem. (2004) 10.1021/jm030651g

Inhibition of 3[H]ATRA binding to retinoid acid receptor gamma expressed in CV-1 cells
Design and synthesis of fluorinated RXR modulators.
Bioorg. Med. Chem. Lett. (2003) 10.1016/s0960-894x(03)00703-0

Transcriptional activation in CV-1 cells expressing human Retinoic acid receptor RAR gamma
Retinoic acid receptor ligands based on the 6-cyclopropyl-2,4-hexadienoic acid.
Bioorg. Med. Chem. Lett. (2003) 10.1016/s0960-894x(02)00924-1

Transcriptional activation in COS cells expressing RAR-gamma, and 1 other assay(s)
Discovery of novel and potent retinoic acid receptor alpha agonists: syntheses and evaluation of benzofuranyl-pyrrole and benzothiophenyl-pyrrole derivatives.
J. Med. Chem. (2000) 10.1021/jm000098s

Source: ChEMBL assays data, BioAssay Ontology classification

Cell-based assays (2/2)

Target-specific assays

Transcriptional activation in COS-1 cells expressing Retinoic Acid Receptor gamma (RAR gamma), and 1 other assay(s)
Syntheses and structure-activity relationships of 5,6,7, 8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxaline derivatives with retinoic acid receptor alpha agonistic activity.
J. Med. Chem. (2000) 10.1021/jm990063w

Transcriptional activation in CV-1 cells expressing human Retinoic acid receptor RAR gamma
Heteroarotinoids inhibit head and neck cancer cell lines in vitro and in vivo through both RAR and RXR retinoic acid receptors.
J. Med. Chem. (1999) 10.1021/jm990292i

Transcriptional activation in CV-1 cells expressing RAR-gamma receptor
Synthesis and characterization of heteroarotinoids demonstrate structure specificity relationships.
J. Med. Chem. (1998) 10.1021/jm980308p

Effective potency in transcriptional activation assay in CV-1 cells expressing retinoic acid receptor RAR gamma
Synthesis and structure-activity relationships of potent retinoid X receptor ligands
Bioorg. Med. Chem. Lett. (1997) 10.1016/S0960-894X(97)00437-X

Protein family assays

Inhibition of RAR in human STF cells at 1 uM after 24 hrs by TCF luciferase promoter reporter assay, and 1 other assay(s)
Design, Synthesis, and Biological Evaluation of a Series of Anthracene-9,10-dione Dioxime -Catenin Pathway Inhibitors.
J. Med. Chem. (2015) 10.1021/acs.jmedchem.5b00460

Activation of RAR in human HepG2 cells assessed as increase in CAR mRNA level at 10 uM after 24 hrs by RT-PCR analysis, and 1 other assay(s)
Retinoic acid receptor agonist activity of naturally occurring diterpenes.
Bioorg. Med. Chem. (2014) 10.1016/j.bmc.2014.03.047

Agonist activity at RAR (unknown origin) expressed in human HCT116 cells co-expressing RARE at 20 to 40 uM after 24 hrs by luciferase reporter gene assay
Synthesis and biological evaluation of halogenated curcumin analogs as potential nuclear receptor selective agonists.
Bioorg. Med. Chem. (2013) 10.1016/j.bmc.2012.11.033

Source: ChEMBL assays data, BioAssay Ontology classification

LIGAND DATA

Ligand data

Summary of public data

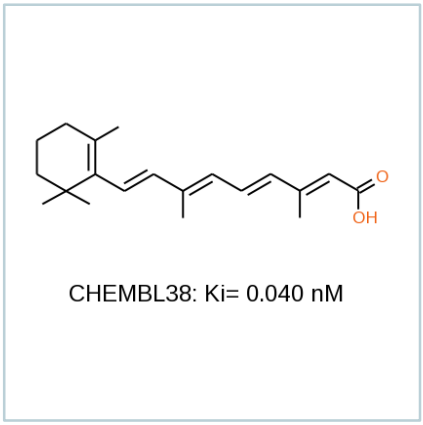
	Number of compounds
Co-crystalized with target[1]	9
Approved drugs and clinical candidates[2]	10
Known inhibitors[2,3]	56

[1] In RCSB Protein Data Bank

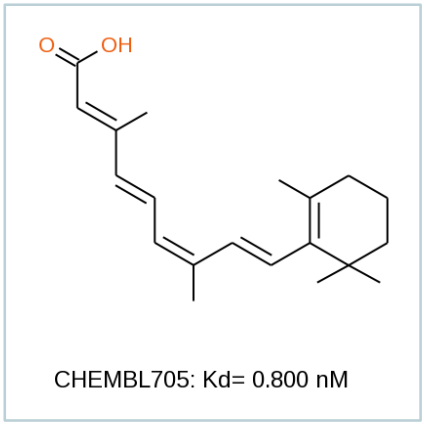
[2] Compounds targeting RARG specifically or its protein family, according to ChEMBL data (release chembl_23).

[3] The definition of an active compound is given on the next page.

