


















THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Introduction and Other Protein Targets

Stephen PH Alexander¹ , Eamonn Kelly², Alistair Mathie³ , John A Peters⁴ , Emma L Veale³ , Jane F Armstrong⁵ , Elena Faccenda⁵ , Simon D Harding⁵ , Adam J Pawson⁵ , Joanna L Sharman⁵ , Christopher Southan⁵ , O Peter Buneman⁶, John A Cidlowski⁷ , Arthur Christopoulos⁸ , Anthony P Davenport⁹ , Dorian Fabbro¹⁰ , Michael Spedding¹¹ , Jörg Striessnig¹² , Jamie A Davies⁵  and CGTP Collaborators

¹School of Life Sciences, University of Nottingham Medical School, Nottingham, NG7 2UH, UK

²School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, BS8 1TD, UK

³Medway School of Pharmacy, The Universities of Greenwich and Kent at Medway, Anson Building, Central Avenue, Chatham Maritime, Chatham, Kent, ME4 4TB, UK

⁴Neuroscience Division, Medical Education Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY, UK

⁵Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, EH8 9XD, UK

⁶Laboratory for Foundations of Computer Science, School of Informatics, University of Edinburgh, Edinburgh, EH8 9LE, UK

⁷National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC 27709, USA

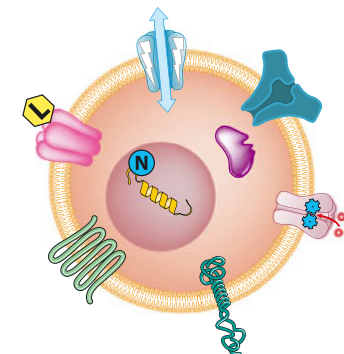
⁸Monash Institute of Pharmaceutical Sciences and Department of Pharmacology, Monash University, Parkville, Victoria 3052, Australia

⁹Clinical Pharmacology Unit, University of Cambridge, Cambridge, CB2 0QQ, UK

¹⁰PIQUR Therapeutics, Basel 4057, Switzerland

¹¹Spedding Research Solutions SARL, Le Vésinet 78110, France

¹²Pharmacology and Toxicology, Institute of Pharmacy, University of Innsbruck, A-6020 Innsbruck, Austria



Abstract

The Concise Guide to PHARMACOLOGY 2019/20 is the fourth in this series of biennial publications. The Concise Guide provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source 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.14747>. In addition to this overview, in which are identified Other protein targets which fall outside of the subsequent categorisation, there are six areas of focus: G protein-coupled receptors, 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-2019, and supersedes data presented in the 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Table of contents

S1 Introduction and Other Protein Targets

S6 Adiponectin receptors
S7 Blood coagulation components
S8 Non-enzymatic BRD containing proteins
S9 Carrier proteins
S9 CD molecules
S11 Methyllysine reader proteins
S11 Fatty acid-binding proteins
S14 Notch receptors
S15 Regulators of G protein Signaling (RGS) proteins
S18 Sigma receptors
S19 Tubulins

S21 G protein-coupled receptors

S23 Orphan and other 7TM receptors
S24 Class A Orphans
S26 Class C Orphans
S33 Taste 1 receptors
S34 Taste 2 receptors
S35 Other 7TM proteins
S36 5-Hydroxytryptamine receptors
S39 Acetylcholine receptors (muscarinic)
S41 Adenosine receptors
S42 Adhesion Class GPCRs
S45 Adrenoceptors
S48 Angiotensin receptors
S50 Apelin receptor
S51 Bile acid receptor
S51 Bombesin receptors
S53 Bradykinin receptors
S54 Calcitonin receptors
S56 Calcium-sensing receptor
S57 Cannabinoid receptors
S58 Chemerin receptors
S59 Chemokine receptors
S63 Cholecystokinin receptors
S64 Class Frizzled GPCRs
S67 Complement peptide receptors
S68 Corticotropin-releasing factor receptors
S69 Dopamine receptors
S71 Endothelin receptors
S72 G protein-coupled estrogen receptor
S73 Formylpeptide receptors
S74 Free fatty acid receptors
S76 GABA_B receptors
S78 Galanin receptors
S79 Ghrelin receptor

S80 Glucagon receptor family
S81 Glycoprotein hormone receptors
S82 Gonadotrophin-releasing hormone receptors
S83 GPR18, GPR55 and GPR119
S84 Histamine receptors
S86 Hydroxycarboxylic acid receptors
S87 Kisspeptin receptor
S88 Leukotriene receptors
S89 Lysophospholipid (LPA) receptors
S90 Lysophospholipid (S1P) receptors
S92 Melanin-concentrating hormone receptors
S93 Melanocortin receptors
S94 Melatonin receptors
S95 Metabotropic glutamate receptors
S97 Motilin receptor
S98 Neuromedin U receptors
S99 Neuropeptide FF/neuropeptide AF receptors
S100 Neuropeptide S receptor
S101 Neuropeptide W/neuropeptide B receptors
S102 Neuropeptide Y receptors
S103 Neurotensin receptors
S104 Opioid receptors
S106 Orexin receptors
S107 Oxoglutarate receptor
S108 P2Y receptors
S110 Parathyroid hormone receptors
S111 Platelet-activating factor receptor
S112 Prokineticin receptors
S113 Prolactin-releasing peptide receptor
S114 Prostanoid receptors
S116 Proteinase-activated receptors
S117 QRFP receptor
S118 Relaxin family peptide receptors
S120 Somatostatin receptors
S121 Succinate receptor
S122 Tachykinin receptors
S123 Thyrotropin-releasing hormone receptors
S124 Trace amine receptor
S125 Urotensin receptor
S126 Vasopressin and oxytocin receptors
S127 VIP and PACAP receptors

S142 Ion channels

S143 Ligand-gated ion channels
S144 5-HT₃ receptors
S146 Acid-sensing (proton-gated) ion channels (ASICs)
S148 Epithelial sodium channel (ENaC)

