The Concise Guide to Pharmacology 2017/18: Overview

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.

In addition to this overview, in which are identified 'Other protein targets' which fall outside of the subsequent categorisation, there are eight as 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 represent a nomenclature 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 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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Searchable database: http://www.guidetopharmacology.org/index.jsp

Overview S1

Introduction

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, the host of the www.guidetopharmacology.org website, previously the International Union of Basic and Clinical Pharmacology (IUPHAR) and now also International Union of Basic and Clinical Pharmacology (NC-IUPHAR). The database is supported by the British Pharmacological Society (BPS), the International Union of Basic and Clinical Pharmacology (IUPHAR), 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. 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 overview of the major pharmacological targets. Thus, there are many fewer targets presented in the Concise Guide compared to other international and national resources. The Concise Guide is intended for students and teaching staff, and support from NC-IUPHAR subcommittees will provide the necessary and appropriate advice and consent from the NC-IUPHAR subcommittees. The tables allow an indication of the status of the nomenclature for the group of targets listed, with a caution to establish the curators as a team of highly experienced and knowledgeable individuals, with a focus on high-quality data input, creating a standardised and usable dataset. The editors of the Concise Guide have compiled the individual records, in consultation with the team of curators, drawing on the expert knowledge of the NC-IUPHAR subcommittees. The priority for inclusion in the Concise Guide is the presence of quantitative pharmacological data. This is derived from references that form the authoritative consensus on nomenclature. The Concise Guide contains data from the online database as a rapid update of the Concise Guide to PHARMACOLOGY 2015/16. It contains data downstream from the Concise Guide to PHARMACOLOGY 2015/16. The tables, developed by the Concise Guide to PHARMACOLOGY 2015/16, are divided into nine sections, which comprise pharmacological targets. These are G protein-coupled receptors, ion channels, nuclear hormone receptors, enzymes, transporters and other protein targets. We hope that the Concise Guide will provide easy access to the most relevant and authoritative information to those interested in the field of pharmacology, whether in the near future. The Concise Guide is intended for students and teaching staff, and support from NC-IUPHAR subcommittees will provide the necessary and appropriate advice and consent from the NC-IUPHAR subcommittees.

Acknowledgements


In order to allow clarity and consistency in pharmacology, there is a need for comprehensive organisation and presentation of the data and tools within the Concise Guide. The Concise Guide, as a companion to the Concise Guide to PHARMACOLOGY 2015/16, produces an authoritative consensus on nomenclature, which are both available by donation or from commercial sources. The Concise Guide has been significantly expanded to include the construction of the Concise Guide to PHARMACOLOGY 2017/18 and the online database. The priority for inclusion in the Concise Guide is the presence of quantitative pharmacological data. This is derived from references that form the authoritative consensus on nomenclature. The Concise Guide contains data from the online database as a rapid update of the Concise Guide to PHARMACOLOGY 2015/16. The tables, developed by the Concise Guide to PHARMACOLOGY 2015/16, are divided into nine sections, which comprise pharmacological targets. These are G protein-coupled receptors, ion channels, nuclear hormone receptors, enzymes, transporters and other protein targets. We hope that the Concise Guide will provide easy access to the most relevant and authoritative information to those interested in the field of pharmacology, whether in the near future. The Concise Guide is intended for students and teaching staff, and support from NC-IUPHAR subcommittees will provide the necessary and appropriate advice and consent from the NC-IUPHAR subcommittees.

Conflict of interest

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

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Adiponectin receptors

Other protein targets

Overview: Adiponectin receptors (provisional nomenclature)

Adiponectin receptors

Overview: Adiponectin receptors (provisional nomenclature)

Protein Targets

Overview: Adiponectin receptors (provisional nomenclature)
Blood coagulation components

<table>
<thead>
<tr>
<th>Coagulation factors</th>
<th>Selective activators</th>
<th>Selective inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>FV (F8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FIX (F7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FII (F5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FVIII (F8)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Further reading on Blood coagulation components


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


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

Non-enzymatic BRD containing proteins

Overview

Bromodomain-containing proteins with acetylated lysine residues, such as histones, regulate gene transcription. List of bromodomain-containing proteins for which sufficient pharmacology exists.

