ACS Chemical Neuroscience

VIEWPOINT

pubs.acs.org/acschemicalneuroscience

IUPHAR-DB: An Open-Access, Expert-Curated Resource for Receptor and Ion Channel Research

Joanna L. Sharman* and Chidochangu P. Mpamhanga*

University/BHF Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, EH16 4TJ, United Kingdom

ABSTRACT: This contribution highlights efforts by the International Union of Basic and Clinical Pharmacology (IUPHAR) Nomenclature Committee (NC-IUPHAR) to classify human receptors and ion channels, to document their properties, and to recommend ligands that are useful for characterization. This effort has inspired the creation of an online database (IUPHAR-DB), which is intended to provide free information to all scientists, summarized from primary literature by experts.

KEYWORDS: Drug target, chemical tool, GPCR, ion channel, biocuration, database

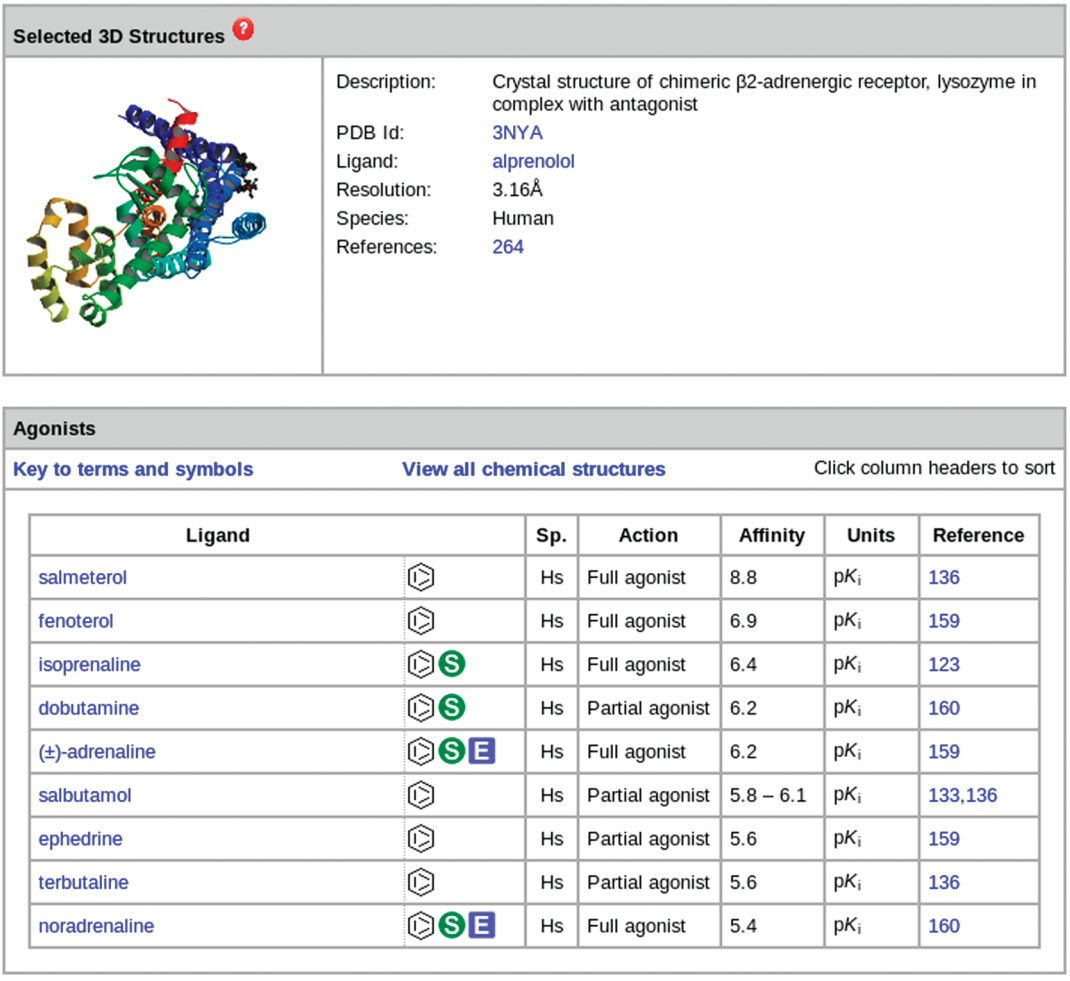
The recent explosion in data generation from high-throughput studies (ligand-screening, genomic and proteomic data sets) as well as the sheer volume of scientific literature represents an enormous, largely untapped data mine relevant to drug discovery and drug target research in neuroscience. Maximizing the benefits of the information requires researchers to keep abreast of new developments in an increasingly complex area and to quickly extract their meaning. There is a fundamental need for resources which distill available data into an easy-to-digest format, identifying the most important information, standardizing it, integrating it with other, often disparate, data sources, placing it in context, and making authoritative recommendations about the data. This time intensive process forms a significant part of what is now referred to as "data curation", which we believe is essential to building trusted public scientific information resources.