S149 GABA_A receptors
S155 Glycine receptors
S158 Ionotropic glutamate receptors
S164 IP₃ receptor
S165 Nicotinic acetylcholine receptors
S168 P2X receptors
S170 ZAC
S171 Voltage-gated ion channels
S171 CatSper and Two-Pore channels
S173 Cyclic nucleotide-regulated channels
S175 Potassium channels
S175 Calcium- and sodium-activated potassium channels
S178 Inwardly rectifying potassium channels
S182 Two P domain potassium channels
S185 Voltage-gated potassium channels
S189 Ryanodine receptors
S190 Transient Receptor Potential channels
S204 Voltage-gated calcium channels
S207 Voltage-gated proton channel
S208 Voltage-gated sodium channels
S210 Other ion channels
S210 Aquaporins
S212 Chloride channels
S213 CIC family
S215 CFTR
S216 Calcium activated chloride channel
S217 Maxi chloride channel
S218 Volume regulated chloride channels
S219 Connexins and Pannexins
S221 Piezo channels
S222 Sodium leak channel, non-selective

S229 Nuclear hormone receptors

S230 1A. Thyroid hormone receptors
S231 1B. Retinoic acid receptors
S232 1C. Peroxisome proliferator-activated receptors
S233 1D. Rev-Erb receptors
S234 1F. Retinoic acid-related orphans
S234 1H. Liver X receptor-like receptors
S235 1I. Vitamin D receptor-like receptors
S236 2A. Hepatocyte nuclear factor-4 receptors
S237 2B. Retinoid X receptors
S238 2C. Testicular receptors
S238 2E. Tailless-like receptors
S239 2F. COUP-TF-like receptors
S239 3B. Estrogen-related receptors
S240 4A. Nerve growth factor IB-like receptors

S241 5A. Fushi tarazu F1-like receptors
 S241 6A. Germ cell nuclear factor receptors
 S242 0B. DAX-like receptors
 S242 Steroid hormone receptors
 S243 3A. Estrogen receptors
 S244 3C. 3-Ketosteroid receptors

S247 Catalytic receptors

S248 Cytokine receptor family
 S249 IL-2 receptor family
 S251 IL-3 receptor family
 S252 IL-6 receptor family
 S254 IL-12 receptor family
 S255 Prolactin receptor family
 S256 Interferon receptor family
 S257 IL-10 receptor family
 S258 Immunoglobulin-like family of IL-1 receptors
 S259 IL-17 receptor family
 S259 GDNF receptor family
 S260 Integrins
 S264 Pattern recognition receptors
 S264 Toll-like receptor family
 S266 NOD-like receptor family
 S268 RIG-I-like receptor family
 S269 Receptor Guanylyl Cyclase (RGC) family
 S269 Transmembrane guanylyl cyclases
 S270 Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase
 S271 Receptor tyrosine kinases (RTKs)
 S272 Type I RTKs: ErbB (epidermal growth factor) receptor family
 S273 Type II RTKs: Insulin receptor family
 S274 Type III RTKs: PDGFR, CSFR, Kit, FLT3 receptor family
 S275 Type IV RTKs: VEGF (vascular endothelial growth factor) receptor family
 S275 Type V RTKs: FGF (broblast growth factor) receptor family
 S276 Type VI RTKs: PTK7/CCK4
 S277 Type VII RTKs: Neurotrophin receptor/Trk family
 S278 Type VIII RTKs: ROR family
 S278 Type IX RTKs: MuSK
 S279 Type X RTKs: HGF (hepatocyte growth factor) receptor family
 S279 Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family
 S280 Type XII RTKs: TIE family of angiopoietin receptors
 S280 Type XIII RTKs: Ephrin receptor family
 S281 Type XIV RTKs: RET
 S282 Type XV RTKs: RYK
 S282 Type XVI RTKs: DDR (collagen receptor) family
 S283 Type XVII RTKs: ROS receptors
 S283 Type XVIII RTKs: LMR family
 S284 Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family

S284 Type XX RTKs: STYK1
 S286 Receptor serine/threonine kinase (RSTK) family
 S286 Type I receptor serine/threonine kinases
 S287 Type II receptor serine/threonine kinases
 S287 Type III receptor serine/threonine kinases
 S287 RSTK functional heteromers
 S289 Receptor tyrosine phosphatase (RTP) family
 S291 Tumour necrosis factor (TNF) receptor family

S297 Enzymes

S301 Acetylcholine turnover
 S302 Adenosine turnover
 S303 Amino acid hydroxylases
 S304 L-Arginine turnover
 S304 2.1.1.- Protein arginine N-methyltransferases
 S305 Arginase
 S305 Arginine:glycine amidinotransferase
 S305 Dimethylarginine dimethylaminohydrolases
 S306 Nitric oxide synthases
 S307 Carbonic anhydrases
 S308 Carboxylases and decarboxylases
 S308 Carboxylases
 S309 Decarboxylases
 S311 Catecholamine turnover
 S313 Ceramide turnover
 S313 Serine palmitoyltransferase
 S314 Ceramide synthase
 S314 Sphingolipid Δ^4 -desaturase
 S315 Sphingomyelin synthase
 S315 Sphingomyelin phosphodiesterase
 S316 Neutral sphingomyelinase coupling factors
 S316 Ceramide glucosyltransferase
 S316 Acid ceramidase
 S317 Neutral ceramidases
 S317 Alkaline ceramidases
 S318 Ceramide kinase
 S319 Chromatin modifying enzymes
 S319 2.1.1.- Protein arginine N-methyltransferases
 S320 3.5.1.- Histone deacetylases (HDACs)
 S321 Cyclic nucleotide turnover/signalling
 S321 Adenylyl cyclases (ACs)
 S323 Exchange protein activated by cyclic AMP (EPACs)
 S323 Phosphodiesterases, 3',5'-cyclic nucleotide (PDEs)
 S327 Cytochrome P450
 S327 CYP2 family
 S328 CYP2 family
 S329 CYP3 family
 S330 CYP4 family
 S331 CYP5, CYP7 and CYP8 families
 S332 CYP11, CYP17, CYP19, CYP20 and CYP21 families

