

# THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Overview

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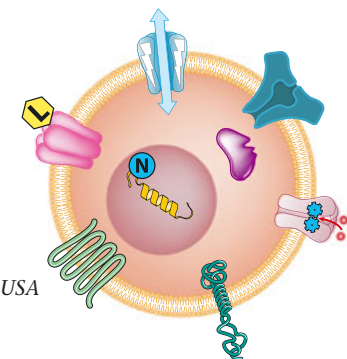
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## Abstract

The Concise Guide to PHARMACOLOGY 2017/18 is the third in this series of biennial publications. This version provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to an open access knowledgebase of drug targets and their ligands ([www.guidetopharmacology.org](http://www.guidetopharmacology.org)), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.13882/full>. In addition to this overview, in which are identified 'Other protein targets' which fall outside of the subsequent categorisation, there are eight areas of focus: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

## Table of contents

### S1 Overview

S6 Other Protein Targets

S6 Adiponectin receptors

S7 Blood coagulation components

S8 Non-enzymatic BRD containing proteins

S8 Carrier proteins

S9 CD molecules

S10 Methyllysine reader proteins

S11 Fatty acid-binding proteins

S13 Notch receptors

S13 Regulators of G protein Signaling (RGS) proteins

S14 Sigma receptors

S15 Tubulins

### S17 G protein-coupled receptors

S19 Orphan and other 7TM receptors

S19 Class A Orphans

S28 Class C Orphans

S28 Taste 1 receptors

S29 Taste 2 receptors

S30 Other 7TM proteins

S31 5-Hydroxytryptamine receptors

S34 Acetylcholine receptors (muscarinic)

S36 Adenosine receptors

S37 Adhesion Class GPCRs

S39 Adrenoceptors

S43 Angiotensin receptors

S44 Apelin receptor

S45 Bile acid receptor

S46 Bombesin receptors

S47 Bradykinin receptors

S48 Calcitonin receptors

S50 Calcium-sensing receptor

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

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.13882/full>

S51 Cannabinoid receptors	S111 Tachykinin receptors	<b>S208 Nuclear hormone receptors</b>
S52 Chemerin receptor	S113 Thyrotropin-releasing hormone receptors	S209 1A. Thyroid hormone receptors
S53 Chemokine receptors	S113 Trace amine receptor	S210 1B. Retinoic acid receptors
S57 Cholecystokinin receptors	S114 Urotensin receptor	S210 1C. Peroxisome proliferator-activated receptors
S58 Class Frizzled GPCRs	S115 Vasopressin and oxytocin receptors	S211 1D. Rev-Erb receptors
S59 Complement peptide receptors	S117 VIP and PACAP receptors	S212 1F. Retinoic acid-related orphans
S60 Corticotropin-releasing factor receptors		S213 1H. Liver X receptor-like receptors
S61 Dopamine receptors		S214 1I. Vitamin D receptor-like receptors
S63 Endothelin receptors	<b>S130 Ligand-gated ion channels</b>	S214 2A. Hepatocyte nuclear factor-4 receptors
S64 G protein-coupled estrogen receptor	S131 5-HT <sub>3</sub> receptors	S215 2B. Retinoid X receptors
S65 Formylpeptide receptors	S133 Acid-sensing (proton-gated) ion channels (ASICs)	S216 2C. Testicular receptors
S66 Free fatty acid receptors	S135 Epithelial sodium channels (ENaC)	S216 2E. Tailless-like receptors
S67 GABA <sub>B</sub> receptors	S137 GABA <sub>A</sub> receptors	S217 2F. COUP-TF-like receptors
S69 Galanin receptors	S142 Glycine receptors	S218 3B. Estrogen-related receptors
S70 Ghrelin receptor	S145 Ionotropic glutamate receptors	S218 4A. Nerve growth factor IB-like receptors
S71 Glucagon receptor family	S150 IP <sub>3</sub> receptor	S219 5A. Fushi tarazu F1-like receptors
S72 Glycoprotein hormone receptors	S151 Nicotinic acetylcholine receptors	S220 6A. Germ cell nuclear factor receptors
S73 Gonadotrophin-releasing hormone receptors	S154 P2X receptors	S220 0B. DAX-like receptors
S75 GPR18, GPR55 and GPR119	S156 ZAC	S221 Steroid hormone receptors
S76 Histamine receptors		S221 3A. Estrogen receptors
S77 Hydroxycarboxylic acid receptors		S222 3C. 3-Ketosteroid receptors
S78 Kisspeptin receptor		
S79 Leukotriene receptors	<b>S160 Voltage-gated ion channels</b>	<b>S225 Catalytic receptors</b>
S81 Lysophospholipid (LPA) receptors	S161 CatSper and Two-Pore channels	S226 Cytokine receptor family
S82 Lysophospholipid (S1P) receptors	S163 Cyclic nucleotide-regulated channels	S227 IL-2 receptor family
S83 Melanin-concentrating hormone receptors	S164 Potassium channels	S229 IL-3 receptor family
S84 Melanocortin receptors	S165 Calcium- and sodium-activated potassium channels	S230 IL-6 receptor family
S85 Melatonin receptors	S166 Inwardly rectifying potassium channels	S231 IL-12 receptor family
S86 Metabotropic glutamate receptors	S169 Two P domain potassium channels	S232 Prolactin receptor family
S88 Motilin receptor	S171 Voltage-gated potassium channels	S233 Interferon receptor family
S89 Neuromedin U receptors	S175 Ryanodine receptor	S234 IL-10 receptor family
S90 Neuropeptide FF/neuropeptide AF receptors	S176 Transient Receptor Potential channels	S235 Immunoglobulin-like family of IL-1 receptors
S91 Neuropeptide S receptor	S186 Voltage-gated calcium channels	S236 IL-17 receptor family
S92 Neuropeptide W/neuropeptide B receptors	S189 Voltage-gated proton channel	S237 GDNF receptor family
S93 Neuropeptide Y receptors	S190 Voltage-gated sodium channels	S237 Integrins
S94 Neurotensin receptors		S241 Natriuretic peptide receptor family
S95 Opioid receptors		S242 Pattern recognition receptors
S97 Orexin receptors		S243 Toll-like receptor family
S98 Oxoglutarate receptor		S244 NOD-like receptor family
S98 P2Y receptors	<b>S195 Other ion channels</b>	S246 Receptor tyrosine kinases (RTKs)
S101 Parathyroid hormone receptors	S196 Aquaporins	S247 Type I RTKs: ErbB (epidermal growth factor) receptor family
S101 Platelet-activating factor receptor	S197 Chloride channels	S248 Type II RTKs: Insulin receptor family
S102 Prokineticin receptors	S197 ClC family	S249 Type III RTKs: PDGFR, CSFR, Kit, FLT3 receptor family
S103 Prolactin-releasing peptide receptor	S199 CFTR	S250 Type IV RTKs: VEGF (vascular endothelial growth factor) receptor family
S104 Prostanoid receptors	S200 Calcium activated chloride channel	S251 Type V RTKs: FGF (fibroblast growth factor) receptor family
S106 Proteinase-activated receptors	S201 Maxi chloride channel	S252 Type VI RTKs: PTK7/CCK4
S107 QRFP receptor	S202 Volume regulated chloride channels	S252 Type VII RTKs: Neurotrophin receptor/Trk family
S108 Relaxin family peptide receptors	S204 Connexins and Pannexins	S253 Type VIII RTKs: ROR family
S110 Somatostatin receptors	S206 Sodium leak channel, non-selective	
S111 Succinate receptor		