In today's interdisciplinary information age, basic pharmacological research can no longer be considered separate from, but must form an integral part of, the rational drug discovery cycle. Discoveries from basic science are essential inputs to the drug development process, and pharmaceutical companies are increasingly recognizing the value of sustained academic and collaborative precompetitive research into drug targets.[1] Such a multidisciplinary, translational approach to pharmacology and drug discovery would benefit from having community-developed public-domain knowledge bases and repositories for information from literature.[2] These would ideally provide details and recommendations on all factors that may influence drug targets and their interactions with ligand molecules, at species, individual, and cellular levels. This would expand the available target information, defining drug targets in their biological contexts and increasing awareness of the range of targets which interact with each compound. Large data warehouses of chemical information such as PubChem[3] and ChemSpider[4] and medicinal chemistry databases such as ChEMBL[5] exist to catalog the vast chemistry space. However, there remains a need for focused public-domain resources to identify the most commonly used chemical tools and drugs and connect them to data on biological targets and clinical relevance.

The International Union of Basic and Clinical Pharmacology (IUPHAR) Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), a voluntary, nonprofit association, issues guidelines for the classification and naming of human receptors and ion channels.[6] Their mission is to provide recommendations for pharmacology (e.g., refs 7 and 8), to distill relevant data from literature on receptors and their properties, to disseminate the information publicly, and to provide a platform for experts to discuss current issues. Their work is communicated through an online database, IUPHAR-DB (http://www.iuphar-db.org), which is intended to provide free information on human drug targets to scientists anywhere in the world.[9] IUPHAR-DB is driven by an expert curation model relying on NC-IUPHAR's >60 subcommittees of international experts (numbering ~700 individuals from academia and industry).

By engaging experts in the data curation process, NC-IUPHAR is trying to address one of the significant issues in drug discovery today: that of identifying the repertoire of human drug targets. In this endeavor, it is essential to recognize all of the factors that can influence receptor structure, function, expression, and pharmacology. Drug targets are defined in a broader sense than "single gene products" to encompass other variables which affect function. Factors that contribute to the definition of a unique target include the particular sequence variant(s) present; specific tissue and subcellular location; a given combination of subunits, cofactors, and ligands; presence of post-translational modifications; pathophysiological context; and the downstream signaling pathway being initiated. These can vary across species, individual, tissue, developmental stage, and disease to give rise to a much more diverse range of potential drug targets than are specified at the gene level. Moreover, there is increasing evidence that ligand selection can influence the specific downstream pathways affected and therefore the functions mediated (for a recent review, see ref 10).