Natural substrate of targeted pocket



all-trans retinoic acid

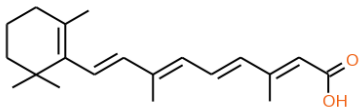


9-cis retinoic acid

Co factor

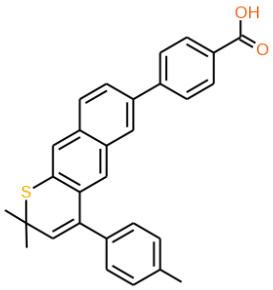
Zinc ion

Top 3 binders



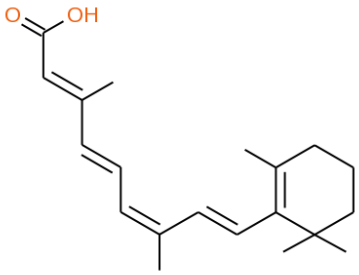
CHEMBL38: Ki= 0.040 nM

Name	Tretinoin



CHEMBL165629: IC50= 0.500 nM

Name	-



CHEMBL705: Kd= 0.800 nM

Name	Alitretinoin

Potential tool compounds

Analysis of ChEMBL data: known target inhibitors

The selectivity of each target inhibitor has been investigating through a complete analysis of the ChEMBL data. The results are presented on the following pages.

The analyis is based on ChEMBL data from the chembl_23 release.

All compounds discussed in this section are summarized in the file **tool_compounds.sdf**

Active compounds are defined as having a **pChEMBL value** >6, or a residual activity <50% in the Millipore data set of kinase inhibitors.

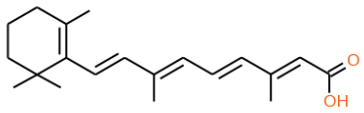
The **pChEMBL value** is defined as the −log molar IC50, XC50, EC50, AC50, Ki, Kd, or potency (in M units). For example, an IC50 measurement of 1 µM would have a pChEMBL value of 6.

The data has also been filtered on the confidence score of the assigned target. Only activities with a score of 9, i.e. direct single protein target assigned, were kept.

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



CHEMBL38: Ki= 0.040 nM

Active on

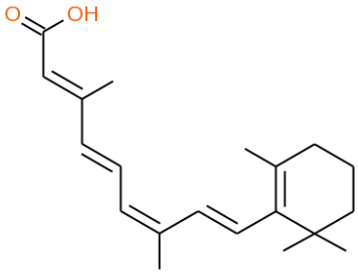
Protein family	Targets
transcription factor	10
enzyme	2
membrane receptor	1
epigenetic regulator	1

Top activities

Target	Activity
RARG	Ki = 0.04 nM
RARA	Ki = 0.10 nM
RORB	IC50 = 0.15 nM
RARB	Kd = 0.40 nM
BLM	Potency = 22.4 nM
RXRA	Kd = 53.0 nM
RXRB	Ki = 54.0 nM
RXRG	Ki = 120.0 nM
RORC	IC50 = 199.5 nM
RORA	IC50 = 199.5 nM

Inactive on

Target	Activity
CYP3A4	Potency=39811 nM



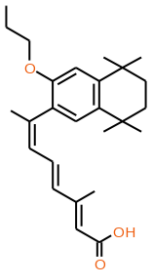
CHEMBL705: Kd= 0.800 nM

Active on

Protein family	Targets
transcription factor	6

Top activities

Target	Activity
RARG	Kd = 0.80 nM
RXRA	Kd = 1.5 nM
RARB	EC50 = 3.3 nM
RXRB	Ki = 3.8 nM
RXRG	Ki = 11.0 nM
RARA	Kd = 93.0 nM



CHEMBL109581: EC50=192.000 nM

Active on

Protein family	Targets
transcription factor	6

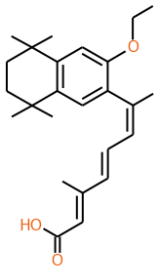
Top activities

Target	Activity
RXRA	EC50 = 2.0 nM
RXRG	EC50 = 4.0 nM
RARA	EC50 = 4.0 nM
RXRB	Ki = 9.0 nM
RARB	EC50 = 10.0 nM
RARG	EC50 = 192.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



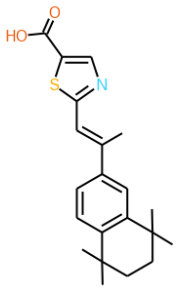
CHEMBL109847: EC50=121.000 nM

Active on

Protein family	Targets
transcription factor	6

Top activities

Target	Activity
RXRA	Ki = 4.0 nM
RXRG	EC50 = 7.0 nM
RXRB	EC50 = 9.0 nM
RARA	EC50 = 14.0 nM
RARB	EC50 = 31.0 nM
RARG	EC50 = 121.0 nM



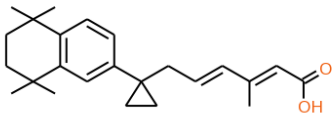
CHEMBL93577: EC50=34.000 nM

Active on

Protein family	Targets
transcription factor	6

Top activities

Target	Activity
RARG	EC50 = 34.0 nM
RARB	EC50 = 46.0 nM
RXRG	EC50 = 160.0 nM
RXRA	EC50 = 210.0 nM
RARA	EC50 = 210.0 nM
RXRB	EC50 = 210.0 nM