S254	Type IX RTKs: MuSK	S287	M28: Aminopeptidase Y	S324	2-Acylglycerol ester turnover
S254	Type X RTKs: HGF (hepatocyte growth factor) receptor family	S287	M19: Membrane dipeptidase	S325	Eicosanoid turnover
S255	Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family	S288	S1: Chymotrypsin	S325	Cyclooxygenase
S255	Type XII RTKs: TIE family of angiopoietin receptors	S288	T1: Proteasome	S326	Prostaglandin synthases
S256	Type XIII RTKs: Ephrin receptor family	S289	S8: Subtilisin	S327	Lipoxygenases
S257	Type XIV RTKs: RET	S289	S9: Prolyl oligopeptidase	S328	Leukotriene and lipoxin metabolism
S257	Type XV RTKs: RYK	S290	Acetylcholine turnover	S329	GABA turnover
S258	Type XVI RTKs: DDR (collagen receptor) family	S291	Adenosine turnover	S331	Glycerophospholipid turnover
S258	Type XVII RTKs: ROS receptors	S292	Amino acid hydroxylases	S331	Phosphoinositide-specific phospholipase C
S259	Type XVIII RTKs: LMR family	S293	L-Arginine turnover	S332	Phospholipase A2
S259	Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family	S294	2.1.1.- Protein arginine N-methyltransferases	S334	Phosphatidylcholine-specific phospholipase D
S260	Type XX RTKs: STYK1	S294	Arginase	S335	Lipid phosphate phosphatases
S260	Receptor serine/threonine kinase (RSTK) family	S294	Arginine:glycine amidinotransferase	S335	Phosphatidylinositol kinases
S261	Type I receptor serine/threonine kinases	S295	Dimethylarginine dimethylaminohydrolases	S336	1-phosphatidylinositol 4-kinase family
S262	Type II receptor serine/threonine kinases	S295	Nitric oxide synthases	S336	Phosphatidylinositol-4-phosphate 3-kinase family
S262	Type III receptor serine/threonine kinases	S296	Carboxylases and decarboxylases	S337	Phosphatidylinositol 3-kinase family
S262	RSTK functional heteromers	S297	Carboxylases	S337	Phosphatidylinositol-4,5-bisphosphate 3-kinase family
S264	Receptor tyrosine phosphatase (RTP) family	S298	Decarboxylases	S338	1-phosphatidylinositol-3-phosphate 5-kinase family
S266	Tumour necrosis factor (TNF) receptor family	S300	Catecholamine turnover	S338	Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)
<b>S272 Enzymes</b>		S302	Ceramide turnover	S339	Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)
S275	Kinases (EC 2.7.x.x)	S303	Serine palmitoyltransferase	S339	Haem oxygenase
S276	Rho kinase	S303	Ceramide synthase	S340	Hydrogen sulphide synthesis
S276	Protein kinase C (PKC)	S304	Sphingolipid $\Delta^4$ -desaturase	S341	Hydrolases
S277	Alpha subfamily	S304	Sphingomyelin synthase	S342	Inositol phosphate turnover
S277	Delta subfamily	S305	Sphingomyelin phosphodiesterase	S342	Inositol 1,4,5-trisphosphate 3-kinases
S278	Eta subfamily	S305	Neutral sphingomyelinase coupling factors	S343	Inositol polyphosphate phosphatases
S278	FRAP subfamily	S306	Ceramide glucosyltransferase	S343	Inositol monophosphatase
S279	Cyclin-dependent kinase (CDK) family	S306	Acid ceramidase	S344	Lanosterol biosynthesis pathway
S279	CDK4 subfamily	S307	Neutral ceramidases	S346	Nucleoside synthesis and metabolism
S279	GSK subfamily	S307	Alkaline ceramidases	S347	Sphingosine 1-phosphate turnover
S280	Polo-like kinase (PLK) family	S308	Ceramide kinase	S348	Sphingosine kinase
S280	STE7 family	S309	Chromatin modifying enzymes	S348	Sphingosine 1-phosphate phosphatase
S281	Abl family	S309	2.1.1.- Protein arginine N-methyltransferases	S349	Sphingosine 1-phosphate lyase
S281	Ack family	S310	3.5.1.- Histone deacetylases (HDACs)	S349	Thyroid hormone turnover
S281	Janus kinase (JAK) family	S310	Cyclic nucleotide turnover/signalling	S350	1.14.11.29 2-oxoglutarate oxygenases
S282	Src family	S310	Adenylyl cyclases (ACs)	S351	1.14.13.9 kynurenine 3-monooxygenase
S283	Tec family	S312	Exchange protein activated by cyclic AMP (EPACs)	S352	2.4.2.30 poly(ADP-ribose)polymerases
S283	RAF family	S312	Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase	S352	2.5.1.58 Protein farnesyltransferase
S284	Peptidases and proteinases	S313	Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)	S353	3.5.1.- Histone deacetylases (HDACs)
S284	A1: Pepsin	S317	Cytochrome P450	S354	3.5.3.15 Peptidyl arginine deiminases (PADI)
S284	A22: Presenilin	S317	CYP1 family	S354	RAS subfamily
S285	C14: Caspase	S318	CYP2 family	S355	4.2.1.1 Carbonate dehydratases
S285	M1: Aminopeptidase N	S318	CYP3 family	S355	5.99.1.2 DNA Topoisomerases
S285	M2: Angiotensin-converting (ACE and ACE2)	S319	CYP4 family		
S286	M10: Matrix metalloproteinase	S320	CYP5, CYP7 and CYP8 families	<b>S360 Transporters</b>	
S286	M12: Astacin/Adamalysin	S320	CYP11, CYP17, CYP19, CYP20 and CYP21 families	S362	ATP-binding cassette transporter family
		S321	CYP24, CYP26 and CYP27 families	S362	ABCA subfamily
		S322	CYP39, CYP46 and CYP51 families	S363	ABCB subfamily
		S323	Endocannabinoid turnover		
		S323	N-Acylethanolamine turnover		

