

THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: OVERVIEW

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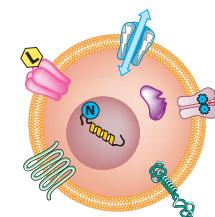
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Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties from the IUPHAR database. The full contents can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full>.

This compilation of the major pharmacological targets is divided into seven areas of focus: G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear hormone receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors & Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and GRAC and provides a permanent, citable, point-in-time record that will survive database updates.

Table of contents

1449 OVERVIEW

- 1454 Adiponectin receptors
- 1455 Fatty acid binding proteins
- 1457 Sigma receptors

1459 G PROTEIN-COUPLED RECEPTORS

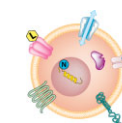
- 1462 Orphan GPCRs
- 1471 5-Hydroxytryptamine receptors
- 1474 Acetylcholine receptors (muscarinic)
- 1476 Adenosine receptors
- 1478 Adhesion Class GPCRs
- 1480 Adrenoceptors
- 1484 Angiotensin receptors

- 1485 Apelin receptor
- 1486 Bile acid receptor
- 1487 Bombesin receptors
- 1488 Bradykinin receptors
- 1489 Calcitonin receptors
- 1491 Calcium-sensing receptors
- 1492 Cannabinoid receptors
- 1494 Chemerin receptor
- 1495 Chemokine receptors
- 1500 Cholecystokinin receptors
- 1501 Complement peptide receptors
- 1502 Corticotropin-releasing factor receptors
- 1503 Dopamine receptors

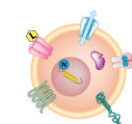
- 1505 Endothelin receptors
- 1506 Estrogen (G protein-coupled) receptor
- 1507 Formylpeptide receptors
- 1508 Free fatty acid receptors
- 1510 Frizzled Class GPCRs
- 1511 GABA_B receptors
- 1513 Galanin receptors
- 1514 Ghrelin receptor
- 1515 Glucagon receptor family
- 1517 Glycoprotein hormone receptors
- 1518 Gonadotrophin-releasing hormone receptors
- 1519 GPR18, GPR55 and GPR119
- 1520 Histamine receptors

Searchable database: <http://www.guidetopharmacology.org/index.jsp>

Full Contents of Concise Guide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full>