CHEMBL89331: EC50=24.000 nM

Active on

Protein family	Targets
transcription factor	5

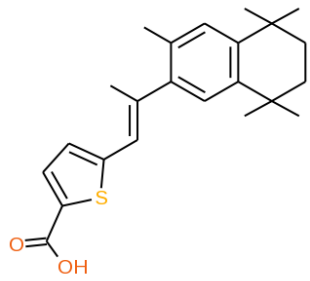
Top activities

Target	Activity
RXRA	Kd = 2.0 nM
RXRG	Kd = 8.0 nM
RARB	EC50 = 17.0 nM
RARG	EC50 = 24.0 nM
RARA	EC50 = 59.0 nM

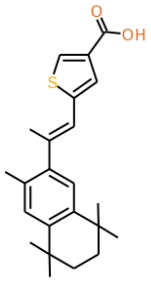
Analysis of ChEMBL data

Target Assessment Report

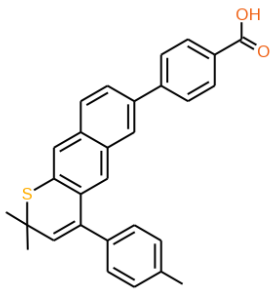
Potential tool compounds



CHEMBL91718: EC50=37.000 nM



CHEMBL93628: EC50=979.000 nM



CHEMBL165629: IC50= 0.500 nM

Active on

Protein family	Targets
transcription factor	5

Active on

Protein family	Targets
transcription factor	4

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RXRA	EC50 = 11.0 nM
RXRB	EC50 = 23.0 nM
RARB	EC50 = 23.0 nM
RXRG	EC50 = 33.0 nM
RARG	EC50 = 37.0 nM

Top activities

Target	Activity
RXRG	EC50 = 105.0 nM
RXRB	EC50 = 180.0 nM
RXRA	EC50 = 201.0 nM
RARG	EC50 = 979.0 nM

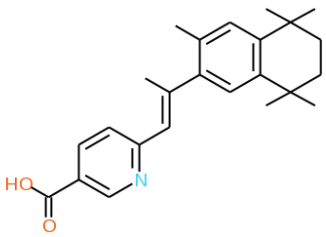
Top activities

Target	Activity
RARG	IC50 = 0.50 nM
RARA	IC50 = 1.5 nM
RARB	IC50 = 2.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



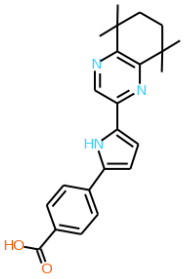
CHEMBL92926: EC50=374.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARB	EC50 = 21.0 nM
RXRA	EC50 = 105.0 nM
RARG	EC50 = 374.0 nM



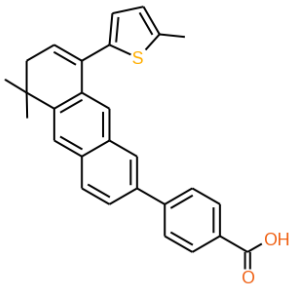
CHEMBL133725: IC50=310.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARA	IC50 = 2.2 nM
RARB	IC50 = 230.0 nM
RARG	IC50 = 310.0 nM



CHEMBL165417: IC50= 2.000 nM

Active on

Protein family	Targets
transcription factor	3

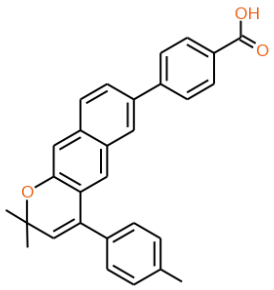
Top activities

Target	Activity
RARG	IC50 = 2.0 nM
RARB	Kd = 6.0 nM
RARA	Kd = 15.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



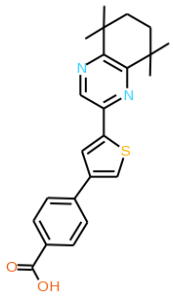
CHEMBL162345: IC50= 2.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	IC50 = 2.0 nM
RARA	IC50 = 5.5 nM
RARB	Kd = 7.0 nM



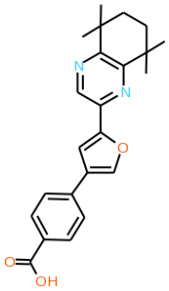
CHEMBL131850: IC50= 2.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	IC50 = 2.0 nM
RARA	IC50 = 2.4 nM
RARB	IC50 = 4.5 nM



CHEMBL131925: IC50=27.000 nM

Active on

Protein family	Targets
transcription factor	3

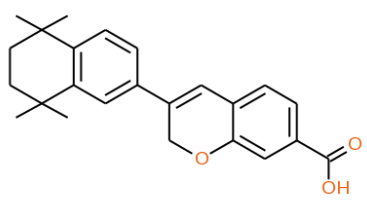
Top activities

Target	Activity
RARB	IC50 = 2.5 nM
RARA	IC50 = 19.0 nM
RARG	IC50 = 27.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



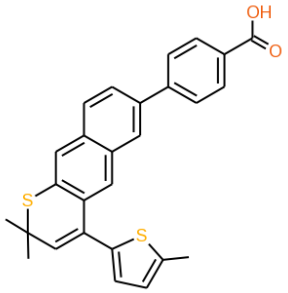
CHEMBL75848: Ki=19.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	Ki = 19.0 nM
RARB	Ki = 36.0 nM
RARA	Ki = 487.0 nM