S333 CYP24, CYP26 and CYP27 families
 S333 CYP39, CYP46 and CYP51 families
 S334 DNA topoisomerases
 S335 Endocannabinoid turnover
 S336 N-Acylethanolamine turnover
 S337 2-Acylglycerol ester turnover
 S338 Eicosanoid turnover
 S338 Cyclooxygenase
 S339 Prostaglandin synthases
 S341 Lipoxygenases
 S342 Leukotriene and lipoxin metabolism
 S343 GABA turnover
 S344 Glycerophospholipid turnover
 S345 Phosphoinositide-specific phospholipase C
 S346 Phospholipase A₂
 S348 Phosphatidylcholine-specific phospholipase D
 S349 Lipid phosphate phosphatases
 S349 Phosphatidylinositol kinases
 S350 1-phosphatidylinositol 4-kinase family
 S351 Phosphatidylinositol-4-phosphate 3-kinase family
 S351 Phosphatidylinositol 3-kinase family
 S351 Phosphatidylinositol-4,5-bisphosphate 3-kinase family
 S352 1-phosphatidylinositol-3-phosphate 5-kinase family
 S353 Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)
 S353 Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)
 S354 Sphingosine kinase
 S356 Phosphatidylinositol phosphate kinases
 S356 Haem oxygenase
 S358 Hydrogen sulphide synthesis
 S358 Hydrolases
 S360 Inositol phosphate turnover
 S360 Inositol 1,4,5-trisphosphate 3-kinases
 S360 Inositol polyphosphate phosphatases
 S361 Inositol monophosphatase
 S361 Kinases (EC 2.7.x.x)
 S362 Rho kinase
 S362 Protein kinase C (PKC) family
 S363 Alpha subfamily
 S363 Delta subfamily
 S364 Eta subfamily
 S364 FRAP subfamily
 S365 Cyclin-dependent kinase (CDK) family
 S365 CDK4 subfamily
 S366 GSK subfamily
 S367 Polo-like kinase (PLK) family
 S367 STE7 family
 S368 Abl family
 S368 Ack family

S369	Janus kinase (JakA) family	S408	Cu ⁺ -ATPases	S446	Organic anion transporters (OATs)
S369	Src family	S409	Phospholipid-transporting ATPases	S446	Urate transporter
S370	Tec family	S409	SLC superfamily of solute carriers	S447	Atypical SLC22B subfamily
S371	RAF family	S410	SLC1 family of amino acid transporters	S448	SLC23 family of ascorbic acid transporters
S372	Lanosterol biosynthesis pathway	S410	Glutamate transporter subfamily	S449	SLC24 family of sodium/potassium/calcium exchangers
S374	Nucleoside synthesis and metabolism	S412	Alanine/serine/cysteine transporter subfamily	S450	SLC25 family of mitochondrial transporters
S376	Paraoxonase (PON) family	S413	SLC2 family of hexose and sugar alcohol transporters	S450	Mitochondrial di- and tri-carboxylic acid transporter subfamily
S377	Peptidases and proteinases	S413	Class I transporters	S451	Mitochondrial amino acid transporter subfamily
S377	A1: Pepsin	S414	Class II transporters	S452	Mitochondrial phosphate transporters
S377	A22: Presenilin	S415	Proton-coupled inositol transporter	S452	Mitochondrial nucleotide transporter subfamily
S378	C14: Caspase	S415	SLC3 and SLC7 families of heteromeric amino acid transporters (HATs)	S453	Mitochondrial uncoupling proteins
S378	M1: Aminopeptidase N	S415	SLC3 family	S454	Miscellaneous SLC25 mitochondrial transporters
S379	M2: Angiotensin-converting (ACE and ACE2)	S416	SLC7 family	S454	SLC26 family of anion exchangers
S379	M10: Matrix metalloproteinase	S417	SLC4 family of bicarbonate transporters	S454	Selective sulphate transporters
S380	M12: Astacin/Adamalysin	S417	Anion exchangers	S455	Chloride/bicarbonate exchangers
S380	M28: Aminopeptidase Y	S418	Sodium-dependent HCO ₃ ⁻ transporters	S455	Anion channels
S381	M19: Membrane dipeptidase	S418	SLC5 family of sodium-dependent glucose transporters	S456	Other SLC26 anion exchangers
S381	S1: Chymotrypsin	S419	Hexose transporter family	S457	SLC27 family of fatty acid transporters
S382	T1: Proteasome	S420	Choline transporter	S458	SLC28 and SLC29 families of nucleoside transporters
S382	S8: Subtilisin	S421	Sodium iodide symporter, sodium-dependent multivitamin transporter and sodium-coupled monocarboxylate transporters	S458	SLC28 family
S383	S9: Prolyl oligopeptidase	S422	Sodium myo-inositol cotransporter transporters	S459	SLC29 family
S383	Poly ADP-ribose polymerases	S423	SLC6 neurotransmitter transporter family	S461	SLC30 zinc transporter family
S384	Prolyl hydroxylases	S423	Monoamine transporter subfamily	S461	SLC31 family of copper transporters
S384	Sphingosine 1-phosphate turnover	S424	GABA transporter subfamily	S462	SLC32 vesicular inhibitory amino acid transporter
S385	Sphingosine kinase	S425	Glycine transporter subfamily	S463	SLC33 acetylCoA transporter
S386	Sphingosine 1-phosphate phosphatase	S427	Neutral amino acid transporter subfamily	S464	SLC34 family of sodium phosphate co-transporters
S387	Sphingosine 1-phosphate lyase	S428	SLC8 family of sodium/calcium exchangers	S465	SLC35 family of nucleotide sugar transporters
S387	Thyroid hormone turnover	S429	SLC9 family of sodium/hydrogen exchangers	S466	SLC36 family of proton-coupled amino acid transporters
S388	1.14.13.9 Kynurenine 3-monooxygenase	S429	SLC10 family of sodium-bile acid co-transporters	S468	SLC37 family of phosphosugar/phosphate exchangers
S389	2.5.1.58 Protein farnesyltransferase	S431	SLC11 family of proton-coupled metal ion transporters	S468	SLC38 family of sodium-dependent neutral amino acid transporters
S390	3.5.1.- Histone deacetylases (HDACs)	S431	SLC12 family of cation-coupled chloride transporters	S469	System A-like transporters
S391	3.5.3.15 Peptidyl arginine deiminases (PADI)	S433	SLC13 family of sodium-dependent sulphate/carboxylate transporters	S469	System N-like transporters
S391	3.6.5.2 Small monomeric GTPases	S434	SLC14 family of facilitative urea transporters	S470	Orphan SLC38 transporters
S391	RAS subfamily	S435	SLC15 family of peptide transporters	S470	SLC39 family of metal ion transporters
S392	RAB subfamily	S437	SLC16 family of monocarboxylate transporters	S471	SLC40 iron transporter
S397 Transporters		S438	SLC17 phosphate and organic anion transporter family	S472	SLC41 family of divalent cation transporters
S399	ATP-binding cassette transporter family	S438	Type I sodium-phosphate co-transporters	S473	SLC42 family of Rhesus glycoprotein ammonium transporters
S399	ABCA subfamily	S439	Sialic acid transporter	S473	SLC43 family of large neutral amino acid transporters
S401	ABCB subfamily	S439	Vesicular glutamate transporters (VGLUTs)	S474	SLC44 choline transporter-like family
S403	ABCC subfamily	S440	Vesicular nucleotide transporter	S475	SLC45 family of putative sugar transporters
S404	ABCD subfamily of peroxisomal ABC transporters	S440	SLC18 family of vesicular amine transporters	S475	SLC46 family of folate transporters
S405	ABCG subfamily	S442	SLC19 family of vitamin transporters	S477	SLC47 family of multidrug and toxin extrusion transporters
S406	F-type and V-type ATPases	S443	SLC20 family of sodium-dependent phosphate transporters	S477	SLC48 heme transporter
S406	F-type ATPase	S443	SLC22 family of organic cation and anion transporters	S478	SLC49 family of FLVCR-related heme transporters
S407	V-type ATPase	S444	Organic cation transporters (OCT)	S479	SLC50 sugar transporter
S407	P-type ATPases	S445	Organic zwitterions/cation transporters (OCTN)	S479	SLC51 family of steroid-derived molecule transporters
S407	Na ⁺ /K ⁺ -ATPases			S480	SLC52 family of riboflavin transporters
S408	Ca ²⁺ -ATPases			S481	SLC53 Phosphate carriers
S408	H ⁺ /K ⁺ -ATPases				