Received: March 11, 2011
Accepted: March 14, 2011
Published: May 18, 2011



Selected 3D Structures

Description: Crystal structure of chimeric β2-adrenergic receptor, lysozyme in complex with antagonist
PDB Id: 3NYA
Ligand: alprenolol
Resolution: 3.16Å
Species: Human
References: 264

Agonists

Key to terms and symbols | View all chemical structures | Click column headers to sort

Ligand	Sp.	Action	Affinity	Units	Reference
salmeterol	Hs	Full agonist	8.8	pK_i	136
fenoterol	Hs	Full agonist	6.9	pK_i	159
isoprenaline	Hs	Full agonist	6.4	pK_i	123
dobutamine	Hs	Partial agonist	6.2	pK_i	160
(±)-adrenaline	Hs	Full agonist	6.2	pK_i	159
salbutamol	Hs	Partial agonist	5.8 – 6.1	pK_i	133,136
ephedrine	Hs	Partial agonist	5.6	pK_i	159
terbutaline	Hs	Partial agonist	5.6	pK_i	136
noradrenaline	Hs	Full agonist	5.4	pK_i	160

Figure 1. Part of the β2-adrenoceptor database page showing the 3D structure along with an expert-selected set of receptor agonists.

IUPHAR-DB has been developed with these principles strongly in mind. Thus, as the concept of "drug target" gradually evolves, so the database is constantly evaluated, revised, and shaped by the scientific community. Presently, the database includes the products of over 600 human genes (and their rodent orthologs) from four superfamilies: G protein-coupled receptors (GPCRs), nuclear hormone receptors (NHRs), and voltage- and ligand-gated ion channels.[11] Members of these protein families constitute the targets of at least a third of licensed therapeutic drugs, as well as several drugs of abuse.[12] IUPHAR-DB also lists proteins with sequence/structural similarities to known receptors but which do not yet have identified endogenous ligands (such as orphan GPCRs), which may nonetheless be of interest as drug targets. The NC-IUPHAR Evolving Pharmacology subcommittee debates the evidence for and issues guidelines on the acceptance of ligand−receptor pairings, with updates broadcast on the Web site.

Information provided on target proteins in IUPHAR-DB covers a diversity of subjects, including the NC-IUPHAR recommended nomenclature, other names found in literature, details of structure, function, expression, clinical relevance, genetic, and splice variants, genetically modified mouse models, ion channel conductance, GPCR signaling mechanisms, NHR target genes, natural ligands, experimental drug tools, and functional assays. Full text search functionality is provided. Most importantly, all data are linked to their primary references in PubMed as well as to further sources of information, for example, UniProt,[13] Ensembl,[14] Entrez Gene and Protein,[15] OMIM,[16] and ChEMBL.

Central to the target concept is the need for appropriate knowledge and recommendations on endogenous and experimental ligands/drugs. This includes documenting their actions (e.g., agonist, antagonist, allosteric regulator, ion channel blocker, or gating inhibitor) and their wider activity spectrum (cross-reactivity and off-target effects), which is of interest to both drug discovery and basic experimental science. An example of how this information is displayed for the β2-adrenoceptor can be seen in Figure 1.

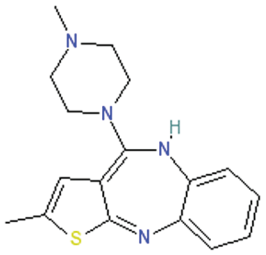
IUPHAR-DB provides curated sets of compounds, their pharmacological actions, and activity data represented as IC_{50}, K_i, K_d, and EC_{50} (as appropriate), linked to their primary literature sources. These include ligands commonly or historically used in experiments, approved drugs, and radio-labeled probes (including 1750 small molecules, 900 peptides, and 80 natural products). Each ligand is represented (where possible) by a common name, synonyms, SMILES strings containing chiral specifications, InChI and InChI Keys, systematic names, and two-dimensional (2D) images. Figure 2 is a screenshot of part of a ligand page showing the bioactivity data and physicochemical properties of the drug olanzapine. Various calculated physicochemical properties are provided, including the five Lipinski

dx.doi.org/10.1021/cn200025w |ACS Chem. Neurosci. 2011, 2, 232–235

IUPHAR-DB Ligand: 47

Ligand name	olanzapine

2D Structure



Calculated Physical-Chemical Properties

Hydrogen bond acceptors	4
Hydrogen bond donors	1
Rotatable bonds	1
Topological polar surface area	59.11
Molecular weight	312.14
XLogP	3.51
No. Lipinski's rules broken	0