- 1521 Hydroxycarboxylic acid receptors
- 1522 Kisspeptin receptors
- 1523 Leukotriene, lipoxin and oxoeicosanoid receptors
- 1525 Lysophospholipid (LPA) receptors
- 1526 Lysophospholipid (S1P) receptors
- 1527 Melanin-concentrating hormone receptors
- 1528 Melanocortin receptors
- 1529 Melatonin receptors
- 1530 Metabotropic glutamate receptors
- 1532 Motilin receptor
- 1533 Neuromedin U receptors
- 1534 Neuropeptide FF/neuropeptide AF receptors
- 1535 Neuropeptide S receptor
- 1536 Neuropeptide W/neuropeptide B receptors
- 1537 Neuropeptide Y receptors
- 1538 Neurotensin receptors
- 1539 Opioid receptors
- 1541 Orexin receptors
- 1542 Oxoglutarate receptor
- 1543 P2Y receptors
- 1545 Parathyroid hormone receptors
- 1546 Peptide P518 receptor
- 1547 Platelet-activating factor receptor
- 1548 Prokineticin receptors
- 1549 Prolactin-releasing peptide receptor
- 1550 Prostanoid receptors
- 1552 Proteinase-activated receptors
- 1553 Relaxin family peptide receptors
- 1555 Somatostatin receptors
- 1556 Succinate receptor
- 1557 Tachykinin receptors
- 1558 Thyrotropin-releasing hormone receptors
- 1559 Trace amine receptor
- 1560 Urotensin receptor
- 1561 Vasopressin and oxytocin receptors
- 1562 VIP and PACAP receptors
- 1582 LIGAND-GATED ION CHANNELS**
- 1584 5-HT₃ receptors
- 1586 GABA_A receptors
- 1590 Glycine receptors
- 1592 Ionotropic glutamate receptors
- 1597 Nicotinic acetylcholine receptors
- 1601 P2X receptors
- 1603 ZAC
- 1607 ION CHANNELS**
- 1609 Acid-sensing (proton-gated) ion channels (ASICs)
- 1611 Aquaporins
- 1612 CatSper and Two-Pore channels
- 1613 Chloride channels
- 1620 Connexins and Pannexins
- 1621 Cyclic nucleotide-regulated channels
- 1623 Epithelial sodium channels (ENaC)
- 1625 IP₃ receptor
- 1626 Potassium channels
- 1630 Ryanodine receptor
- 1632 Sodium leak channel, non-selective
- 1633 Transient receptor potential channels
- 1643 Voltage-gated calcium channels
- 1645 Voltage-gated proton channel
- 1646 Voltage-gated sodium channels
- 1652 NUCLEAR HORMONE RECEPTORS**
- 1654 1A. Thyroid Hormone Receptors
- 1655 1B. Retinoic acid receptors
- 1656 1C. Peroxisome proliferator-activated receptors
- 1657 1D. Rev-Erb receptors
- 1658 1F. Retinoic acid-related orphans
- 1659 1H. Liver X receptor-like receptors
- 1660 1I. Vitamin D receptor-like receptors
- 1661 2A. Hepatocyte nuclear factor-4 receptors
- 1662 2B. Retinoid X receptors
- 1663 2C. Testicular receptors
- 1664 2E. Tailless-like receptors
- 1665 2F. COUP-TF-like receptors
- 1666 3B. Estrogen-related receptors
- 1667 4A. Nerve growth factor IB-like receptors
- 1668 5A. Fushi tarazu F1-like receptors
- 1669 6A. Germ cell nuclear factor receptors
- 1670 0B. DAX-like receptors
- 1671 Steroid hormone receptors
- 1676 CATALYTIC RECEPTORS**
- 1678 Cytokine receptor family
- 1684 GDNF receptor family
- 1685 Integrins
- 1688 Natriuretic peptide receptor family
- 1689 Pattern Recognition receptors
- 1692 Receptor serine/threonine kinase (RSTK) family
- 1695 Receptor tyrosine kinases
- 1702 Receptor tyrosine phosphatases (RTP)
- 1703 Tumour necrosis factor (TNF) receptor family
- 1706 TRANSPORTERS**
- 1708 ATP-binding cassette transporter family
- 1712 F-type and V-type ATPases
- 1714 P-type ATPases
- 1717 SLC1 family of amino acid transporters
- 1719 SLC2 family of hexose and sugar alcohol transporters
- 1721 SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)
- 1723 SLC4 family of bicarbonate transporters
- 1724 SLC5 family of sodium-dependent glucose transporters
- 1728 SLC6 neurotransmitter transporter family
- 1732 SLC8 family of sodium/calcium exchangers
- 1733 SLC9 family of sodium/hydrogen exchangers
- 1734 SLC10 family of sodium-bile acid co-transporters
- 1736 SLC11 family of proton-coupled metal ion transporters
- 1737 SLC12 family of cation-coupled chloride transporters
- 1739 SLC13 family of sodium-dependent sulphate/carboxylate transporters
- 1740 SLC14 family of facilitative urea transporters
- 1741 SLC15 family of peptide transporters
- 1742 SLC16 family of monocarboxylate transporters
- 1744 SLC17 phosphate and organic anion transporter family
- 1746 SLC18 family of vesicular amine transporters
- 1748 SLC19 family of vitamin transporters
- 1749 SLC20 family of sodium-dependent phosphate transporters
- 1750 SLC22 family of organic cation and anion transporters
- 1753 SLC23 family of ascorbic acid transporters
- 1754 SLC24 family of sodium/potassium/calcium exchangers
- 1755 SLC25 family of mitochondrial transporters
- 1760 SLC26 family of anion exchangers
- 1762 SLC27 family of fatty acid transporters
- 1763 SLC28 and SLC29 families of nucleoside transporters
- 1765 SLC30 zinc transporter family
- 1766 SLC31 family of copper transporters
- 1767 SLC32 vesicular inhibitory amino acid transporter
- 1768 SLC33 acetylCoA transporter
- 1769 SLC34 family of sodium phosphate co-transporters
- 1770 SLC35 family of nucleotide sugar transporters
- 1772 SLC36 family of proton-coupled amino acid transporters
- 1773 SLC37 family of phosphosugar/phosphate exchangers
- 1774 SLC38 family of sodium-dependent neutral amino acid transporters
- 1776 SLC39 family of metal ion transporters
- 1777 SLC40 iron transporter
- 1778 SLC41 family of divalent cation transporters
- 1779 SLC42 family of Rhesus glycoprotein ammonium transporters
- 1780 SLC43 family of large neutral amino acid transporters
- 1781 SLC44 choline transporter-like family
- 1782 SLC45 family of putative sugar transporters
- 1783 SLC46 family of folate transporters