S365	ABCC subfamily	S389	Neutral amino acid transporter subfamily	S417	SLC27 family of fatty acid transporters
S366	ABCD subfamily of peroxisomal ABC transporters	S390	SLC8 family of sodium/calcium exchangers	S418	SLC28 and SLC29 families of nucleoside transporters
S367	ABCG subfamily	S390	SLC9 family of sodium/hydrogen exchangers	S418	SLC28 family
S368	F-type and V-type ATPases	S391	SLC10 family of sodium-bile acid co-transporters	S419	SLC29 family
S368	F-type ATPase	S392	SLC11 family of proton-coupled metal ion transporters	S420	SLC30 zinc transporter family
S368	V-type ATPase	S393	SLC12 family of cation-coupled chloride transporters	S421	SLC31 family of copper transporters
S369	P-type ATPases	S395	SLC13 family of sodium-dependent sulphate/carboxylate transporters	S422	SLC32 vesicular inhibitory amino acid transporter
S369	Na <sup>+</sup> /K <sup>+</sup> -ATPases	S395	SLC14 family of facilitative urea transporters	S422	SLC33 acetylCoA transporter
S369	Ca <sup>2+</sup> -ATPases	S396	SLC15 family of peptide transporters	S423	SLC34 family of sodium phosphate co-transporters
S370	H <sup>+</sup> /K <sup>+</sup> -ATPases	S398	SLC16 family of monocarboxylate transporters	S424	SLC35 family of nucleotide sugar transporters
S370	Cu <sup>+</sup> -ATPases	S399	SLC17 phosphate and organic anion transporter family	S425	SLC36 family of proton-coupled amino acid transporters
S370	Phospholipid-transporting ATPases	S399	Type I sodium-phosphate co-transporters	S426	SLC37 family of phosphosugar/phosphate exchangers
S371	Major facilitator superfamily (MFS) of transporters	S400	Sialic acid transporter	S427	SLC38 family of sodium-dependent neutral amino acid transporters
S371	SLC superfamily of solute carriers	S400	Vesicular glutamate transporters (VGLUTs)	S427	System A-like transporters
S372	SLC1 family of amino acid transporters	S401	Vesicular nucleotide transporter	S428	System N-like transporters
S372	Glutamate transporter subfamily	S401	SLC18 family of vesicular amine transporters	S428	Orphan SLC38 transporters
S374	Alanine/serine/cysteine transporter subfamily	S403	SLC19 family of vitamin transporters	S429	SLC39 family of metal ion transporters
S375	SLC2 family of hexose and sugar alcohol	S403	SLC20 family of sodium-dependent phosphate transporters	S430	SLC40 iron transporter
S375	Class I transporters	S404	SLC22 family of organic cation and anion transporters	S430	SLC41 family of divalent cation transporters
S376	Class II transporters	S404	Organic cation transporters (OCT)	S431	SLC42 family of Rhesus glycoprotein ammonium transporters
S377	Proton-coupled inositol transporter	S405	Organic zwitterions/cation transporters (OCTN)	S432	SLC43 family of large neutral amino acid transporters
S377	SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)	S406	Organic anion transporters (OATs)	S433	SLC44 choline transporter-like family
S377	SLC3 family	S407	Urate transporter	S433	SLC45 family of putative sugar transporters
S378	SLC7 family	S407	SLC23 family of ascorbic acid transporters	S434	SLC46 family of folate transporters
S379	SLC4 family of bicarbonate transporters	S409	SLC24 family of sodium/potassium/calcium exchangers	S435	SLC47 family of multidrug and toxin extrusion transporters
S380	Anion exchangers	S409	SLC25 family of mitochondrial transporters	S436	SLC48 heme transporter
S380	Sodium-dependent HCO <sub>3</sub> <sup>-</sup> transporters	S410	Mitochondrial di- and tri-carboxylic acid transporter subfamily	S436	SLC49 family of FLVCR-related heme transporters
S381	SLC5 family of sodium-dependent glucose transporters	S411	Mitochondrial amino acid transporter subfamily	S437	SLC50 sugar transporter
S381	Hexose transporter family	S412	Mitochondrial phosphate transporters	S438	SLC51 family of steroid-derived molecule transporters
S382	Choline transporter	S412	Mitochondrial nucleotide transporter subfamily	S438	SLC52 family of riboflavin transporters
S383	Sodium iodide symporter, sodium-dependent multivitamin transporter and sodium-coupled monocarboxylate transporters	S413	Mitochondrial uncoupling proteins	S439	SLCO family of organic anion transporting polypeptides
S384	Sodium <i>myo</i> -inositol cotransporter transporters	S414	Miscellaneous SLC25 mitochondrial transporters	S442	Patched family
S385	SLC6 neurotransmitter transporter family	S414	SLC26 family of anion exchangers		
S385	Monoamine transporter subfamily	S415	Selective sulphate transporters		
S386	GABA transporter subfamily	S415	Chloride/bicarbonate exchangers		
S387	Glycine transporter subfamily	S416	Anion channels		
		S416	Other SLC26 anion exchangers		