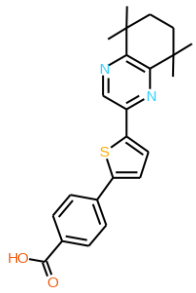
CHEMBL163223: Kd=18.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARA	Kd = 13.0 nM
RARB	Kd = 13.0 nM
RARG	Kd = 18.0 nM



CHEMBL131810: IC50=17.000 nM

Active on

Protein family	Targets
transcription factor	3

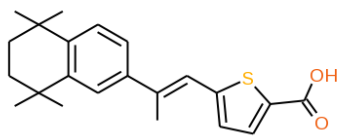
Top activities

Target	Activity
RARG	IC50 = 17.0 nM
RARB	IC50 = 36.0 nM
RARA	IC50 = 130.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



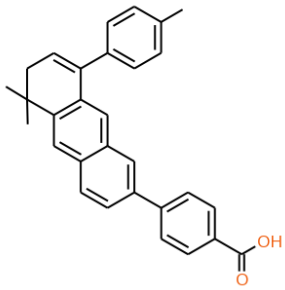
CHEMBL93538: EC50=15.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	EC50 = 15.0 nM
RARB	EC50 = 29.0 nM
RARA	EC50 = 690.0 nM



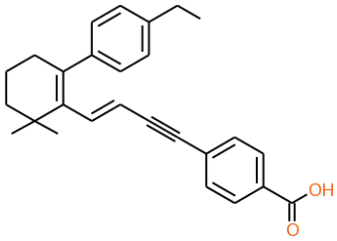
CHEMBL162393: IC50= 2.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	IC50 = 2.0 nM
RARB	Kd = 4.0 nM
RARA	Kd = 13.0 nM



CHEMBL349935: IC50= 3.000 nM

Active on

Protein family	Targets
transcription factor	3

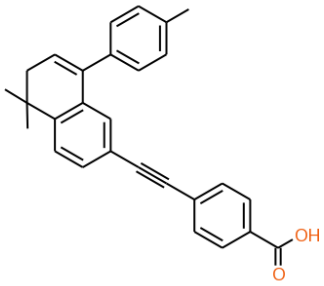
Top activities

Target	Activity
RARG	IC50 = 3.0 nM
RARB	Kd = 4.0 nM
RARA	Kd = 136.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



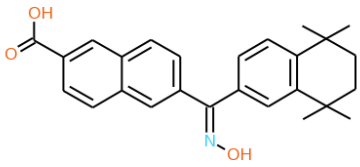
CHEMBL358145: IC50= 3.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	IC50 = 3.0 nM
RARB	Kd = 7.0 nM
RARA	Kd = 17.0 nM



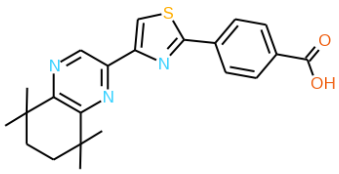
CHEMBL77961: Kd= 3.300 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	Kd = 3.3 nM
RARB	Kd = 50.0 nM
RARA	Kd = 700.0 nM



CHEMBL336311: IC50= 3.600 nM

Active on

Protein family	Targets
transcription factor	3

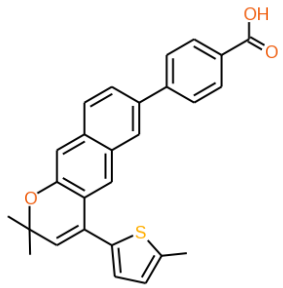
Top activities

Target	Activity
RARG	IC50 = 3.6 nM
RARB	IC50 = 21.0 nM
RARA	IC50 = 83.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



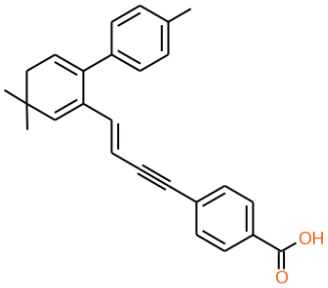
CHEMBL163530: IC50= 4.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	IC50 = 4.0 nM
RARB	IC50 = 6.5 nM
RARA	IC50 = 6.5 nM



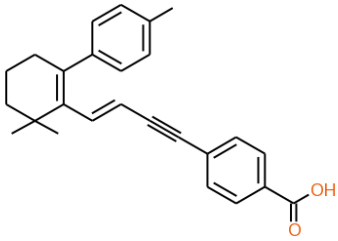
CHEMBL350485: Kd= 4.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	Kd = 4.0 nM
RARB	Kd = 35.0 nM
RARA	Kd = 129.0 nM



CHEMBL349018: IC50= 5.000 nM

Active on

Protein family	Targets
transcription factor	3

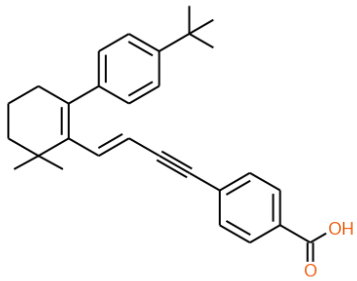
Top activities

Target	Activity
RARG	IC50 = 5.0 nM
RARB	Kd = 6.0 nM
RARA	Kd = 148.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