1784	SLC47 family of multidrug and toxin extrusion transporters	1800	Adenosine turnover	1832	Glycerophospholipid turnover
1785	SLC48 heme transporter	1801	Amino acid hydroxylases	1838	Haem oxygenase
1786	SLC49 family of FLVCR-related heme transporters	1802	L-Arginine turnover	1839	Hydrogen sulfide synthesis
1787	SLC50 sugar transporter	1805	Carboxylases and decarboxylases	1840	Inositol phosphate turnover
1788	SLC51 family of steroid-derived molecule transporters	1807	Catecholamine turnover	1842	Lanosterol biosynthesis pathway
1789	SLC52 family of riboflavin transporters	1810	Ceramide turnover	1845	Peptidases and proteinases
1790	SLCO family of organic anion transporting polypeptides	1815	Cyclic nucleotide turnover	1853	Protein serine/threonine kinases
1797	ENZYMES	1820	Cytochrome P450	1860	Sphingosine 1-phosphate turnover
1799	Acetylcholine turnover	1824	Eicosanoid turnover	1862	Thyroid hormone turnover
		1828	Endocannabinoid turnover		
		1830	GABA turnover		

An Introduction to the Concise Guide to PHARMACOLOGY 2013/14

The great proliferation of drug targets in recent years has driven the need to provide a logically-organised synopsis of the nomenclature and pharmacology of these targets. This is the underlying reason for this Guide to PHARMACOLOGY 2013/14, distributed with the *British Journal of Pharmacology*, and produced in association with NC-IUPHAR, the Nomenclature Committees of the International Union of Basic and Clinical Pharmacology. Our intent is to produce an authoritative but user-friendly publication, which allows a rapid overview of the key properties of a wide range of established or potential pharmacological targets. The aim is to provide information succinctly, so that a newcomer to a particular target group can identify the main elements 'at a glance'. It is not our goal to produce all-inclusive reviews of the targets presented; references to these are included in the Further Reading sections of the entries or, for many targets, the website www.guidetopharmacology.org provides access to more extensive information. The Guide to PHARMACOLOGY 2013/14 presents each entry, typically a circumscribed target class family on, wherever possible, a single page, so as to allow easy access and rapid oversight.

The list of targets present is, in many cases, a comprehensive reflection of the known targets within the particular group. Our philosophy has been to present data on human proteins wherever possible, both in terms of structural information and pharmacology. To this end, the HGNC gene nomenclature and UniProt unique ID are indicated to allow rapid access through free online databases for further information. In a few cases, where structural or pharmacological information is not available for human targets, we have used data from other species, as indicated. A priority in constructing these tables was to present agents which represent the most selective and which are available by donation or from commercial sources, now or in the near future.

The Guide is divided into seven further sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, nuclear hormone receptors, transporters and enzymes. In this overview are listed protein targets of pharmacological interest, which are not G protein-coupled receptors, ligand-gated ion channels, ion channels, nuclear

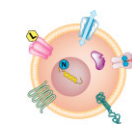
hormone receptors, catalytic receptors, transporters or enzymes. In comparison with the Fifth Edition of the Guide to Receptors & Channels [1], we have added a number of new records, expanding the total to include over 2000 protein targets, primarily from increasing the content on transporters and enzymes.