## Introduction

In order to allow clarity and consistency in pharmacology, there is a need for a comprehensive organisation and presentation of the targets of drugs. This is the philosophy of the IUPHAR/BPS Guide to PHARMACOLOGY presented on the online free access database (<http://www.guidetopharmacology.org/>). This database is supported by the British Pharmacological Society (BPS), the International Union of Basic and Clinical Pharmacology (IUPHAR), the University of Edinburgh and previously the Wellcome Trust. Data included in the Guide to PHARMACOLOGY are derived in large part from interactions with the subcommittees of the Nomenclature Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR). A major influence on the development of the database was Tony Harmar (1951–2014), who worked with a passion to establish the curators as a team of highly informed and informative individuals, with a focus on high-quality data input, ensuring a suitably validated dataset. The Editors of the Concise Guide have compiled the individual records, in concert with the team of Curators, drawing on the expert knowledge of these latter subcommittees. The tables allow an indication of the status of the nomenclature for the group of targets listed, usually previously published in Pharmacological Reviews. In the absence of an established subcommittee, advice from several prominent, independent experts has generally been obtained to

produce an authoritative consensus on nomenclature, which attempts to fit in within the general guidelines from NC-IUPHAR. This current edition, the Concise Guide to PHARMACOLOGY 2017/18, is the latest snapshot of the database in print form, following on from the Concise Guide to PHARMACOLOGY 2015/16. It contains data drawn from the online database as a rapid overview of the major pharmacological targets. Thus, there are many fewer targets presented in the Concise Guide compared to the online database. The priority for inclusion in the Concise Guide is the presence of quantitative pharmacological data. This means that often orphan family members are not presented in the Concise Guide, although structural information is available on the online database. The organisation of the data is tabular (where appropriate) with a standardised format, where possible on a single page, intended to aid understanding of, and comparison within, a particular target group. The Concise Guide is intended as an initial resource, with links to additional reviews and resources for greater depth and information. Pharmacological and structural data focus primarily on human gene products, wherever possible, with links to HGNC gene nomenclature and UniProt IDs. In a few cases, where data from human proteins are limited, data from other species are indicated. Pharmacological tools listed are prioritised on the basis of selectivity and availability. That is, agents (agonists,

antagonists, inhibitors, activators, etc.) are included where they are both available (by donation or from commercial sources, now or in the near future) AND the most selective. The Concise Guide is divided into nine sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, catalytic receptors, nuclear hormone receptors, enzymes, transporters and other protein targets. We hope that the Concise Guide will provide for researchers, teachers and students a state-of-the art source of accurate, curated information on the background to their work that they will use in the Introductions to their Research Papers or Reviews, or in supporting their teaching and studies. We recommend that any citations to information in the Concise Guide are presented in the following format:

Alexander SPH *et al.* (2017). The Concise Guide to PHARMACOLOGY 2017/18: Overview. *Br J Pharmacol* 174: S1–S16.

In this overview are listed protein targets of pharmacological interest, which are not G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, ion channels, nuclear hormone receptors, catalytic receptors, transporters or enzymes.

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## Conflict of interest

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

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## Other Protein Targets

### Family structure

S6	Adiponectin receptors	–	Heat shock proteins	–	Pentaxins
–	B-cell lymphoma 2 (Bcl-2) protein family	–	Immunoglobulins	–	Serum pentaxins
S7	Blood coagulation components	–	Inhibitors of apoptosis (IAP) protein family	S13	Regulators of G protein Signaling (RGS) proteins
–	Bromodomain-containing proteins	–	Kelch-like proteins	S14	R4 family
S7	Non-enzymatic BRD containing proteins	–	Kinesins	–	Repulsive guidance molecules
S8	Carrier proteins	–	Leucine-rich repeat proteins	–	Reticulons and associated proteins
S9	CD molecules	–	Lymphocyte antigens	–	Ribosomal factors
–	Chromatin-interacting transcriptional repressors	–	Mitochondrial-associated proteins	S14	Sigma receptors
S10	Methyllysine reader proteins	–	Myosin binding proteins	S15	Tubulins
–	Circadian clock proteins	–	Non-catalytic pattern recognition receptors	–	Tumour-associated proteins
–	Claudins	–	Absent in melanoma (AIM)-like receptors (ALRs)	–	WD repeat-containing proteins
–	EF-hand domain containing	–	C-type lectin-like receptors (CLRs)		
S11	Fatty acid-binding proteins	–	Other pattern recognition receptors		
–	G-alpha family G(q) subfamily	S12	Notch receptors		

## Adiponectin receptors

Other protein targets → [Adiponectin receptors](#)

**Overview:** Adiponectin receptors (**provisional nomenclature**, [ENSMFM00500000270960](#)) 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 [49]. 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 [90]. Signalling through these receptors

appears to avoid G proteins; modelling based on the crystal structures of the adiponectin receptors suggested ceramidase activity, which would make these the first in a new family of catalytic receptors [93].

Nomenclature	Adipo1 receptor	Adipo2 receptor
HGNC, UniProt	<i>ADIPOR1</i> , <a href="#">Q96A54</a>	<i>ADIPOR2</i> , <a href="#">Q86V24</a>
Rank order of potency	globular adiponectin ( <i>ADIPOQ</i> , <a href="#">Q15848</a> ) > adiponectin ( <i>ADIPOQ</i> , <a href="#">Q15848</a> )	globular adiponectin ( <i>ADIPOQ</i> , <a href="#">Q15848</a> ) = adiponectin ( <i>ADIPOQ</i> , <a href="#">Q15848</a> )

**Comments:** T-Cadherin (*CDH13*, [P55290](#)) has also been suggested to be a receptor for (hexameric) adiponectin [33].