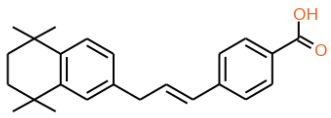
CHEMBL424190: Kd= 5.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	Kd = 5.0 nM
RARB	IC50 = 25.0 nM
RARA	Kd = 350.0 nM



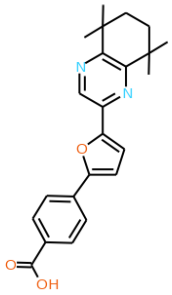
CHEMBL165843: EC50= 4.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARG	EC50 = 4.0 nM
RARB	Kd = 5.0 nM
RARA	EC50 = 30.0 nM



CHEMBL132033: IC50= 4.600 nM

Active on

Protein family	Targets
transcription factor	3

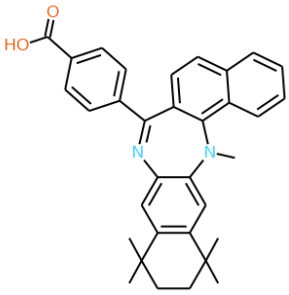
Top activities

Target	Activity
RARG	IC50 = 4.6 nM
RARA	IC50 = 32.0 nM
RARB	IC50 = 39.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



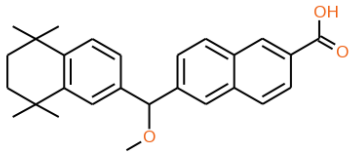
CHEMBL298373: Ki=490.000 nM

Active on

Protein family	Targets
transcription factor	2

Top activities

Target	Activity
RARG	Ki = 490.0 nM
RARB	Ki = 500.0 nM



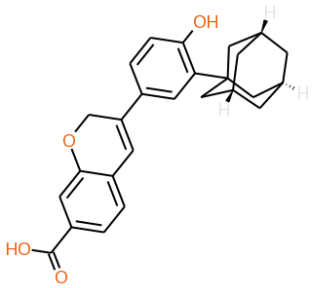
CHEMBL78835: Kd=400.000 nM

Active on

Protein family	Targets
transcription factor	2

Top activities

Target	Activity
RARB	Kd = 250.0 nM
RARG	Kd = 400.0 nM



CHEMBL75048: Ki=148.000 nM

Active on

Protein family	Targets
transcription factor	2

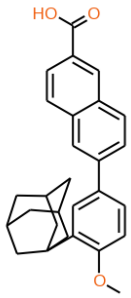
Top activities

Target	Activity
RARG	Ki = 148.0 nM
RARA	Ki = 821.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



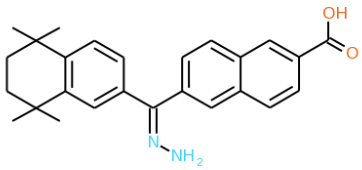
CHEMBL1265: Ki=130.000 nM

Active on

Protein family	Targets
transcription factor	2

Top activities

Target	Activity
RARB	Ki = 34.0 nM
RARG	Ki = 130.0 nM



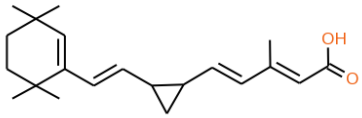
CHEMBL82609: Kd=95.000 nM

Active on

Protein family	Targets
transcription factor	2

Top activities

Target	Activity
RARB	Kd = 43.0 nM
RARG	Kd = 95.0 nM



CHEMBL74331: Ki=32.000 nM

Active on

Protein family	Targets
transcription factor	2

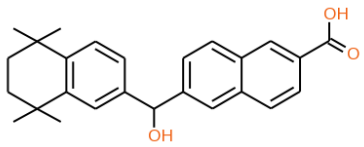
Top activities

Target	Activity
RARA	Ki = 3.1 nM
RARG	Ki = 32.0 nM

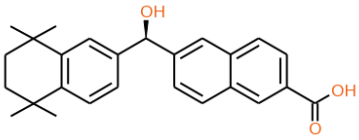
Analysis of ChEMBL data

Target Assessment Report

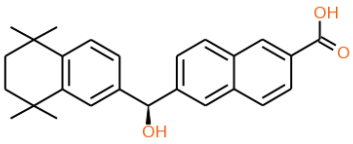
Potential tool compounds



CHEMBL82089: Kd=64.000 nM



CHEMBL81273: Kd=75.000 nM



CHEMBL80992: Kd=816.000 nM

Active on

Protein family	Targets
transcription factor	2

Active on

Protein family	Targets
transcription factor	2

Active on

Protein family	Targets
transcription factor	1

Top activities

Target	Activity
RARG	Kd = 64.0 nM
RARB	Kd = 679.0 nM

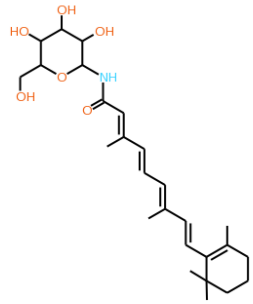
Top activities

Target	Activity
RARG	Kd = 75.0 nM
RARB	Kd = 531.0 nM

Analysis of ChEMBL data

Target Assessment Report

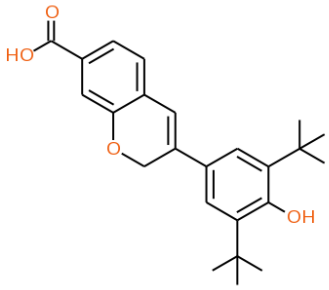
Potential tool compounds



CHEMBL66228: Ki=710.000 nM

Active on

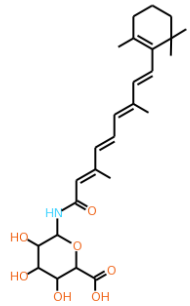
Protein family	Targets
transcription factor	1



