THE CONCISE GUIDE TO PHARMACOLOGY 2017/18

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THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Overview

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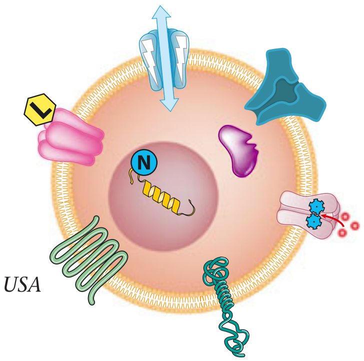

Abstract

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), 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.

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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.

Acknowledgements

We are extremely grateful to the British Pharmacological Society and the International Union of Basic and Clinical Pharmacology, for financial support of the website and for advice from the NC-IUPHAR subcommittees. We thank the University of Edinburgh, who host the www.guidetopharmacology.org website. Previously, the International Union of Basic and Clinical Pharmacology and the Wellcome Trust (099156/Z/12/Z]) also supported the initiation and expansion of the database. We are also tremendously grateful to the long list of collaborators from NC-IUPHAR subcommittees and beyond, who have assisted in the construction of the Concise Guide to PHARMACOLOGY 2017/18 and the online database www.GuideToPHARMACOLOGY.org. Further, we wish to thank Toni Wigglesworth for her assistance in the co-ordination of correspondence with these collaborators.

Conflict of interest

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

Other Protein Targets

Family structure

Adiponectin receptors

Other protein targets → 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 [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 acivity, which would make these the first in a new family of catalytic receptors [93].

Nomenclature	Adipo1 receptor	Adipo2 receptor
HGNC, UniProt	*ADIPOR1*, Q96A54	*ADIPOR2*, Q86V24
Rank order of potency	globular adiponectin (*ADIPOQ*, Q15848) > adiponectin (*ADIPOQ*, Q15848)	globular adiponectin (*ADIPOQ*, Q15848) = adiponectin (*ADIPOQ*, Q15848)

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

Further reading on Adiponectin receptors

Fisman EZ *et al.* (2014) Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? *Cardiovasc Diabetol* **13**: 103 [PMID:24957699]
Matsuda M *et al.* (2014) Roles of adiponectin and oxidative stress in obesity-associated metabolic and cardiovascular diseases. *Rev Endocr Metab Disord* **15**: 1-10 [PMID:24026768]
Ruan H *et al.* (2016) Adiponectin signaling and function in insulin target tissues. *J Mol Cell Biol* **8**: 101-9 [PMID:26993044]
Wang Y *et al.* (2017) Cardiovascular Adiponectin Resistance: The Critical Role of Adiponectin Receptor Modification. *Trends Endocrinol Metab* **28**: 519-530 [PMID:28473178]
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 targetted by agents in current clinical usage.

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

Further reading on Blood coagulation components

Astermark J. (2015) FVIII inhibitors: pathogenesis and avoidance. *Blood* **125**: 2045-51 [PMID:25712994]
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	*BAZ2A*, Q9UIF9	*BAZ2B*, Q9UIF8	*CREBBP*, Q92793	*PBRM1*, Q86U86	*SMARCA4*, P51532
Selective inhibitors	GSK2801 (pK_d 6.6) [73]	GSK2801 (pK_d 6.9) [73]	I-CBP112 (pK_d 6.8) [72]	PFI-3 (pK_d 7.3) [79]	PFI-3 (pK_d 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 theapeutic 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	*TTR*, P02766
Common abreviation	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]

Delliere S *et al.* (2017) Is transthyretin a good marker of nutritional status? *Clin Nutr* **36**: 364-370 [PMID:27381508]

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 targetted 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 targetted for therapeutic gain.

Nomenclature	CD2	CD3e	CD20 (membrane-spanning 4-domains, subfamily A, member 1)	CD33	CD52
HGNC, UniProt	*CD2*, P06729	*CD3E*, P07766	*MS4A1*, P11836	*CD33*, P20138	*CD52*, P31358
Common abreviation	–	–	–	SIGLEC-3	–
Selective inhibitors	alefacept (Inhibition) [17, 53]	–	–	–	–
Antibodies	–	catumaxomab (Binding) [43], muromonab-CD3 (Binding) [25], otelixizumab (Binding) [9]	ofatumumab (Binding) (pK_d 9.9) [47], rituximab (Binding) (pK_d 8.5) [75], ibritumomab tiuxetan (Binding), obinutuzumab (Binding) [3, 66], tositumomab (Binding)	lintuzumab (Binding) (pK_d ~10) [10], gemtuzumab ozogamicin (Binding) [7]	alemtuzumab (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 abreviation	–	–	CTLA-4	PD-1	–
Antibodies	–	–	ipilimumab (pK_d >9) [28], tremelimumab (pK_d 8.9) [30]	pembrolizumab (pK_d ~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

Gabius HJ *et al.* (2015) The glycobiology of the CD system: a dictionary for translating marker designations into glycan/lectin structure and function. *Trends Biochem Sci* **40**: 360-76 [PMID:25981696]

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	l(3)mbt-like 3 (Drosophila)
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]