The Editors of the Guide have compiled the individual records, taking advice from many Collaborators (listed on page 1452). Where appropriate, an indication is given of the status of the nomenclature, as proposed by NC-IUPHAR, published in *Pharmacological Reviews*. Where this guidance is lacking, advice from several prominent, independent experts has generally been obtained to produce an authoritative consensus, which attempts to fit in within the general guidelines from NC-IUPHAR [2]. Tabulated data provide ready comparison of selective agents and probes (radioligands and PET ligands, where available) within a family of targets and additional commentary highlights whether species differences or ligand metabolism are potential confounding factors. We recommend that any citations to information in the Concise Guide are presented in the following format:

Alexander SPH *et al.* (2013). The Concise Guide to PHARMACOLOGY 2013/14. *Br J Pharmacol* 170: 1449–1867.

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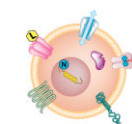
We are extremely grateful for the financial contributions from the British Pharmacological Society, the International Union of Basic and Clinical Pharmacology, the Wellcome Trust (099156/Z/12/Z), which support the website and the University of Edinburgh, who host the [guidetopharmacology.org](http://www.guidetopharmacology.org) website.



Acknowledgement of Collaborators

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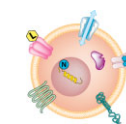


Conflict of interest

The authors state that there are no conflicts of interest to disclose.

List of records presented

- 1454 Adiponectin receptors
- 1455 Fatty acid binding proteins
- 1457 Sigma receptors



Adiponectin receptors

Overview: Adiponectin receptors (provisional nomenclature, ENSFM00500000270960) respond to the 30 kDa complement-related protein hormone adiponectin (also known as *ADIPOQ*: adipocyte, C1q and collagen domain-containing protein; ACRP30, adipose most abundant gene transcript 1; apM-1; gelatin-binding protein: Q15848) originally cloned from adipocytes [4]. Although sequence data suggest 7TM domains,

immunological evidence indicates that, contrary to typical 7TM topology, the carboxyl terminus is extracellular, while the amino terminus is intracellular [6]. Signalling through these receptors appears to avoid G proteins. Adiponectin receptors appear rather to stimulate protein phosphorylation via AMP-activated protein kinase and MAP kinase pathways [6], possibly through the protein partner *APPL1* (adaptor protein, phosphotyrosine

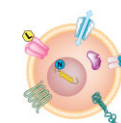
interaction, PH domain and leucine zipper containing 1, Q9UKG1 [5]). The adiponectin receptors are a class of proteins (along with membrane progesterin receptors), which contain seven sequences of aliphatic amino acids reminiscent of GPCRs, but which are structurally and functionally distinct from that class of receptor.

Nomenclature	Adipo1 receptor	Adipo2 receptor
HGNC, UniProt	<i>ADIPOR1</i> , Q96A54	<i>ADIPOR2</i> , Q86V24
Rank order of potency	globular adiponectin > adiponectin	globular adiponectin = adiponectin

Comments: T-Cadherin (*CDH13*, P55290) has also been suggested to be a receptor for (hexameric) adiponectin [3].

Further reading

- Buechler C, Wanninger J, Neumeier M. (2010) Adiponectin receptor binding proteins—recent advances in elucidating adiponectin signalling pathways. *FEBS Lett* **584**: 4280–4286. [PMID:20875820]
- Dalamaga M, Diakopoulos KN, Mantzoros CS. (2012) The role of adiponectin in cancer: a review of current evidence. *Endocr Rev* **33**: 547–594. [PMID:22547160]
- Goldstein BJ, Scalia RG, Ma XL. (2009) Protective vascular and myocardial effects of adiponectin. *Nat Clin Pract Cardiovasc Med* **6**: 27–35. [PMID:19029992]
- Juhl C, Beck-Sickinger AG. (2012) Molecular tools to characterize adiponectin activity. *Vitam Horm* **90**: 31–56. [PMID:23017711]
- Shetty S, Kusminski CM, Scherer PE. (2009) Adiponectin in health and disease: evaluation of adiponectin-targeted drug development strategies. *Trends Pharmacol Sci* **30**: 234–239. [PMID:19359049]
- Sun Y, Xun K, Wang C, Zhao H, Bi H, Chen X, Wang Y. (2009) Adiponectin, an unlocking adipocytokine. *Cardiovasc Ther* **27**: 59–75. [PMID:19207481]
- Thundiyil J, Pavlovski D, Sobey CG, Arumugam TV. (2012) Adiponectin receptor signalling in the brain. *Br J Pharmacol* **165**: 313–327. [PMID:21718299]