CHEMBL308170: Ki=531.000 nM

Active on

Protein family	Targets
transcription factor	1



CHEMBL305760: Ki=280.000 nM

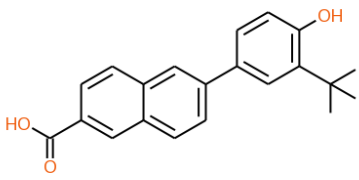
Active on

Protein family	Targets
transcription factor	1

Analysis of ChEMBL data

Target Assessment Report

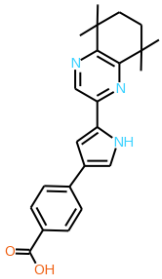
Potential tool compounds



CHEMBL74218: Ki=200.000 nM

Active on

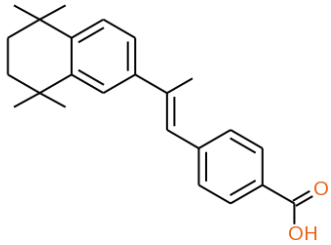
Protein family	Targets
transcription factor	1



CHEMBL337003: IC50=150.000 nM

Active on

Protein family	Targets
transcription factor	1



CHEMBL275311: EC50= 2.000 nM

Active on

Protein family	Targets
transcription factor	3
enzyme	2

Top activities

Target	Activity
RARA	EC50 = 0.18 nM
RARG	EC50 = 2.0 nM
RARB	EC50 = 3.0 nM
CYP2D6	Potency = 12.6 nM
MTOR	Potency = 521.2 nM

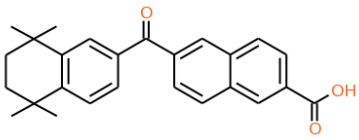
Inactive on

Target	Activity
HSD17B10	Potency=25119 nM
CYP2C19	Potency= 3981 nM
TP53	Potency=12589 nM
NFKB1	Potency=10000 nM
GMNN	Potency=11220 nM
SMN1	Potency= 5623 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



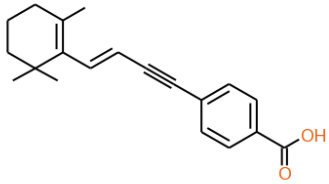
CHEMBL309282: Kd= 3.000 nM

Active on

Protein family	Targets
transcription factor	3
enzyme	1

Top activities

Target	Activity
RARB	Kd = 1.2 nM
RARG	Kd = 3.0 nM
RARA	Kd = 118.0 nM
CYP26B1	IC50 = 520.0 nM



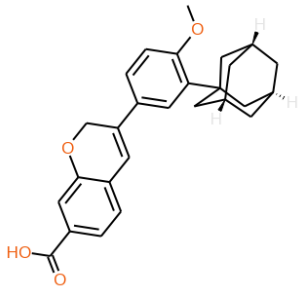
CHEMBL151870: EC50=10.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARB	EC50 = 7.0 nM
RARG	EC50 = 10.0 nM
RARA	Kd = 135.0 nM



CHEMBL75732: Ki=174.000 nM

Active on

Protein family	Targets
transcription factor	3

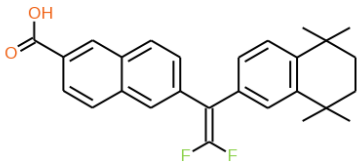
Top activities

Target	Activity
RARB	Ki = 71.0 nM
RARG	Ki = 174.0 nM
RARA	Ki = 764.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



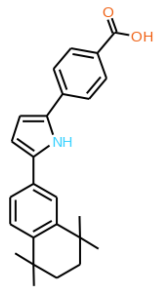
CHEMBL78587: Kd= 7.500 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARB	Kd = 1.7 nM
RARG	Kd = 7.5 nM
RARA	Kd = 73.0 nM



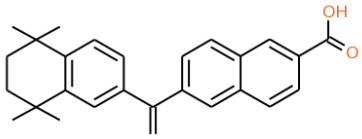
CHEMBL134375: IC50=21.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARA	IC50 = 0.45 nM
RARG	IC50 = 21.0 nM
RARB	IC50 = 100.0 nM



CHEMBL82716: Kd= 1.300 nM

Active on

Protein family	Targets
transcription factor	3

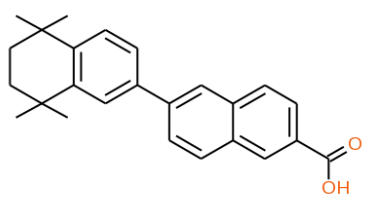
Top activities

Target	Activity
RARB	Kd = 1.1 nM
RARG	Kd = 1.3 nM
RARA	Kd = 68.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