S481 SLC54 Mitochondrial pyruvate carriers
 S482 SLC55 Mitochondrial cation/proton exchangers
 S482 SLC56 Sideroflexins
 S483 SLC57 NiPA-like magnesium transporter family
 S483 SLC58 MagT-like magnesium transporter family
 S484 SLC59 Sodium-dependent lysophosphatidylcholine symporter family

S484 SLC60 Glucose transporters
 S485 SLC61 Molybdate transporter family
 S485 SLC62 Pyrophosphate transporters
 S486 SLC63 Sphingosine phosphate transporters

S486 SLC64 Golgi Ca²⁺/H⁺ exchangers
 S487 SLC65 NPC-type cholesterol transporters
 S488 SLCO family of organic anion transporting polypeptides

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 (<https://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 2019/20, is the latest snapshot of the database in print form, following on from the Concise Guide to PHARMACOLOGY 2017/18. 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 for human proteins. 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 seven sections, which comprise pharmacological targets of similar structure/function. These are G protein-coupled receptors, ion channels (combining previous records of ligand-gated, voltage-gated and 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.* (2019). The Concise Guide to PHARMACOLOGY 2019/20: Introduction and Other Protein Targets. *Br J Pharmacol* 176: S1–S20. In this overview are listed protein targets of pharmacological interest, which are not G protein-coupled receptors, 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 2019/20 and the online database www.guidetopharmacology.org.

Conflict of interest

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

© 2019 The Authors. *British Journal of Pharmacology* published by John Wiley & Sons Ltd on behalf of The British Pharmacological Society.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

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

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.14747/full>

Other protein targets S5

Family structure

- Absciscic acid receptor complex
- S6 Adiponectin receptors
- Anti-infective targets
 - Antimalarial targets
 - Other anti-infective targets
- Aryl hydrocarbon receptor complex
- B-cell lymphoma 2 (Bcl-2) protein family
- S7 Blood coagulation components
- Bromodomain-containing proteins
- S8 Non-enzymatic BRD containing proteins
- Butyrophilin and butyrophilin-like proteins
- S9 Carrier proteins
- S9 CD molecules
- Chaperone proteins
 - Lipid binding chaperones
- Chitinase-like proteins
- Chromatin-interacting transcriptional repressors
- S11 Methyllysine reader proteins
- Circadian clock proteins
- Claudins
- EF-hand domain containing proteins
- S11 Fatty acid-binding proteins
- Fc epsilon receptors
- G-alpha family G(q) subfamily
- Heat shock proteins
- Immune checkpoint proteins
 - Other immune checkpoint proteins
- Immunoglobulin C1-set domain-containing proteins
- Immunoglobulin C2-set domain-containing proteins
- Immunoglobulin like domain containing proteins
- Immunoglobulins
- Inhibitors of apoptosis (IAP) protein family
- Kelch-like proteins
- Kinesins
- Leucine-rich repeat proteins
- Lymphocyte antigens
- Mitochondrial-associated proteins
- Myosin binding proteins
- Neuropilins and Plexins
- Non-catalytic pattern recognition receptors
 - Absent in melanoma (AIM)-like receptors (ALRs)
 - C-type lectin-like receptors (CLRs)
 - Other pattern recognition receptors
- S14 Notch receptors
- Nuclear export proteins
- Pentaxins
- Serum pentaxins
- S15 Regulators of G protein Signaling (RGS) proteins
- S15 RZ family
- S15 R4 family
- S16 R7 family
- S17 R12 family
- Repulsive guidance molecules
- Reticulons and associated proteins
- Ribosomal factors
- Sialic acid binding Ig like lectins
- S18 Sigma receptors
- Signal regulatory proteins
- Transcription factors
 - Basic leucine zipper domain TFs
 - BTB (POZ) domain containing TFs
 - Forkhead box TFs
 - STAT transcription factors
- Transcription factor regulators
 - NF-κB regulators
- S19 Tubulins
- Tumour-associated antigens
- WD repeat-containing proteins

Adiponectin receptors

Other protein targets → Adiponectin receptors

Overview: Adiponectin receptors (**provisional nomenclature**, [ENSM00500000270960](#)) 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 [57]. 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 [111]. 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 [98].

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 [36].