Fatty acid binding proteins

Overview: Fatty acid-binding proteins are low molecular weight (100–130 aa) chaperones for long chain fatty acids, fatty acyl CoA esters, eicosanoids, retinols, retinoic acids and related metabolites and are usually regarded as being responsible for

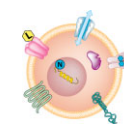
allowing the otherwise hydrophobic ligands to be mobile in aqueous media. These binding proteins may perform functions extracellularly (*e.g.* in plasma) or transport these agents; to the nucleus to interact with nuclear receptors (principally PPARs and

retinoic acid receptors [16]) or for interaction with metabolic enzymes. Although sequence homology is limited, crystallographic studies suggest conserved 3D structures across the group of binding proteins.

Preferred abbreviation	FABP1	FABP2	FABP3	FABP4	FABP5
Nomenclature	fatty acid binding protein 1, liver	fatty acid binding protein 2, intestinal	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	fatty acid binding protein 4, adipocyte	fatty acid binding protein 5 (psoriasis-associated)
HGNC, UniProt	<i>FABP1</i> , P07148	<i>FABP2</i> , P12104	<i>FABP3</i> , P05413	<i>FABP4</i> , P15090	<i>FABP5</i> , Q01469
Rank order of potency	stearic acid, oleic acid > palmitic acid, linoleic acid > arachidonic acid, α -linolenic acid [13]	stearic acid > palmitic acid, oleic acid > linoleic acid > arachidonic acid, α -linolenic acid [13]	stearic acid, oleic acid, palmitic acid > linoleic acid, α -linolenic acid, arachidonic acid [13]	oleic acid, palmitic acid, stearic acid, linoleic acid > α -linolenic acid, arachidonic acid [13]	–
Comment	A broader substrate specificity than other FABPs, binding two fatty acids per protein [18]	Crystal structure of the rat FABP2 [15]	Crystal structure of the human FABP3 [19]	–	Crystal structure of the human FABP5 [11]

Preferred abbreviation	FABP6	FABP7	FABP8	FABP9	FABP12
Nomenclature	fatty acid binding protein 6, ileal	fatty acid binding protein 7, brain	peripheral myelin protein 2	fatty acid binding protein 9, testis	fatty acid binding protein 12
HGNC, UniProt	<i>FABP6</i> , P51161	<i>FABP7</i> , O15540	<i>PMP2</i> , P02689	<i>FABP9</i> , Q0Z7S8	<i>FABP12</i> , A6NFH5
Comment	Able to transport bile acids [20]	Crystal structure of the human FABP7 [7]	<i>In silico</i> modelling suggests that FABP8 can bind both fatty acids and cholesterol [12]	–	–

Preferred abbreviation	RBP1	RBP2	RBP3	RBP4	RBP5
Nomenclature	retinol binding protein 1, cellular	retinol binding protein 2, cellular	retinol binding protein 3, interstitial	retinol binding protein 4, plasma	retinol binding protein 5, cellular
HGNC, UniProt	<i>RBP1</i> , P09455	<i>RBP2</i> , P50120	<i>RBP3</i> , P10745	<i>RBP4</i> , P02753	<i>RBP5</i> , P82980
Rank order of potency	–	stearic acid > palmitic acid, oleic acid, linoleic acid, α -linolenic acid, arachidonic acid [14]	–	–	–