Molecular properties generated using the CDK

Summary | **Biological activity** | References | Structure | Similar ligands

Selectivity at human GPCRs

Key to terms and symbols — Click column headers to sort

Receptor	Type	Action	Affinity	Units	Concentration range (M)	Reference
H_1	Antagonist	Antagonist	8.7 – 9.2	pK_i	-	2,4
5-HT_{2A}	Antagonist	Antagonist	8.6 – 8.7	pK_i	-	2,4-5
5-HT_{2C}	Antagonist	Inverse agonist	8.1 – 8.2	pK_i	-	4,6
5-HT_6	Antagonist	Inverse agonist	8.0	pK_i	-	7,9
5-HT_{1F}	Agonist	Full agonist	6.5	pK_i	-	2
5-HT_7	Antagonist	Antagonist	6.5	pK_i	-	10
5-HT_{1B}	Agonist	Full agonist	6.3	pK_i	-	2
5-HT_{1D}	Agonist	Full agonist	6.2	pK_i	-	2
5-HT_{1A}	Agonist	Full agonist	5.6 – 5.8	pK_i	-	1-2
5-ht_{1e}	Agonist	Full agonist	5.7	pK_i	-	2

Figure 2. Part of the ligand page for the drug olanzapine, displaying the calculated physicochemical properties and a summary of the literature reporting its binding activity at human GPCRs.

"drug-likeness" measures:[17] polar surface area, predicted LogP, molecular weight, and number of hydrogen bond donors and acceptors. Integrated links provide access to supplementary knowledge in other online resources with biological, chemical, and structural information (e.g., DrugBank,[18] RCSB Protein Data Bank,[19] PubChem, and ChEMBL).

Figure 3 shows that, in terms of their physicochemical profiles, the majority of small molecule compounds in the database obey the Lipinski drug-likeness rules, with greater than 80% of the compounds breaking fewer than two rules.

IUPHAR-DB is widely used as a quick online reference resource for neuroscientists looking for information relevant to pharmacology and drug discovery. Other useful features include the ability to launch a chemical editor and search tool (from the interactive ligand image or from a link on the page sidebar), allowing structures to be modified and used as queries for structure-based searching. This is the first of a series of planned improvements designed to make the information more accessible. Ongoing work aims to curate the IUPHAR-DB peptide ligands, which remain under-represented in terms of structural properties and searchability. We also intend to broaden the target coverage and to enhance chemical information by providing expert-recommended sets of chemical tools with optimum profiles for practical use in *in vitro* and *in vivo* test systems.

dx.doi.org/10.1021/cn200025w |*ACS Chem. Neurosci.* 2011, 2, 232–235

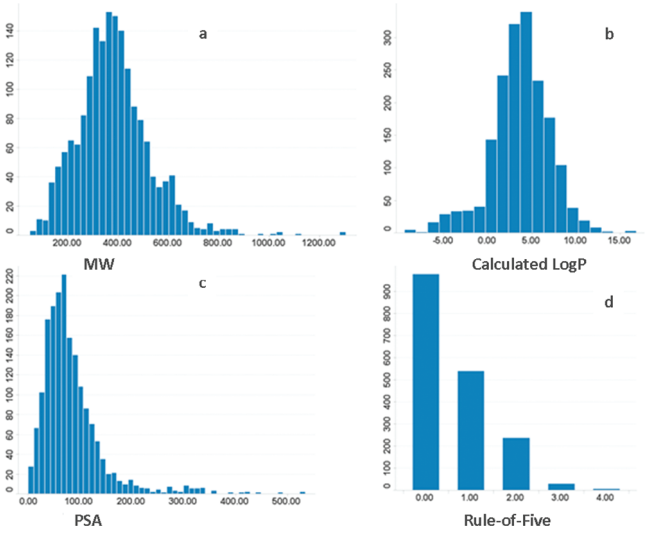


Figure 3. Physicochemical properties of the IUPHAR-DB small molecule ligands, indicating the molecular weight (MW) (a), calculated LogP (b), polar surface area (PSA) (c), and Lipinski's rule-of-five (d). The *y*-axes represent the number of compounds.