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]

Okada-Iwabu M *et al.* (2018) Structure and function analysis of adiponectin receptors toward development of novel antidiabetic agents promoting healthy longevity. *Endocr J* **65**: 971-977 [PMID:30282888]

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 targeted 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) [29], fondaparinux (pK _d 7.5) [72], dalteparin [35], danaparoid [18, 65], enoxaparin [21], tinzaparin [22]
Selective inhibitors	drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [39, 40]	drotrecogin alfa (Antithrombotic effect thought to occur via inhibition of factors Va and VIIIa) [39, 40]	–

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) [85]	GSK2801 (Binding) (pK _d 6.9) [85]	I-CBP112 (pK _d 6.8) [84]	PFI-3 (Binding) (pK _d 7.3) [95]	PFI-3 (Binding) (pK _d 7.1) [95]

Further reading on Non-enzymatic BRD containing proteins

- 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]
- Myrianthopoulos V & Mikros E. (2019) From bench to bedside, via desktop. Recent advances in the application of cutting-edge in silico tools in the research of drugs targeting bromodomain modules. *Biochem Pharmacol* **159**: 40–51 [PMID:30414936]
- 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]
- Ramadoss M & Mahadevan V. (2018) Targeting the cancer epigenome: synergistic therapy with bromodomain inhibitors. *Drug Discov Today* **23**: 76–89 [PMID:28943305]
- Yang CY *et al.* (2019) Small-molecule PROTAC degraders of the Bromodomain and Extra Terminal (BET) proteins - A review. *Drug Discov Today Technol* **31**: 43–51 [PMID:31200858]

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 [73]. These amyloido-

genic mutants are linked to the development of pathological amyloidoses, including familial amyloid polyneuropathy (FAP) [6, 16], familial amyloid cardiomyopathy (FAC) [37], amyloidotic vitreous opacities, carpal tunnel syndrome [63] and others. In old age, non-mutated TTR can also form pathological amyloid fibrils [108]. Pharmacological intervention to reduce or prevent TTR dis-

sociation 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
Common abbreviation	TTR
HGNC, UniProt	TTR, P02766

Further reading on Carrier proteins

Adams D *et al.* (2019) Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. *Nat Rev Neurol* **15**: 387-404 [PMID:31209302]
 Dellièrè 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.* **131**: 395-409 [PMID:28213611]

Yokoyama T & Mizuguchi M. (2018) Inhibition of the Amyloidogenesis of Transthyretin by Natural Products and Synthetic Compounds. *Biol Pharm Bull* **41**: 979-984 [PMID:29962408]
 Ruberg FL *et al.* (2019) Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol* **73**: 2872-2891 [PMID:31171094]

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

proteins is not possible in the Guide to PHARMACOLOGY; listed herein are selected members of the family targeted for therapeutic gain.

Nomenclature	CD2	CD3e	CD6	CD20 (membrane-spanning 4-domains, subfamily A, member 1)	CD33
Common abbreviation	–	–	–	–	SIGLEC-3
HGNC, UniProt	CD2 , P06729	CD3E , P07766	CD6 , P30203	MS4A1 , P11836	CD33 , P20138
Selective inhibitors	alefacept [19 , 62]	–	–	–	–
Antibodies	–	catumaxomab (Binding) [50], muromonab-CD3 (Binding) [28], otelixizumab (Binding) [11]	–	ofatumumab (Binding) (pK_d 9.9) [52], rituximab (Binding) (pK_d 8.5) [91], ibritumomab tiuxetan (Binding), obinutuzumab (Binding) [4 , 76], tositumomab (Binding)	lintuzumab (Binding) (pK_d ~10) [12], gemtuzumab ozogamicin (Binding) [9]

Nomenclature	CD52	CD80	CD86	cytotoxic T-lymphocyte-associated protein 4 (CD152)	programmed cell death 1 (CD279)	CD300a
Common abbreviation	–	–	–	CTLA-4	PD-1	–
HGNC, UniProt	CD52 , P31358	CD80 , P33681	CD86 , P42081	CTLA4 , P16410	PDCD1 , Q15116	CD300A , Q9UGN4
Endogenous ligands	–	–	–	–	programmed cell death 1 ligand 1 (CD274 , Q9NZQ7) (Binding)	–
Selective inhibitors	–	abatacept (pK_d ~7.9) [51 , 103]	abatacept (pK_d ~7.9) [51 , 103], belatacept [44]	–	–	–
Antibodies	alemtuzumab (Binding) [26 , 86]	–	–	ipilimumab (Binding) (pK_d > 9) [30], tremelimumab (Binding) (pK_d 8.9) [32]	pembrolizumab (Binding) (pK_d ~10) [13], nivolumab (Binding) (pK_d 9.1) [31 , 42 , 43]	–

Comments: 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]

Vosoughi T *et al.* (2019) CD markers variations in chronic lymphocytic leukemia: New insights into prognosis. *J Cell Physiol.* **234**: 19420–39 [PMID:31049958]

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	L3MBTL histone methyl-lysine binding protein 3
HGNC, UniProt	L3MBTL3, Q96JM7
Selective agonists	UNC1215 [38]

Further reading on Methyllysine reader proteins

Daskalaki MG *et al.* (2018) Histone methylation and acetylation in macrophages as a mechanism for regulation of inflammatory responses. *J Cell Physiol.* **233**: 6495–9507 [PMID:29574768]

Furuya K *et al.* (2019) Epigenetic interplays between DNA demethylation and histone methylation for protecting oncogenesis. *J Biochem.* **165**: 297–299 [PMID:30605533]

Levy D. (2019) Lysine methylation signaling of non-histone proteins in the nucleus. *Cell Mol Life Sci* **76**: 2873–83 [PMID:31123776]

Li J *et al.* (2019) Understanding histone H3 lysine 36 methylation and its deregulation in disease. *Cell Mol Life Sci* in press [PMID:31147750]

Shafabakhsh R *et al.* (2019) Role of histone modification and DNA methylation in signaling pathways involved in diabetic retinopathy. *J Cell Physiol.* **234**: 7839–7846 [PMID:30515789]

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 recep-

tors [82]) 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	fatty acid binding protein 5
HGNC, UniProt	FABP1 , P07148	FABP2 , P12104	FABP3 , P05413	FABP4 , P15090	FABP5 , Q01469
Rank order of potency	stearic acid, oleic acid > palmitic acid, linoleic acid > arachidonic acid, α -linolenic acid [77]	stearic acid > palmitic acid, oleic acid > linoleic acid > arachidonic acid, α -linolenic acid [77]	stearic acid, oleic acid, palmitic acid > linoleic acid, α -linolenic acid, arachidonic acid [77]	oleic acid, palmitic acid, stearic acid, linoleic acid > α -linolenic acid, arachidonic acid [77]	–
Inhibitors	fenofibrate (pK_i 7.6) [14] – Rat, fenofibric acid (pK_i 6.5) [14] – Rat, HTS01037 (pK_i 5.1) [33] – Mouse	–	–	–	compound 13 (pK_i 8.7) [97]
Selective inhibitors	–	–	–	HM50316 (pK_i > 9) [53]	–
Comments	A broader substrate specificity than other FABPs, binding two fatty acids per protein [101].	Crystal structure of the rat FABP2 [79].	Crystal structure of the human FABP3 [112].	–	Crystal structure of the human FABP5 [34].