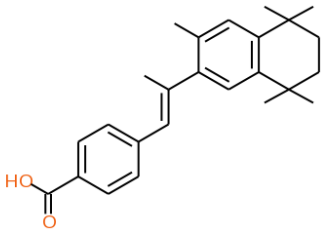
CHEMBL25361: Ki=40.000 nM

Active on

Protein family	Targets
transcription factor	3

Top activities

Target	Activity
RARB	Ki = 13.0 nM
RARG	Ki = 40.0 nM
RARA	Ki = 580.0 nM



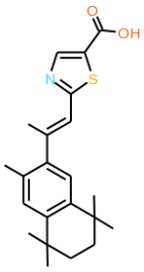
CHEMBL32505: EC50=152.000 nM

Active on

Protein family	Targets
transcription factor	4

Top activities

Target	Activity
RXRA	Kd = 32.0 nM
RARB	EC50 = 74.0 nM
RARG	EC50 = 152.0 nM
RARA	EC50 = 340.0 nM



CHEMBL328481: EC50=200.000 nM

Active on

Protein family	Targets
transcription factor	5

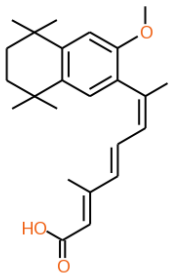
Top activities

Target	Activity
RXRB	EC50 = 3.0 nM
RXRA	EC50 = 4.0 nM
RXRG	EC50 = 4.0 nM
RARG	EC50 = 200.0 nM
RARB	EC50 = 220.0 nM

Analysis of ChEMBL data

Target Assessment Report

Potential tool compounds



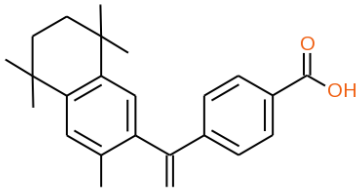
CHEMBL111589: EC50=17.000 nM

Active on

Protein family	Targets
transcription factor	6

Top activities

Target	Activity
RXRB	Ki = 2.0 nM
RXRA	Ki = 2.0 nM
RXRG	Ki = 4.0 nM
RARB	EC50 = 8.0 nM
RARG	EC50 = 17.0 nM
RARA	EC50 = 40.0 nM



CHEMBL1023: Ki=130.000 nM

Active on

Protein family	Targets
transcription factor	6

Top activities

Target	Activity
RXRA	EC50 = 2.7 nM
RXRB	Ki = 5.9 nM
RXRG	Ki = 8.3 nM
RARB	Ki = 50.0 nM
RARG	Ki = 130.0 nM
RARA	Ki = 180.0 nM

Inactive on

Target	Activity
BLM	Potency=68050 nM

Ligand data

Conclusion and comments

There are a large number of known RARG inhibitors. The most efficient inhibitor reported in ChEMBL is Tretinoin with a Ki of 0.04 nM.

There is no clear evidence of a RARG selective inhibitor within the ChEMBL data. The most potent RARG inhibitors are promiscuous binders within the protein subfamily.

STRUCTURAL DATA

Structural data

3D structures of target

Methods	Structures
Experimentally resolved (RCSB PDB)	10
Homology models (Swiss model)	16

Protein domains	Experimentally resolved structures
Ligand-binding domain	1fd0, 1fcy, 1exa, 2lbd, 1fcx, 4lbd, 5m24, 1fcz, 3lbd, 1exx
Zinc finger, C4 type (two domains)	Not resolved
DNA-binding region	Not resolved

Bound ligands (Name)	Structure
156	1fcz
184	1fcx
254	1fd0
394	1exa
564	1fcy
961	4lbd, 1exx
9CR	3lbd, 5m24
LMU	5m24, 1fd0, 1exa, 1exx, 1fcx, 1fcz, 1fcy
REA	2lbd

Protein-protein complexes	Structure
None	-

Relevant 3D structures of homologs

Unresolved protein domains

DNA-binding domain

Homolog	Structures	PDB codes
RARA	1	1dsz*
RARB	2	1hra*, 5uan
RXRA	13	1dsz*, 4cn3*, 1by4*, 4cn7*, 3dzu*, 1ynw*, 4cn5*, 4cn2*, 3e00*, 3dzy*, 1r0n*, 5uan*, 2nll*

Unresolved protein complexes

The RARG – RXRB complex

Homolog complex	Structures
NR1H2 (LBD) - RXRB (LBD)	5i4v (chain E, F), 5kya (chain A, B), 5kyj (chain E, F), 5hjp (chain D, C)
NR1H3 (LBD) - RXRB (LBD)	1uhl (chain B, A)
RXRB (LBD) - RXRB (LBD)	1h9u (chain C, D), 5kya (chain B, F)

The RARG – RXRG complex

Homolog complex	Structures
RXRG (LBD) - RXRG (LBD)	2gl8 (chain C, D)