### Further reading on Adiponectin receptors

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 Zhao L *et al.* (2014) Adiponectin and insulin cross talk: the microvascular connection. *Trends Cardiovasc Med* **24**: 319-24 [PMID:25220977]

## Blood coagulation components

Other protein targets → [Blood coagulation components](#)

**Overview:** Coagulation as a process is interpreted as a mechanism for reducing excessive blood loss through the generation of a gel-like clot local to the site of injury. The process involves the activation, adhesion (see [Integrins](#)), degranulation and aggregation of platelets, as well as proteins circulating in the plasma. The coagulation cascade involves multiple proteins being converted to more active forms from less active precursors, typically through proteolysis (see [Proteases](#)). Listed here are the components of the coagulation cascade targeted by agents in current clinical usage.

Nomenclature	<a href="#">coagulation factor V</a>	<a href="#">coagulation factor VIII</a>	<a href="#">serpin family C member 1</a>
HGNC, UniProt	<a href="#">F5</a> , <a href="#">P12259</a>	<a href="#">F8</a> , <a href="#">P00451</a>	<a href="#">SERPINC1</a> , <a href="#">P01008</a>
Selective activators	–	–	<a href="#">heparin</a> ( $pK_d$ 7.8) [26], <a href="#">fondaparinux</a> ( $pK_d$ 7.5) [62], <a href="#">dalteparin</a> [32], <a href="#">danaparoid</a> [16, 56], <a href="#">enoxaparin</a> [19], <a href="#">tinzaparin</a> [20]
Selective inhibitors	<a href="#">drotrecogin alfa</a> [36, 37]	<a href="#">drotrecogin alfa</a> [36, 37]	–

### Further reading on Blood coagulation components

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 Girolami A *et al.* (2017) New clotting disorders that cast new light on blood coagulation and may play a role in clinical practice. *J Thromb Thrombolysis* **44**: 71-75 [PMID:28251495]

Rana K *et al.* (2016) Blood flow and mass transfer regulation of coagulation. *Blood Rev* **30**: 357-68 [PMID:27133256]

## Non-enzymatic BRD containing proteins

Other protein targets → Bromodomain-containing proteins → Non-enzymatic BRD containing proteins

**Overview:** Bromodomains bind proteins with acetylated lysine residues, such as histones, to regulate gene transcription. Listed herein are examples of bromodomain-containing proteins for which sufficient pharmacology exists.

Nomenclature	bromodomain adjacent to zinc finger domain 2A	bromodomain adjacent to zinc finger domain 2B	CREB binding protein	polybromo 1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
HGNC, UniProt	<a href="#">BAZ2A</a> , <a href="#">Q9UIF9</a>	<a href="#">BAZ2B</a> , <a href="#">Q9UIF8</a>	<a href="#">CREBBP</a> , <a href="#">Q92793</a>	<a href="#">PBRM1</a> , <a href="#">Q86U86</a>	<a href="#">SMARCA4</a> , <a href="#">P51532</a>
Selective inhibitors	<a href="#">GSK2801</a> (p <i>K</i> <sub>d</sub> 6.6) [73]	<a href="#">GSK2801</a> (p <i>K</i> <sub>d</sub> 6.9) [73]	<a href="#">I-CBP112</a> (p <i>K</i> <sub>d</sub> 6.8) [72]	<a href="#">PFI-3</a> (p <i>K</i> <sub>d</sub> 7.3) [79]	<a href="#">PFI-3</a> (p <i>K</i> <sub>d</sub> 7.1) [79]

### Further reading on Non-enzymatic BRD containing proteins

Brand M *et al.* (2015) Small molecule inhibitors of bromodomain-acetyl-lysine interactions. *ACS Chem. Biol.* **10**: 22-39 [PMID:25549280]

Fujisawa T *et al.* (2017) Functions of bromodomain-containing proteins and their roles in homeostasis and cancer *Nat Rev Mol Cell Biol* **18**: 246-262 [PMID:28053347]

Nicholas DA *et al.* (2017) BET bromodomain proteins and epigenetic regulation of inflammation: implications for type 2 diabetes and breast cancer. *Cell Mol Life Sci* **74**: 231-243 [PMID:27491296]

Theodoulou NH *et al.* (2016) Clinical progress and pharmacology of small molecule bromodomain inhibitors. *Curr Opin Chem Biol* **33**: 58-66 [PMID:27295577]

Theodoulou NH *et al.* (2016) Progress in the Development of non-BET Bromodomain Chemical Probes. *ChemMedChem* **11**: 477-87 [PMID:26749027]

## Carrier proteins

Other protein targets → Carrier proteins

**Overview:** Transthyretin (TTR) is a homo-tetrameric protein which transports thyroxine in the plasma and cerebrospinal fluid and retinol (vitamin A) in the plasma. Many disease causing mutations in the protein have been reported, many of which cause complex dissociation and protein mis-assembly and deposition of toxic aggregates amyloid fibril formation [63]. These

amyloidogenic mutants are linked to the development of pathological amyloidoses, including familial amyloid polyneuropathy (FAP) [4, 14], familial amyloid cardiomyopathy (FAC) [34], amyloidotic vitreous opacities, carpal tunnel syndrome [54] and others. In old age, non-mutated TTR can also form pathological amyloid fibrils [88]. Pharmacological intervention to reduce or

prevent TTR dissociation is being pursued as a therapeutic strategy. To date one small molecule kinetic stabilising molecule ([tafamidis](#)) has been approved for FAP, and is being evaluated in clinical trials for other TTR amyloidoses.