### Nomenclature

- **bromodomain adjacent to zinc finger domain 2A**
  - Nomenclature: BAZ2A
  - HGNC: Q9UIF9

- **bromodomain adjacent to zinc finger domain 2B**
  - Nomenclature: BAZ2B
  - HGNC: Q9UIF8

- **CREB binding protein polybromo 1**
  - Nomenclature: CREBBP
  - HGNC: Q92793

- **SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4**
  - Nomenclature: SMARCA4
  - HGNC: P51532

### Selective inhibitors

- **GSK2801 (pKd 6.6)**
  - Reference: 73

- **I-CBP112 (pKd 6.8)**
  - Reference: 72

- **PFI-3 (pKd 7.3)**
  - Reference: 79

- **PFI-3 (pKd 7.1)**
  - Reference: 79

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


Other protein targets

CD molecules

Overview: Cluster of differentiation refers to a group of over 300 cell-surface proteins associated with immunophenotyping. Many members of the family have important functions of proliferation, development, and adhesion.

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

Full contents of Concise Guide: http://www.guidetopharmacology.org/index.jsp

Further reading on Carrier proteins


CD2 molecules

| CD2 | CD3 | CD4 | CD5 | CD6 | CD7 | CD8 | CD9 | CD10 | CD11a | CD11b | CD11c | CD12 | CD13 | CD14 | CD15 | CD16 | CD17 | CD18 | CD19 | CD20 | CD21 | CD22 | CD23 | CD24 | CD25 | CD26 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|-------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| —   | —   | —   | —   | —   | —   | —   | —   | —   | —     | —     | —     | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    |
| —   | —   | —   | —   | —   | —   | —   | —   | —   | —     | —     | —     | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    | —    |

HGNC, UniProt

CD2, P06729
CD3E, P07766
MS4A1, P11836
CD33, P20138
CD52, P31358

Common abbreviation

– SIGLEC-3 –

Selective inhibitors

alefacept (Inhibition) [17, 53] –

Antibodies –
catumaxomab (Binding) [43],
muromonab-CD3 (Binding) [25],
otelixizumab (Binding) [9],
ofatumumab (Binding) (pKd 9.9) [47],
rituximab (Binding) (pKd 8.5) [75],
ibritumomab tiuxetan (Binding),
obinutuzumab (Binding) [3, 66],
tositumomab (Binding)
lintuzumab (Binding) (pKd ∼10) [10],
gemtuzumab ozogamicin (Binding) [7]

alemtuzumab (Binding) [24, 79]

Accessibility of protein targets is limited by cell-surface expression of the family members. The family includes many members of the family that are expressed on the surface of various cell types, including lymphocytes, macrophages, and neutrophils.

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 (pKd > 9) [28]
- tremelimumab (pKd 8.9) [30]
- pembrolizumab (pKd ∼10) [11], nivolumab (pKd 9.1) [28, 38, 40]

Comment:
The endogenous ligand for human PD-1 is programmed cell death 1 ligand 1 (PD-L1, aka 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. Effective anti-PD-1 antibodies include pembrolizumab, nivolumab, and atezolizumab.

Further reading on CD molecules:

Further reading on Methyllysine reader proteins:

Searchable database:
http://www.guidetopharmacology.org/index.jsp
Fatty acid-binding proteins

Other protein targets

→ Fatty acid-binding proteins

Overview: Fatty acid-binding proteins are low molecular weight proteins involved in aqueous medium as chaperones for long chain fatty acids, fatty acyl CoA esters, eicosanoids, retinols, retinoic acids, and related metabolites. These binding proteins may perform extracellular functions (e.g. in plasma) or transport agents to the nucleus to interact with nuclear receptors (principally PPARs and retinoic acid receptors) or for interaction with metabolic enzymes.