Nomenclature	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	FABP6 , P51161	FABP7 , O15540	PMP2 , P02689	FABP9 , Q0Z7S8	FABP12 , A6NFH5
Comments	Able to transport bile acids [113].	Crystal structure of the human FABP7 [7].	<i>In silico</i> modelling suggests that PMP2/FABP8 can bind both fatty acids and cholesterol [58].	–	–

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	RBPS , P82980	RBP7 , Q96R05
Rank order of potency	–	stearic acid > palmitic acid, oleic acid, linoleic acid, α -linolenic acid, arachidonic acid [78]	–	–	–	–
Inhibitors	–	–	–	A1120 (pIC_{50} 7.8) [106]	–	–

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- <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 [17]	tretinoin > alitretinoin stearic acid > palmitic acid, oleic acid, linoleic acid, α -linolenic acid, arachidonic acid [78]	–

Comments: Although not tested at all FABPs, [BMS309403](#) exhibits high affinity for FABP4 (pIC₅₀ 8.8) compared to FABP3 or FABP5 (pIC₅₀ <6.6) [23, 97]. [HTS01037](#) is reported to interfere with FABP4 action [33]. Ibuprofen displays some selectivity for FABP4 (pIC₅₀ 5.5) relative to FABP3 (pIC₅₀ 3.5) and FABP5 (pIC₅₀ 3.8) [56]. Fenofibric acid displays some selectivity for FABP5 (pIC₅₀ 5.5) relative to FABP3 (pIC₅₀ 4.5) and FABP4 (pIC₅₀ 4.6) [56]. 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 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 [3]. 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 [20, 66, 83, 109]. 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 [54], although development of this compound has been terminated

following an unsuccessful Phase II single agent clinical trial in metastatic colorectal cancer [94].

Aberrant Notch signalling is implicated in a number of human cancers [46, 68, 88, 104], with demcizumab and tarextumab identified as antibody inhibitors of ligand:receptor binding [74].

Nomenclature	notch receptor 1	notch receptor 2	notch receptor 3	notch receptor 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 [25, 61], Adams-Oliver syndrome 5 [92], T-cell acute lymphoblastic leukemia (T-ALL) [107], chronic lymphocytic leukemia (CLL) [75] and head and neck squamous cell carcinoma [1, 93].	–	–	Notch receptor 4 is a potential therapeutic molecular target for triple-negative breast cancer [47, 64].

Further reading on Notch receptors

Arumugam TV *et al.* (2018) Notch signaling and neuronal death in stroke. *Prog. Neurobiol.* **165**:167: 103-116 [PMID:29574014]
Borggreffe T *et al.* (2016) The Notch intracellular domain integrates signals from Wnt, Hedgehog, TGF β /BMP and hypoxia pathways. *Biochim. Biophys. Acta* **1863**: 303-13 [PMID:26592459]
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**: 445-64 [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 display a common RGS domain that interacts with the GTP-bound $G\alpha$ subunits of heterotrimeric G proteins, enhancing GTP hydrolysis by stabilising the transition state [8, 99, 100], leading to a termination of GPCR signalling. Interactions through protein:protein interactions of many RGS proteins have been identified for targets other than heteromeric G proteins. Sequence analysis of the 20 RGS proteins suggests four families of RGS: RZ, R4, R7 and R12 families. Many of these proteins have been identified to have effects other than through targetting G proteins. Included here is RGS4 for which a number of pharmacological inhibitors have been described.

RZ family

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

Overview: The RZ family of RGS proteins is less well characterized than the other families [69]. It consists of RGS17 (also known as RGSZ2), RGS19 (also known as GAIP) and RGS20 (with several splice variants including RGSZ1 and Ret-RGS). All members contain an N-terminal cysteine string motif [49] which is a site of palmitoylation and could serve functions in membrane targeting, protein stability or aid protein-protein interactions [2, 49]. However, the function in the case of RZ family RGS proteins is not yet fully understood. Members of the RZ family of RGS proteins are the only RGS proteins that have selective GTPase activating-protein (GAP) activity for $G\alpha_z$, a function that resulted in the name of the family [27, 59, 105, 110]. However, the members of the RZ family are able to also GAP $G\alpha_{i/o}$ members with varying selectivity.

Nomenclature	regulator of G-protein signaling 17	regulator of G-protein signaling 19	regulator of G-protein signaling 20
Common abbreviation	RGS17	RGS19	RGS20
HGNC, UniProt	RGS17, Q9UGC6	RGS19, P49795	RGS20, O76081

R4 family

Other protein targets → Regulators of G protein Signaling (RGS) proteins → R4 family

Overview: This is the largest family of RGS proteins.

Nomenclature	regulator of G-protein signaling 1	regulator of G-protein signaling 2	regulator of G-protein signaling 3	regulator of G-protein signaling 4
Common abbreviation	RGS1	RGS2	RGS3	RGS4
HGNC, UniProt	<i>RGS1</i> , Q08116	<i>RGS2</i> , P41220	<i>RGS3</i> , P49796	<i>RGS4</i> , P49798
Selective inhibitors	–	–	–	<i>RGS4 inhibitor 11b</i> (pIC ₅₀ 7.8) [102], <i>CCG-50014</i> (pIC ₅₀ 7.5) [10, 102], <i>RGS4 inhibitor 13</i> (pIC ₅₀ 7.3) [102]

Nomenclature	regulator of G-protein signaling 5	regulator of G-protein signaling 8	regulator of G-protein signaling 13	regulator of G-protein signaling 16	regulator of G-protein signaling 18	regulator of G-protein signaling 21
Common abbreviation	RGS5	RGS8	RGS13	RGS16	RGS18	RGS21
HGNC, UniProt	<i>RGS5</i> , O15539	<i>RGS8</i> , P57771	<i>RGS13</i> , O14921	<i>RGS16</i> , O15492	<i>RGS18</i> , Q9NS28	<i>RGS21</i> , Q2M5E4

R7 family

Other protein targets → Regulators of G protein Signaling (RGS) proteins → R7 family

Overview: This family of RGS proteins shows some selectivity for Gai/o proteins.