Nomenclature	transthyretin
HGNC, UniProt	<a href="#">TTR</a> , <a href="#">P02766</a>
Common abbreviation	TTR



**Further reading on Carrier proteins**

Alshehri B *et al.* (2015) The diversity of mechanisms influenced by transthyretin in neurobiology: development, disease and endocrine disruption. *J Neuroendocrinol* **27**: 303-23 [PMID:25737004]  
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Galant NJ *et al.* (2017) Transthyretin amyloidosis: an under-recognized neuropathy and cardiomyopathy. *Clin Sci (Lond)* **131**: 395-409 [PMID:28213611]

## CD molecules

Other protein targets → [CD molecules](#)

**Overview:** Cluster of differentiation refers to an attempt to catalogue systematically a series of over 300 cell-surface proteins associated with immunotyping. Many members of the group have identified functions as enzymes (for example, see [CD73 ecto-5'-nucleotidase](#)) or receptors (for example, see [CD41 integrin, alpha 2b subunit](#)). Many CDs are targeted for therapeutic gain using antibodies for the treatment of proliferative disorders. A full listing of all the Clusters of Differentiation is not possible in the Guide to PHARMACOLOGY; listed herein are selected members of the family targeted for therapeutic gain.

Nomenclature	CD2	CD3e	CD20 (membrane-spanning 4-domains, subfamily A, member 1)	CD33	CD52
HGNC, UniProt	<a href="#">CD2</a> , <a href="#">P06729</a>	<a href="#">CD3E</a> , <a href="#">P07766</a>	<a href="#">MS4A1</a> , <a href="#">P11836</a>	<a href="#">CD33</a> , <a href="#">P20138</a>	<a href="#">CD52</a> , <a href="#">P31358</a>
Common abbreviation	–	–	–	SIGLEC-3	–
Selective inhibitors	<a href="#">alefacept</a> (Inhibition) [17, 53]	–	–	–	–
Antibodies	–	<a href="#">catumaxomab</a> (Binding) [43], <a href="#">muromonab-CD3</a> (Binding) [25], <a href="#">otelixizumab</a> (Binding) [9]	<a href="#">ofatumumab</a> (Binding) ( $pK_d$ 9.9) [47], <a href="#">rituximab</a> (Binding) ( $pK_d$ 8.5) [75], <a href="#">ibritumomab tiuxetan</a> (Binding), <a href="#">obinutuzumab</a> (Binding) [3, 66], <a href="#">tositumomab</a> (Binding)	<a href="#">lintuzumab</a> (Binding) ( $pK_d$ ~10) [10], <a href="#">gemtuzumab ozogamicin</a> (Binding) [7]	<a href="#">alemtuzumab</a> (Binding) [24, 79]

Nomenclature	CD80	CD86	cytotoxic T-lymphocyte-associated protein 4 (CD152)	programmed cell death 1 (CD279)	CD300a
HGNC, UniProt	CD80, P33681	CD86, P42081	CTLA4, P16410	PDCD1, Q15116	CD300A, Q9UGN4
Common abbreviation	–	–	CTLA-4	PD-1	–
Antibodies	–	–	ipilimumab ( $pK_d > 9$ ) [28], tremelimumab ( $pK_d$ 8.9) [30]	pembrolizumab ( $pK_d \sim 10$ ) [11], nivolumab ( $pK_d$ 9.1) [28, 38, 40]	–

**Comment:** The endogenous ligands for human PD-1 are programmed cell death 1 ligand 1 (PD-L1 *aka* CD274 (CD274, Q9NZQ7)) and programmed cell death 1 ligand 2 (PD-L2; *PDCD1LG2*). These ligands are cell surface peptides, normally involved in immune system regulation. Expression of PD-1 by cancer cells induces immune tolerance and evasion of immune system attack. Anti-PD-1 monoclonal antibodies are used to induce immune checkpoint blockade as a therapeutic intervention in cancer, effectively re-establishing immune vigilance. **pembrolizumab** was the first anti-PD-1 antibody to be approved by the US FDA.

#### Further reading on CD molecules

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## Methyllysine reader proteins

Other protein targets → Chromatin-interacting transcriptional repressors → Methyllysine reader proteins

**Overview:** Methyllysine reader proteins bind to methylated proteins, such as histones, allowing regulation of gene expression.

Nomenclature	I(3)mbt-like 3 ( <i>Drosophila</i> )
HGNC, UniProt	L3MBTL3, Q96JM7
Selective agonists	UNC1215 [35]

#### Further reading on Methyllysine reader proteins

Liu K *et al.* (2015) Epigenetic targets and drug discovery Part 2: Histone demethylation and DNA methylation. *Pharmacol. Ther.* **151**: 121-40 [PMID:25857453]

Milosevich N *et al.* (2016) Chemical Inhibitors of Epigenetic Methyllysine Reader Proteins. *Biochemistry* **55**: 1570-83 [PMID:26650180]

Sadakierska-Chudy A *et al.* (2015) A comprehensive view of the epigenetic landscape part I: DNA methylation, passive and active DNA demethylation pathways and histone variants. *Neurotox Res* **27**: 84-97 [PMID:25362550]

Teske KA *et al.* (2017) Methyllysine binding domains: Structural insight and small molecule probe development. *Eur J Med Chem* **136**: 14-35 [PMID:28478342]

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## Fatty acid-binding proteins

Other protein targets → [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 [70]) or for interaction with metabolic enzymes. Although sequence homology is limited, crystallographic studies suggest conserved 3D structures across the group of binding proteins.

Nomenclature	<a href="#">fatty acid binding protein 1</a>	<a href="#">fatty acid binding protein 2</a>	<a href="#">fatty acid binding protein 3</a>	<a href="#">fatty acid binding protein 4</a>
HGNC, UniProt	<a href="#">FABP1</a> , P07148	<a href="#">FABP2</a> , P12104	<a href="#">FABP3</a> , P05413	<a href="#">FABP4</a> , P15090
Rank order of potency	stearic acid, oleic acid > palmitic acid, linoleic acid > arachidonic acid, $\alpha$ -linolenic acid [67]	stearic acid > palmitic acid, oleic acid > linoleic acid > arachidonic acid, $\alpha$ -linolenic acid [67]	stearic acid, oleic acid, palmitic acid > linoleic acid, $\alpha$ -linolenic acid, arachidonic acid [67]	oleic acid, palmitic acid, stearic acid, linoleic acid > $\alpha$ -linolenic acid, arachidonic acid [67]
Inhibitors	fenofibrate ( $pK_i$ 7.6) [12] – Rat, fenofibric acid ( $pK_i$ 6.5) [12] – Rat, HTS01037 ( $pK_i$ 5.1) [30] – Mouse	–	–	–
Selective inhibitors	–	–	–	HM50316 ( $pK_i$ >9) [46]
Comments	A broader substrate specificity than other FABPs, binding two fatty acids per protein [82].	Crystal structure of the rat FABP2 [69].	Crystal structure of the human FABP3 [91].	–