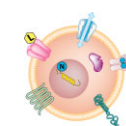


Preferred abbreviation	RBP7	RLBP1	CRABP1	CRABP2
Nomenclature	retinol binding protein 7, cellular	retinaldehyde binding protein 1	cellular retinoic acid binding protein 1	cellular retinoic acid binding protein 2
HGNC, UniProt	<i>RBP7</i> , Q96R05	<i>RLBP1</i> , P12271	<i>CRABP1</i> , P29762	<i>CRABP2</i> , P29373
Rank order of potency	–	11- <i>cis</i> -retinal, 11- <i>cis</i> -retinol > 9- <i>cis</i> -retinal, 13- <i>cis</i> -retinal, 13- <i>cis</i> -retinol, all- <i>trans</i> -retinal, retinol [8]	all- <i>trans</i> -retinoic acid > 9- <i>cis</i> -retinoic acid stearic acid > palmitic acid, oleic acid, linoleic acid, α -linolenic acid, arachidonic acid [14]	–

Comments: Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC_{50} ~8.8) compared to FABP3 or FABP5 (pIC_{50} <6.6, [9,17]). HTS01037 is reported to interfere with FABP4 action [10]. Multiple pseudogenes for the FABPs have been identified in the human genome.

Further reading

- Chmurzyńska A. (2006) The multigene family of fatty acid-binding proteins (FABPs): function, structure and polymorphism. *J Appl Genet* **47**: 39–48. [PMID:16424607]
- Furuhashi M, Hotamisligil GS. (2008) Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. *Nat Rev Drug Discov* **7**: 489–503. [PMID:18511927]
- Kralisch S, Fasshauer M. (2013) Adipocyte fatty acid binding protein: a novel adipokine involved in the pathogenesis of metabolic and vascular disease?. *Diabetologia* **56**: 10–21. [PMID:23052058]
- Schroeder F, Petrescu AD, Huang H, Atshaves BP, McIntosh AL, Martin GG, Hostetler HA, Vespa A, Landrock D, Landrock KK *et al.* (2008) Role of fatty acid binding proteins and long chain fatty acids in modulating nuclear receptors and gene transcription. *Lipids* **43**: 1–17. [PMID:17882463]
- Storch J, Thumser AE. (2010) Tissue-specific functions in the fatty acid-binding protein family. *J Biol Chem* **285**: 32679–32683. [PMID:20716527]
- Yamamoto T, Yamamoto A, Watanabe M, Matsuo T, Yamazaki N, Kataoka M, Terada H, Shinohara Y. (2009) Classification of FABP isoforms and tissues based on quantitative evaluation of transcript levels of these isoforms in various rat tissues. *Biotechnol Lett* **31**: 1695–1701. [PMID:19565192]



Sigma receptors

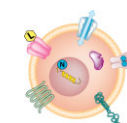
Overview: Although termed ‘receptors’, the evidence for coupling through conventional signalling pathways is lacking. Initially described as a subtype of opioid receptors, there is only a modest pharmacological overlap and no structural convergence with the G protein-coupled receptors. A wide range of compounds, ranging from psychoactive agents to antihistamines, have been observed to bind to these sites, which appear to be intracellular.

Nomenclature	$\sigma 1$ (sigma non-opioid intracellular receptor 1)	$\sigma 2$
HGNC, UniProt	<i>SIGMAR1</i> , Q99720	–
Selective agonists	(+)-SK&F10047, (RS)-PPCC (pK_i 8.8) [25], PRE-084 (pIC_{50} 7.4) [26]	PB-28 (pK_i 8.3) [21]
Selective antagonists	NE-100 (pIC_{50} 8.4) [24], BD-1047 (pIC_{50} 7.4) [23]	(RS)-SM21 (pIC_{50} 7.2) [22]
Radioligands (K_d)	[3H]-pentazocine (Agonist)	[3H]-di-o-tolylguanidine (Agonist)

Comments: (-)-pentazocine also shows activity at opioid receptors. There is no molecular correlate of the sigma2 receptor.