Zahnow CA *et al.* (2016) Inhibitors of DNA Methylation, Histone Deacetylation, and Histone Demethylation: A Perfect Combination for Cancer Therapy. *Adv Cancer Res* **130**: 55-111 [PMID:27037751]

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	fatty acid binding protein 1	fatty acid binding protein 2	fatty acid binding protein 3	fatty acid binding protein 4
HGNC, UniProt	*FABP1*, P07148	*FABP2*, P12104	*FABP3*, P05413	*FABP4*, P15090
Rank order of potency	stearic acid, oleic acid > palmitic acid, linoleic acid > arachidonic acid, α-linolenic acid [67]	stearic acid > palmitic acid,oleic acid > linoleic acid > arachidonic acid, α-linolenic acid [67]	stearic acid, oleic acid, palmitic acid > linoleic acid, α-linolenic acid, arachidonic acid [67]	oleic acid, palmitic acid, stearic acid, linoleic acid > α-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	fatty acid binding protein 5	fatty acid binding protein 6	fatty acid binding protein 7	peripheral myelin protein 2	fatty acid binding protein 9	fatty acid binding protein 12
HGNC, UniProt	*FABP5*, Q01469	*FABP6*, P51161	*FABP7*, O15540	*PMP2*, P02689	*FABP9*, Q0Z7S8	*FABP12*, A6NFH5
Comments	Crystal structure of the human FABP5 [31].	Able to transport bile acids [95].	Crystal structure of the human FABP7 [5].	*In silico* 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	*RBP1*, P09455	*RBP2*, P50120	*RBP3*, P10745	*RBP4*, P02753	*RBP5*, P82980	*RBP7*, Q96R05
Rank order of potency	–	stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [68]	–	–	–	–
Inhibitors	–	–	–	A1120 (pIC_{50} 7.8) [86]	–	–

Nomenclature	retinaldehyde binding protein 1	cellular retinoic acid binding protein 1	cellular retinoic acid binding protein 2
HGNC, UniProt	*RLBP1*, P12271	*CRABP1*, P29762	*CRABP2*, P29373
Rank order of potency	11-*cis*-retinal, 11-*cis*-retinol > 9-*cis*-retinal, 13-*cis*-retinal, 13-*cis*-retinol, all-*trans*-retinal, retinol [15]	tretinoin > alitretinoin stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid [68]	–

Comments: Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC50 8.8) compared to FABP3 or FABP5 (pIC50 <6.6) [21, 81]. HTS01037 is reported to interfere with FABP4 action [30]. Ibuprofen displays some selectivity for FABP4 (pIC_{50} 5.5) relative to FABP3 (pIC_{50} 3.5) and FABP5 (pIC_{50} 3.8) [48]. Fenofibric acid displays some selectivity for FABP5 (pIC_{50} 5.5) relative to FABP3 (pIC_{50} 4.5) and FABP4 (pIC_{50} 4.6) [48]. Multiple pseudogenes for the FABPs have been identified in the human genome.

Further reading on Fatty acid-binding proteins

Gajda AM *et al.* (2015) Enterocyte fatty acid-binding proteins (FABPs): different functions of liver and intestinal FABPs in the intestine. *Prostaglandins Leukot. Essent. Fatty Acids* **93**: 9-16 [PMID:25458898]

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 canonocal 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 γ-secretase is required for downstream signalling and Notch-induced transcriptional modulation [18, 57, 71, 89]. This is why γ-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

Borggrefe T *et al.* (2016) The Notch intracellular domain integrates signals from Wnt, Hedgehog, TGFbeta/BMP and hypoxia pathways. *Biochim Biophys Acta* **1863**: 303-313 [PMID:26592459]

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	regulator of G-protein signaling 4
HGNC, UniProt	*RGS4*, P49798
Common abreviation	RGS4
Selective inhibitors	RGS4 inhibitor 11b (pIC_{50} 7.8) [83], CCG-50014 (pIC_{50} 7.5) [8, 83], RGS4 inhibitor 13 (pIC_{50} 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]

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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	sigma non-opioid intracellular receptor 1	*σ* 2
HGNC, UniProt	*SIGMAR1*, Q99720	–
Selective agonists	PRE-084 [80], (+)-SKF 10.047	–
Selective antagonists	NE-100 (pIC_{50} 8.4) [60], BD-1047 (pIC_{50} 7.4) [51]	–
Labelled ligands	[^{3}H]pentazocine (Agonist)	[^{3}H]-di-o-tolylguanidine (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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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 β-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	*TUBA1A*, Q71U36	*TUBA4A*, P68366	*TUBB*, P07437	*TUBB3*, Q13509	*TUBB4B*, P68371	*TUBB8*, Q3ZCM7
Inhibitors	–	–	vinblastine (pIC_{50} 9), vincristine, eribulin (pIC_{50} 8.2) [58], paclitaxel (pEC_{50} 8.1) [61], colchicine (pIC_{50} 8) [13], cabazitaxel, docetaxel, ixabepilone	combretastatin A4 (pIC_{50} 8.2) [22]	–	–

Further reading on Tubulins

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