Nomenclature

- Fatty acid binding protein 1 (FABP1)
  - HGNC, UniProt: FABP1, P07148
- Fatty acid binding protein 2 (FABP2)
  - HGNC, UniProt: FABP2, P12104
- Fatty acid binding protein 3 (FABP3)
  - HGNC, UniProt: FABP3, P05413
- Fatty acid binding protein 4 (FABP4)
  - HGNC, UniProt: FABP4, P15090

Rank order of potency:

- Stearic acid > Palmitic acid, Oleic acid
- Linoleic acid > Arachidonic acid, α-Linolenic acid

Inhibitors

- Fenofibrate ($pK_{i}$ 7.6) [12]
- Fenofibric acid ($pK_{i}$ 6.5) [12]
- HTS01037 ($pK_{i}$ 5.1) [30]

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].
- In silico modelling suggests that PMP2/FABP8 can bind both fatty acids and cholesterol [50].


Searchable database: http://www.guidetopharmacology.org/index.jsp
Nomenclature

- Retinol binding protein 1 (RBP1, P09455)
- Retinol binding protein 2 (RBP2, P50120)
- Retinol binding protein 3 (RBP3, P10745)
- Retinol binding protein 4 (RBP4, P02753)
- Retinol binding protein 5 (RBP5, P82980)
- Retinol binding protein 7 (RBP7, Q96R05)

Rank order of potency:
- Stearic acid > Palmitic acid, Oleic acid, Linoleic acid, α-Linolenic acid, Arachidonic acid

Inhibitors:
- A1120 (pIC₅₀ 7.8)

Comments: Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC₅₀ 8.8) compared to FABP3 or FABP5 (pIC₅₀ < 6.6). HTS01037 is reported to interfere with FABP4 action. Ibuprofen displays some selectivity for FABP4 (pIC₅₀ 5.5) relative to FABP3 (pIC₅₀ 3.5) and FABP5 (pIC₅₀ 3.8). Fenofibric acid displays some selectivity for FABP5 (pIC₅₀ 5.5) relative to FABP3 (pIC₅₀ 4.5) and FABP4 (pIC₅₀ 4.6).

Further reading on Fatty acid-binding proteins:
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 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].

Regulators of G protein Signalling (RGS) proteins

Overview: Regulators of G protein signalling (RGS) proteins

Regulators of G protein signalling (RGS) proteins increase the deactivation rate of G protein-coupled receptors through enhancing the GTPase activity of the G protein alpha subunit. Interactions through protein:protein interactions of many RGS proteins have been described. The 20 RGS proteins are commonly divided into our 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.

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

Further reading on Notch receptors


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 suggests a trimeric structure consisting of a single 7 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 –
Selective agonists
PRE-084
(pIC50 8.4) [60], (+)-SKF 10.047 –
Selective antagonists
NE-100
(pIC50 7.4) [51] –
Labelled ligands
[3H]pentazocine (Agonist)
[3H]-di-o-tolylguanidine (Agonist)

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

Further reading on Sigma receptors
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 they function as targets for agents derived from a variety of natural products: taxanes, colchicine and vinca alkaloids. These are thought to primarily interfere with the normal processes of tubulin polymer formation and disassembly.

Tubulins

Nomenclature

<table>
<thead>
<tr>
<th>Tubulin</th>
<th>HGNC</th>
<th>UniProt</th>
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</thead>
<tbody>
<tr>
<td>α1a</td>
<td>TUBA1A</td>
<td>Q71U36</td>
</tr>
<tr>
<td>α4a</td>
<td>TUBA4A</td>
<td>P68366</td>
</tr>
<tr>
<td>β1</td>
<td>TUBB</td>
<td>P07437</td>
</tr>
<tr>
<td>β3</td>
<td>TUBB3</td>
<td>Q13509</td>
</tr>
<tr>
<td>β4B</td>
<td>TUBB4B</td>
<td>P68371</td>
</tr>
<tr>
<td>β8</td>
<td>TUBB8</td>
<td>Q3ZCM7</td>
</tr>
</tbody>
</table>

Inhibitors

- vinblastine (pIC50 9)
- vincristine
- eribulin (pIC50 8.2)
- paclitaxel (pEC50 8.1)
- colchicine (pIC50 8)
- cabazitaxel
- docetaxel
- ixabepilone
- combretastatin A4 (pIC50 8.2)

Further reading on Tubulins