Further reading

- de Medina P, Paillasse MR, Ségala G, Khallouki F, Brillouet S, Dalenc F, Courbon F, Record M, Poirot M, Silvente-Poirot S. (2011) Importance of cholesterol and oxysterols metabolism in the pharmacology of tamoxifen and other AEBS ligands. *Chem Phys Lipids* **164**: 432–437. [PMID:21641337]
- Dubrovsky B. (2006) Neurosteroids, neuroactive steroids, and symptoms of affective disorders. *Pharmacol Biochem Behav* **84**: 644–655. [PMID:16962651]
- Guitart X, Codony X, Monroy X. (2004) Sigma receptors: biology and therapeutic potential. *Psychopharmacology (Berl)* **174**: 301–319. [PMID:15197533]
- Matsumoto RR, Liu Y, Lerner M, Howard EW, Brackett DJ. (2003) Sigma receptors: potential medications development target for anti-cocaine agents. *Eur J Pharmacol* **469**: 1–12. [PMID:12782179]



References

1. Alexander SPH *et al.* (2011) *Br J Pharmacol* **164**: S1–S324. PM:22040146
2. Vanhoutte PM *et al.* (1996) *Pharmacol Rev* **48**: 1–2. PM:8685244
3. Hug C *et al.* (2004) *Proc Natl Acad Sci U S A* **101**: 10308–10313. [PMID:15210937]
4. Maeda K *et al.* (1996) *Biochem Biophys Res Commun* **221**: 286–289. [PMID:8619847]
5. Mao X *et al.* (2006) *Nat Cell Biol* **8**: 516–523. [PMID:16622416]
6. Yamauchi T *et al.* (2003) *Nature* **423**: 762–769. [PMID:12802337]
7. Balendiran GK *et al.* (2000) *J Biol Chem* **275**: 27045–27054. [PMID:10854433]
8. Crabb JW *et al.* (1998) *Protein Sci* **7**: 746–757. [PMID:9541407]
9. Furuhashi M *et al.* (2007) *Nature* **447**: 959–965. [PMID:17554340]
10. Hertz AV *et al.* (2009) *J Med Chem* **52**: 6024–6031. [PMID:19754198]
11. Hohoff C *et al.* (1999) *Biochemistry* **38**: 12229–12239. [PMID:10493790]
12. Majava V *et al.* (2010) *PLoS ONE* **5**: e10300. [PMID:20421974]
13. Richieri GV *et al.* (1994) *J Biol Chem* **269**: 23918–23930. [PMID:7929039]
14. Richieri GV *et al.* (2000) *Biochemistry* **39**: 7197–7204. [PMID:10852718]
15. Sacchettini JC *et al.* (1989) *J Mol Biol* **208**: 327–339. [PMID:2671390]
16. Schroeder F *et al.* (2008) *Lipids* **43**: 1–17. [PMID:17882463]
17. Sulsky R *et al.* (2007) *Bioorg Med Chem Lett* **17**: 3511–3515. [PMID:17502136]
18. Thompson J *et al.* (1997) *J Biol Chem* **272**: 7140–7150. [PMID:9054409]
19. Young AC *et al.* (1994) *Structure* **2**: 523–534. [PMID:7922029]
20. Zwicker BL, Agellon LB. (2013) *Int J Biochem Cell Biol* **45**: 1389–1398. [PMID:23603607]
21. Berardi F *et al.* (1996) *J Med Chem* **39**: 176–182. [PMID:8568804]
22. Mach RH *et al.* (1999) *Life Sci* **64**: PL131–PL137. [PMID:10096443]
23. Matsumoto RR *et al.* (1995) *Eur J Pharmacol* **280**: 301–310. [PMID:8566098]
24. Okuyama S *et al.* (1993) *Life Sci* **53**: PL285–PL290. [PMID:7901723]
25. Prezzavento O *et al.* (2007) *J Med Chem* **50**: 951–961. [PMID:17328523]
26. Su TP, *et al.* (1991) *J Pharmacol Exp Ther* **259**: 543–550. [PMID:1658302]