Nomenclature	regulator of G-protein signaling 6	regulator of G-protein signaling 7	regulator of G-protein signaling 9	regulator of G-protein signaling 11
Common abbreviation	RGS6	RGS7	RGS9	RGS11
HGNC, UniProt	<i>RGS6</i> , P49758	<i>RGS7</i> , P49802	<i>RGS9</i> , O75916	<i>RGS11</i> , O94810

R12 family

Other protein targets → Regulators of G protein Signaling (RGS) proteins → R12 family

Overview: The R12 family consists of RGS10, 12 and 14. RGS12 and 14 are large proteins with additional domains that can participate in protein-protein interactions and other functions. In contrast, RGS10 is a small protein consisting of the RGS domain and small N- and C-termini, similar to members of the R4 family.

However, sequence homology of the RGS10 RGS domain clearly places it in the R12 family [45]. The $G\alpha_{i/o}$ -Loco (GoLoco) motif in RGS12 and 14 has GDI activity (for Guanine nucleotide Dissociation Inhibitor) towards $G\alpha_{i1}$, $G\alpha_{i2}$ and $G\alpha_{i3}$ [41, 87]. Through this activity RGS12 and RGS14 can inhibit G protein signaling both by

accelerating GTP hydrolysis and by preventing G protein activation. Splice variants of RGS12 and RGS14 also contain membrane targeting and protein-protein interaction domains [80, 89, 90].

Nomenclature	regulator of G-protein signaling 10	regulator of G-protein signaling 12	regulator of G-protein signaling 14
Common abbreviation	RGS10	RGS12	RGS14
HGNC, UniProt	RGS10 , O43665	RGS12 , O14924	RGS14 , O43566

Further reading on Regulators of G protein Signaling (RGS) proteins

Alqinyah M *et al.* (2018) Regulating the regulators: Epigenetic, transcriptional, and post-translational regulation of RGS proteins. *Cell. Signal.* **42**: 77-87 [[PMID:29042285](#)]
 Neubig RR *et al.* (2002) Regulators of G-protein signalling as new central nervous system drug targets. *Nat Rev Drug Discov* **1**: 187-97 [[PMID:12120503](#)]
 Sethakorn N *et al.* (2010) Non-canonical functions of RGS proteins. *Cell. Signal.* **22**: 1274-81 [[PMID:20363320](#)]

Sjögren 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](#)]
 Sjögren 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](#)]

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 [81] 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	σ2
HGNC, UniProt	SIGMAR1 , Q99720	TMEM97 , Q5BJF2
Agonists	–	1,3-ditolylguanidine [48] – Guinea pig
Selective agonists	PRE-084 [96], (+)-SKF 10.047	–
Antagonists	–	SM 21 (pIC ₅₀ 7.2) [55]
Selective antagonists	NE-100 (pIC ₅₀ 8.4) [70], BD-1047 (pIC ₅₀ 7.4) [60]	–
Labelled ligands	[³H]pentazocine (Agonist)	[³H]-di-o-tolylguanidine (Agonist)
Comments	–	The sigma2 receptor has been reported to be TMEM97 [5], a 4TM protein partner of NPC1, the Niemann-Pick C1 protein, a 13TM cholesterol-binding protein.

Comments: [\(-\)-pentazocine](#) also shows activity at opioid receptors. The sigma2 receptor has recently been reported to be [TMEM97](#) [5], a 4TM protein partner of NPC1, the Niemann-Pick C1 protein, a 13TM cholesterol-binding protein.

Further reading on Sigma receptors

- Chu UB *et al.* (2016) Biochemical Pharmacology of the Sigma-1 Receptor. *Mol. Pharmacol.* **89**: 142–53 [[PMID:26560551](#)]
- Gris G *et al.* (2015) Sigma-1 receptor and inflammatory pain. *Inflamm. Res.* **64**: 377–81 [[PMID:25902777](#)]
- Rousseaux CG *et al.* (2016) Sigma receptors [σRs]: biology in normal and diseased states. *J. Recept. Signal Transduct. Res.* **36**: 327–388 [[PMID:26056947](#)]
- Sambo DO *et al.* (2018) The sigma-1 receptor as a regulator of dopamine neurotransmission: A potential therapeutic target for methamphetamine addiction. *Pharmacol Ther* **186**: 152–167 [[PMID:29360540](#)]
- Su TP *et al.* (2016) The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems. *Trends Pharmacol. Sci.* **37**: 262–278 [[PMID:26869505](#)]
- Vavers E *et al.* (2019) Allosteric Modulators of Sigma-1 Receptor: A Review. *Front Pharmacol* **10**: 223 [[PMID:30941035](#)]

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), eribulin (pIC ₅₀ 8.2) [67], paclitaxel (Mitotic cell cycle arrest in A431 cells) (pEC ₅₀ 8.1) [71], colchicine (pIC ₅₀ 8) [15], cabazitaxel, docetaxel, ixabepilone, vincristine	combretastatin A4 (pIC ₅₀ 8.2) [24]	–	–

Further reading on Tubulins

- Arnst KE *et al.* (2019) Current advances of tubulin inhibitors as dual acting small molecules for cancer therapy. *Med Res Rev* **39**: 1398–1426 [PMID:30746734]
- Eshun-Wilson L. (2019) Effects of alpha-tubulin acetylation on microtubule structure and stability. *Proc Natl Acad Sci U S A* **116**: 10366–10371 [PMID:31072936]
- Gadadhar S *et al.* (2017) The tubulin code at a glance. *J. Cell. Sci.* **130**: 1347–1353 [PMID:28325758]
- Magiera MM *et al.* (2018) Tubulin Posttranslational Modifications and Emerging Links to Human Disease. *Cell* **173**: 1323–1327 [PMID:29856952]
- Penna LS *et al.* (2017) Anti-mitotic agents: Are they emerging molecules for cancer treatment? *Pharmacol. Ther.* **173**: 67–82 [PMID:28174095]