* Bound to DNA
LBD = Ligand-binding domain
DBD = DNA-binding domain

Relevant 3D structures of homologs

The RARG – RXRA complex

Homolog complex	Structures
THRB (LBD) - RXRA (LBD)	4zo1 (chain X, B)
THRA (LBD) - RXRA (LBD)	3uvv (chain A, B)
Nr1h3 (LBD) - RXRA (LBD)	3fc6 (chain B, A), 2acl (chain H, G), 3fal (chain B, C)
RXRA (LBD) - RXRA (LBD)	1xvp (chain A, C), 1fby (chain A, B), 1xv9 (chain A, C), 3fc6 (chain A, C), 4n5g (chain A, C), 5tbp (chain B, D)
RXRA (LBD) - RXRA (LBD)	3ozj (chain A, C), 2acl (chain A, E), 5mk4 (chain A, C), 3nsq (chain A, B), 3nsp (chain A, B), 2zy0 (chain A, C), 1mzn (chain E, G), 1fm6 (chain A, U), 3r2a (chain C, D), 3r29 (chain A, B), 3r5m (chain A, C), 1xls (chain A, B), 1g5y (chain B, D), 1g1u (chain B, D), 5gym (chain D, F), 4n8r (chain A, C)
PPARG (LBD) - RXRA (LBD)	3e00 (chain D, A), 5ji0 (chain D, A), 1fm9 (chain D, A), 1k74 (chain D, A), 1fm6 (chain D, A), 1rdt (chain D, A), 3h0a (chain D, A)
NR1I3 (LBD) - RXRA (LBD)	1xvp (chain D, C), 1xv9 (chain B, A)
NR1I2 (LBD) - RXRA (LBD)	4j5w (chain A, D), 4j5x (chain A, D)
Nr1i3 (LBD) - RXRA (LBD)	1xls (chain E, A)
PPARG (LBD) - RXRA (DBD)	3dzy* (chain D, A)
RARA (DBD) - RXRA (Hinge)	1dsz* (chain A, B)
RARB (DBD) - RXRA (Hinge)	5uan (chain B, A)
PPARG (DBD) - RXRA (Hinge)	3dzu* (chain D, A)
THRB (DBD) - RXRA (DBD)	2nll* (chain B, A)
RXRA (DBD) - RXRA (Hinge)	4cn2* (chain C, D), 4cn3* (chain A, B), 1by4* (chain B, C), 4cn7* (chain A, B), 4cn5* (chain A, B)
EcR (DBD) - RXRA (DBD)	1r0n* (chain B, A)

The RARG – NCOR2 complex

Homolog complex	Structures
RORC (LBD) - NCOR2	5x8q (chain G, H)
RXRA (LBD) - NCOR2	3r29 (chain A, C), 3r2a (chain D, F)
PPARA (LBD) - NCOR2	1kkq (chain A, E)

* Bound to DNA
LBD = Ligand-binding domain
DBD = DNA-binding domain

Relevant 3D structures of homologs

The RARG – NCOA3 complex

Homolog complex	Structures
AR - NCOA3	3l3x (chain A, B), 1xj7 (chain A, B)

* Bound to DNA
LBD = Ligand-binding domain
DBD = DNA-binding domain

CONCLUSION

Conclusion and comments

Gene-disease association

The RARG gene plays an important role in the progression of several cancers. These observations makes RARG an interesting target for oncology.

Druggability

One druggable pocket was identified on the ligand-binding domain.

RARG has been shown to be inhibited by several small molecules. Several of these are compounds have already been approved as drugs (Tretinoin, Isotretinoin, Tazarotene, Adapalene, Acitretin, Alitretinoin), or is currently investigated (Palovarotene). This data confirms that RARG is a druggable target. It should be noted that one drug targeting RARG has been withdrawn from the market because of a high risk of birth defects (Etretinate).

Selectivity

The sequence difference between the four isoforms does not alter the druggable pockets identified on the ligand-binding domain. Drugs targeting this pocket are therefore likely to have a very similar affinity for the four isoforms.

There are no currently known sequence variation or mutation situated within in the druggable pocket. However, in order to minimize the risk of drug resistance caused by a mutation in the binding site, we recommend that you continuously verify updates on sequence variation for your target.

Several of the RARG-inhibiting compounds reported in ChEMBL also inhibit other targets (a total of 27 different targets). These potential off-targets should be considered in the design of a drug candidate.

The structural similarity search revealed 9 targets having a pocket similar to the druggable pocket identified on RARG. In all of these off-targets, the structural data can be exploited to guide the design of more selective drug candidates.

The druggable pocket in the human RARG was compared to the pocket in the RARG animal orthologs. The pockets was found to be identical in the RARG ortholog of mouse, rat, guinea pig, dog, cat, sheep, rhesus macaque, chimpanzee, pig, and golden hamster. There are several factors to be considered when choosing an in vivo model but based on the pocket similarity, these are all suitable models

Ligand data

There are a large number of known RARG inhibitors. The most efficient inhibitor reported in ChEMBL is Tretinoin with a Ki of 0.04 nM. There is no clear evidence of a RARG selective inhibitor within the ChEMBL data. The most potent RARG inhibitors are promiscuous binders within the protein subfamily.

Structural data

There are 10 resolved 3D structures of RARG. They are all structures of a monomer of the ligand-binding domain bound to a ligand. The DNA-binding domain has been resolved for close homologs (RARA, RARB and RXRA). There are also structures of close homologs in complexes similar to those of RARG.