Nomenclature	<a href="#">fatty acid binding protein 5</a>	<a href="#">fatty acid binding protein 6</a>	<a href="#">fatty acid binding protein 7</a>	<a href="#">peripheral myelin protein 2</a>	<a href="#">fatty acid binding protein 9</a>	<a href="#">fatty acid binding protein 12</a>
HGNC, UniProt	<a href="#">FABP5</a> , Q01469	<a href="#">FABP6</a> , P51161	<a href="#">FABP7</a> , O15540	<a href="#">PMP2</a> , P02689	<a href="#">FABP9</a> , Q0Z7S8	<a href="#">FABP12</a> , A6NFH5
Comments	Crystal structure of the human FABP5 [31].	Able to transport bile acids [95].	Crystal structure of the human FABP7 [5].	<i>In silico</i> modelling suggests that PMP2/FABP8 can bind both fatty acids and cholesterol [50].	–	–

Nomenclature	retinol binding protein 1	retinol binding protein 2	retinol binding protein 3	retinol binding protein 4	retinol binding protein 5	retinol binding protein 7
HGNC, UniProt	<a href="#">RBP1</a> , <a href="#">P09455</a>	<a href="#">RBP2</a> , <a href="#">P50120</a>	<a href="#">RBP3</a> , <a href="#">P10745</a>	<a href="#">RBP4</a> , <a href="#">P02753</a>	<a href="#">RBP5</a> , <a href="#">P82980</a>	<a href="#">RBP7</a> , <a href="#">Q96R05</a>
Rank order of potency	–	stearic acid > palmitic acid, oleic acid, linoleic acid, $\alpha$ -linolenic acid, arachidonic acid [68]	–	–	–	–
Inhibitors	–	–	–	A1120 (pIC <sub>50</sub> 7.8) [86]	–	–

Nomenclature	retinaldehyde binding protein 1	cellular retinoic acid binding protein 1	cellular retinoic acid binding protein 2
HGNC, UniProt	<a href="#">RLBP1</a> , <a href="#">P12271</a>	<a href="#">CRABP1</a> , <a href="#">P29762</a>	<a href="#">CRABP2</a> , <a href="#">P29373</a>
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 [15]	tretinoin > alitretinoin stearic acid > palmitic acid, oleic acid, linoleic acid, $\alpha$ -linolenic acid, arachidonic acid [68]	–

**Comments:** Although not tested at all FABPs, [BMS309403](#) exhibits high affinity for FABP4 (pIC<sub>50</sub> 8.8) compared to FABP3 or FABP5 (pIC<sub>50</sub> <6.6) [21, 81]. [HTS01037](#) is reported to interfere with FABP4 action [30]. Ibuprofen displays some selectivity for FABP4 (pIC<sub>50</sub> 5.5) relative to FABP3 (pIC<sub>50</sub> 3.5) and FABP5 (pIC<sub>50</sub> 3.8) [48]. Fenofibric acid displays some selectivity for FABP5 (pIC<sub>50</sub> 5.5) relative to FABP3 (pIC<sub>50</sub> 4.5) and FABP4 (pIC<sub>50</sub> 4.6) [48]. Multiple pseudogenes for the FABPs have been identified in the human genome.

#### Further reading on Fatty acid-binding proteins

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- Glatz JF. (2015) Lipids and lipid binding proteins: a perfect match. *Prostaglandins Leukot. Essent. Fatty Acids* **93**: 45-9 [PMID:25154384]
- Hotamisligil GS *et al.* (2015) Metabolic functions of FABPs-mechanisms and therapeutic implications. *Nat Rev Endocrinol* **11**: 592-605 [PMID:26260145]

- Matsumata M *et al.* (2016) Fatty acid binding proteins and the nervous system: Their impact on mental conditions. *Neurosci. Res.* **102**: 47-55 [PMID:25205626]
- Osumi T *et al.* (2016) Heart lipid droplets and lipid droplet-binding proteins: Biochemistry, physiology, and pathology. *Exp Cell Res* **340**: 198-204 [PMID:26524506]

## Notch receptors

Other protein targets → Notch receptors

**Overview:** The canonical Notch signalling pathway has four type I transmembrane Notch receptors (Notch1-4) and five ligands (DLL1, 2 and 3, and Jagged 1-2). Each member of this highly conserved receptor family plays a unique role in cell-fate determination during embryogenesis, differentiation, tissue patterning, proliferation and cell death [2]. As the Notch ligands are also membrane bound, cells have to be in close proximity for

receptor-ligand interactions to occur. Cleavage of the intracellular domain (ICD) of activated Notch receptors by  $\gamma$ -secretase is required for downstream signalling and Notch-induced transcriptional modulation [18, 57, 71, 89]. This is why  $\gamma$ -secretase inhibitors can be used to downregulate Notch signalling and explains their anti-cancer action. One such small molecule is RO4929097 [47], although development of this compound has

been terminated following an unsuccessful Phase II single agent clinical trial in metastatic colorectal cancer [78].

Aberrant Notch signalling is implicated in a number of human cancers [41, 59, 74, 85]. Pharmaceutical inhibitors of Notch signalling such as demcizumab and tarextumab are being actively investigated as novel anti-cancer agents [64].

Nomenclature	notch 1	notch 2	notch 3	notch 4
HGNC, UniProt	NOTCH1, P46531	NOTCH2, Q04721	NOTCH3, Q9UM47	NOTCH4, Q99466
Comments	Various types of activating and inactivating NOTCH1 mutations have been reported to be associated with human diseases, for example: aortic valve disease [23, 52], Adams-Oliver syndrome 5 [76], T-cell acute lymphoblastic leukemia (T-ALL) [87], chronic lymphocytic leukemia (CLL) [65] and head and neck squamous cell carcinoma [1, 77].	–	–	Notch 4 is a potential therapeutic molecular target for triple-negative breast cancer [42, 55].