References

1. Agrawal N *et al.* (2011) [21798897]
2. Ajit SK *et al.* (2007) [17126529]
3. Al-Hussaini H *et al.* (2011) [20971825]
4. Alduaij W *et al.* (2011) [21378274]
5. Alon A *et al.* (2017) [28559337]
6. ANDRADE C. (1952) [12978172]
7. Balendiran GK *et al.* (2000) [10854433]
8. Berman DM *et al.* (1996) [8756726]
9. Bernstein ID. (2000) [10720144]
10. Blazer LL *et al.* (2011) [21329361]
11. Bolt S *et al.* (1993) [8436176]
12. Caron PC *et al.* (1992) [1458463]
13. Carven GJ *et al.* (2010) Patent number: US20100266617.
14. Chuang S *et al.* (2008) [18533710]
15. Cifuentes M *et al.* (2006) [16504507]
16. Coelho T. (1996) [8894411]
17. Crabb JW *et al.* (1998) [9541407]
18. Cziraky MJ *et al.* (1993) [8137606]
19. da Silva AJ *et al.* (2002) [11970990]
20. De Strooper B *et al.* (1999) [10206645]
21. Eriksson BI *et al.* (1995) [7667822]
22. Friedel HA *et al.* (1994) [7528134]
23. Furuhashi M *et al.* (2007) [17554340]
24. Gangjee A *et al.* (2013) [23895532]
25. Garg V *et al.* (2005) [16025100]
26. Ginaldi L *et al.* (1998) [9593475]
27. Glick JL *et al.* (1998) [9748279]
28. Goldstein G. (1987) [3105134]
29. Gotti R *et al.* (2013) [23598032]
30. Halk EL *et al.* (2001) Patent number: WO2001014424.
31. Hall RD *et al.* (2013) [23302904]
32. Hanson DC *et al.* (2004) Human monoclonal antibodies to CTLA-4. Patent number: US6682736 B1.
33. Hertz AV *et al.* (2009) [19754198]
34. Hohoff C *et al.* (1999) [10493790]
35. Holmer E *et al.* (1986) [3744129]
36. Hug C *et al.* (2004) [15210937]
37. Jacobson DR *et al.* (1997) [9017939]
38. James LI *et al.* (2013) [23292653]
39. Kanji S *et al.* (2001) [11714212]
40. Kapur S *et al.* (2001) [11463021]
41. Kimple RJ *et al.* (2001) [11387333]
42. Kline J *et al.* (2010) [21154117]
43. Korman AJ *et al.* (2006) Patent number: WO2006121168.
44. Latek R *et al.* (2009) [19300198]
45. Lee JK *et al.* (2015) [26123306]
46. Lefort K *et al.* (2007) [17344417]
47. Lehmann BD *et al.* (2015) [25993190]
48. Lever JR *et al.* (2006) [16463398]
49. Linder ME *et al.* (2007) [17183362]
50. Linke R *et al.* (2010) [20190561]
51. Linsley PS *et al.* (1991) [1714933]
52. Liu Q. (2013) Fully human antibodies against human cd20. Patent number: WO2013007052.
53. Liu X *et al.* (2011) [21481589]
54. Luistro L *et al.* (2009) [19773430]
55. Mach RH *et al.* (1999) [10096443]
56. Machbub B *et al.* (1988) [24248795]
57. Maeda K *et al.* (1996) [8619847]
58. Majava V *et al.* (2010) [20421974]
59. Mao H *et al.* (2004) [15096504]
60. Matsumoto RR *et al.* (1995) [8566098]
61. McBride KL *et al.* (2008) [18593716]
62. Mitchell P. (2002) [12089534]
63. Murakami K *et al.* (1999) [10403814]
64. Nagamatsu I *et al.* (2014) [24403446]
65. Nakase J *et al.* (2009) [19398784]
66. Nam Y *et al.* (2006) [16530044]
67. Narayan S *et al.* (2011) [21324687]
68. Ntziachristos P *et al.* (2014) [24651013]
69. Nunn C *et al.* (2006) [16765607]
70. Okuyama S *et al.* (1993) [7901723]
71. Ouyang X *et al.* (2006) [16377187]
72. Paolucci F *et al.* (2002) [12383040]
73. Penchala SC *et al.* (2013) [23716704]
74. Previs RA *et al.* (2015) [25388163]
75. Puente XS *et al.* (2011) [21642962]
76. Reslan L *et al.* (2014) [23537278]
77. Richieri GV *et al.* (1994) [7929039]
78. Richieri GV *et al.* (2000) [10852718]
79. Sacchettini JC *et al.* (1989) [2671390]
80. Schiff ML *et al.* (2000) [11130074]
81. Schmidt HR *et al.* (2016) [27042935]
82. Schroeder F *et al.* (2008) [17882463]
83. Schroeter EH *et al.* (1998) [9620803]
84. SGC. I-CBP112 - a CREBBP/EP300-selective chemical probe.
85. SGC. GSK2801: A Selective Chemical Probe for BAZ2B/A bromodomains.
86. Shitara K *et al.* (2011) Patent number: US7923538 B2.
87. Siderovski DP *et al.* (2005) [15951850]
88. Sjölund J *et al.* (2008) [18079963]
89. Snow BE *et al.* (2002) [11771424]
90. Snow BE *et al.* (1998) [9651375]
91. Stein R *et al.* (2004) [15102696]
92. Stittrich AB *et al.* (2014) [25132448]
93. Stransky N *et al.* (2011) [21798893]
94. Strosberg JR *et al.* (2012) [22445247]
95. Structural Genomics Consortium. PFI-3: Selective chemical probe for SMARCA bromodomains.
96. Su TP *et al.* (1991) [1658302]
97. Sulsky R *et al.* (2007) [17502136]
98. Tanabe H *et al.* (2015) [25855295]
99. Tesmer JJ *et al.* (1997) [9108480]
100. Tesmer JJ *et al.* (1997) [9417641]
101. Thompson J *et al.* (1997) [9054409]
102. Turner EM *et al.* (2012) [22368763]
103. Vicente Rabaneda EF *et al.* (2013) [23899231]
104. Vilimas T *et al.* (2007) [17173050]
105. Wang J *et al.* (1998) [9748280]
106. Wang Y *et al.* (2014) [24835984]
107. Weng AP *et al.* (2004) [15472075]
108. Westermarck P *et al.* (1981) [7016817]
109. Wilson JJ *et al.* (2006) [16530045]
110. Wong YH *et al.* (1992) [1347957]
111. Yamauchi T *et al.* (2003) [12802337]
112. Young AC *et al.* (1994) [7922029]