### Further reading on Notch receptors

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 Cheng YL *et al.* (2015) Emerging roles of the gamma-secretase-notch axis in inflammation. *Pharmacol Ther* **147**: 80-90 [PMID:25448038]  
 Palmer WH *et al.* (2015) Ligand-Independent Mechanisms of Notch Activity. *Trends Cell Biol* **25**: 697-707 [PMID:26437585]

Previs RA *et al.* (2015) Molecular pathways: translational and therapeutic implications of the Notch signaling pathway in cancer. *Clin Cancer Res* **21**: 955-61 [PMID:25388163]  
 Takebe N *et al.* (2015) Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. *Nat Rev Clin Oncol* **12**: 445-464 [PMID:25850553]

## Regulators of G protein Signaling (RGS) proteins

Other protein targets → Regulators of G protein Signaling (RGS) proteins

**Overview:** Regulators of G protein signalling (RGS) proteins increase the deactivation rates of G protein signalling pathways through enhancing the GTPase activity of the G protein alpha subunit. Interactions through protein:protein interactions of many RGS proteins have been identified for targets other than heteromeric G proteins. The 20 RGS proteins are commonly divided into four families (R4, R7, R12 and RZ) based on sequence and domain homology. Described here is RGS4 for which a number of pharmacological inhibitors have been described.

Nomenclature	<a href="#">regulator of G-protein signaling 4</a>
HGNC, UniProt	<a href="#">RGS4, P49798</a>
Common abbreviation	RGS4
Selective inhibitors	<a href="#">RGS4 inhibitor 11b</a> (pIC <sub>50</sub> 7.8) [83], <a href="#">CCG-50014</a> (pIC <sub>50</sub> 7.5) [8, 83], <a href="#">RGS4 inhibitor 13</a> (pIC <sub>50</sub> 7.3) [83]

### Further reading on RGS proteins

- Sethakorn N *et al.* (2010) Non-canonical functions of RGS proteins. *Cell Signal* **22**: 1274-81 [PMID:20363320]
- Sjogren B (2017) The evolution of regulators of G protein signalling proteins as drug targets - 20 years in the making: IUPHAR Review 21. *Br J Pharmacol* **174**: 427-437 [PMID:28098342]
- Sjogren B *et al.* (2010) Thinking outside of the "RGS box": new approaches to therapeutic targeting of regulators of G protein signaling. *Mol Pharmacol* **78**: 550-7 [PMID:20664002]
- Turner EM *et al.* (2012) Small Molecule Inhibitors of Regulator of G Protein Signalling (RGS) Proteins. *ACS Med Chem Lett* **3**: 146-150 [PMID:22368763]

## Sigma receptors

[Other protein targets](#) → [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; the crystal structure of the sigma1 receptor [94] suggests a trimeric structure of a single short transmembrane domain traversing the endoplasmic reticulum membrane, with the bulk of the protein facing the cytosol. A wide range of compounds, ranging from psychoactive agents to antihistamines, have been observed to bind to these sites.

Nomenclature	<a href="#">sigma non-opioid intracellular receptor 1</a>	$\sigma 2$
HGNC, UniProt	<a href="#">SIGMARI, Q99720</a>	–
Selective agonists	<a href="#">PRE-084</a> [80], <a href="#">(+)-SKF 10.047</a>	–
Selective antagonists	<a href="#">NE-100</a> (pIC <sub>50</sub> 8.4) [60], <a href="#">BD-1047</a> (pIC <sub>50</sub> 7.4) [51]	–
Labelled ligands	<a href="#">[<sup>3</sup>H]pentazocine</a> (Agonist)	<a href="#">[<sup>3</sup>H]-di-o-tolylguanidine</a> (Agonist)

**Comments:** (-)-pentazocine also shows activity at opioid receptors. The sigma2 receptor has recently been reported to be TMEM97 [Q5BJF2](#) [92], a 4TM protein partner of NPC1, the Niemann-Pick C1 protein, a 13TM cholesterol-binding protein.

### Further reading on Sigma receptors

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- Gris G *et al.* (2015) Sigma-1 receptor and inflammatory pain. *Inflamm Res* **64**: 377-81 [PMID:25902777]
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Searchable database: <http://www.guidetopharmacology.org/index.jsp>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.13882/full>

## Tubulins

Other protein targets → Tubulins

**Overview:** Tubulins are a family of intracellular proteins most commonly associated with microtubules, part of the cytoskeleton. They are exploited for therapeutic gain in cancer chemotherapy as targets for agents derived from a variety of natural products: taxanes, colchicine and vinca alkaloids. These are thought to act primarily through  $\beta$ -tubulin, thereby interfering with the normal processes of tubulin polymer formation and disassembly.

Nomenclature	tubulin alpha 1a	tubulin alpha 4a	tubulin beta class I	tubulin beta 3 class III	tubulin beta 4B class IVb	tubulin beta 8 class VIII
HGNC, UniProt	<i>TUBA1A</i> , Q71U36	<i>TUBA4A</i> , P68366	<i>TUBB</i> , P07437	<i>TUBB3</i> , Q13509	<i>TUBB4B</i> , P68371	<i>TUBB8</i> , Q3ZCM7
Inhibitors	–	–	vinblastine (pIC <sub>50</sub> 9), vincristine, eribulin (pIC <sub>50</sub> 8.2) [58], paclitaxel (pEC <sub>50</sub> 8.1) [61], colchicine (pIC <sub>50</sub> 8) [13], cabazitaxel, docetaxel, ixabepilone	combretastatin A4 (pIC <sub>50</sub> 8.2) [22]	–	–

### Further reading on Tubulins

Gadadhar S *et al.* (2017) The tubulin code at a glance. *J Cell Sci* **130**: 1347-1353 [PMID:28325758]

Penna LS *et al.* (2017) Anti-mitotic agents: Are they emerging molecules for cancer treatment? *Pharmacol Ther* **173**: 67-82 [PMID:28174095]

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