AUTHOR INFORMATION

Corresponding Author

*E-mail: curators@iuphar-db.org.

Funding Sources

IUPHAR-DB has been developed with financial support from the British Pharmacological Society, Abbott, GlaxoSmithKline, Incyte, Millipore, Novartis, Servier, UNESCO, and Wyeth.

ACKNOWLEDGMENT

The authors thank all contributors and members of NC-IUPHAR and its subcommittees for their ongoing support. NC-IUPHAR members: S. P. H. Alexander, T. I. Bonner, W. A. Catterall, A. P. Davenport, C. T. Dollery, S. Enna, P. Germain, A. J. Harmar, V. Laudet, A. Mathie, R. R. Neubig, E. H. Ohlstein, J. Peters, U. Ruegg, D. B. Searls, P. du Souich, M. Spedding, and M. W. Wright.

ABBREVIATIONS

IUPHAR, International Union of Basic and Clinical Pharmacology; NC-IUPHAR, IUPHAR Committee on Receptor Nomenclature and Drug Classification.

REFERENCES

(1) Hughes, B. (2008) Pharma pursues novel models for academic collaboration. *Nat. Rev. 7*, 631–632.

(2) Barnes, M. R., Harland, L., Foord, S. M., Hall, M. D., Dix, I., Thomas, S., Williams-Jones, B. I., and Brouwer, C. R. (2009) Lowering industry firewalls: pre-competitive informatics initiatives in drug discovery. *Nat. Rev. 8*, 701–708.

(3) Wang, Y., Xiao, J., Suzek, T. O., Zhang, J., Wang, J., and Bryant, S. H. (2009) PubChem: a public information system for analyzing bioactivities of small molecules. *Nucleic Acids Res. 37*, W623–633.

(4) ChemSpider, http://www.chemspider.com/.

(5) Overington, J. (2009) ChEMBL. An interview with John Overington, team leader, chemogenomics at the European Bioinformatics Institute Outstation of the European Molecular Biology Laboratory (EMBL-EBI). Interview by Wendy A. Warr. *J. Comput.-Aided Mol. Des. 23*, 195–198.

(6) NC-IUPHAR, http://www.iuphar.org/nciuphar.html.

(7) Pin, J. P., Neubig, R., Bouvier, M., Devi, L., Filizola, M., Javitch, J. A., Lohse, M. J., Milligan, G., Palczewski, K., Parmentier, M., and Spedding, M. (2007) International Union of Basic and Clinical Pharmacology. LXVII. Recommendations for the recognition and nomenclature of G protein-coupled receptor heteromultimers. *Pharmacological reviews 59*, 5–13.

(8) Collingridge, G. L., Olsen, R. W., Peters, J., and Spedding, M. (2009) A nomenclature for ligand-gated ion channels. *Neuropharmacology 56*, 2–5.

(9) Harmar, A. J., Hills, R. A., Rosser, E. M., Jones, M., Buneman, O. P., Dunbar, D. R., Greenhill, S. D., Hale, V. A., Sharman, J. L., Bonner, T. I., Catterall, W. A., Davenport, A. P., Delagrange, P., Dollery, C. T., Foord, S. M., Gutman, G. A., Laudet, V., Neubig, R. R., Ohlstein, E. H., Olsen, R. W., Peters, J., Pin, J. P., Ruffolo, R. R., Searls, D. B., Wright, M. W., and Spedding, M. (2009) IUPHAR-DB: the IUPHAR database of G protein-coupled receptors and ion channels. *Nucleic Acids Res. 37*, D680–685.

(10) Spedding, M. (2011) Resolution of controversies in drug/receptor interactions by protein structure. Limitations and pharmacological solutions. *Neuropharmacology 60*, 3–6.

(11) Sharman, J. L., Mpamhanga, C. P., Spedding, M., Germain, P., Staels, B., Dacquet, C., Laudet, V., and Harmar, A. J. (2011) IUPHAR-DB: new receptors and tools for easy searching and visualization of pharmacological data. *Nucleic Acids Res. 39*, D534–538.

(12) Hopkins, A. L., and Groom, C. R. (2002) The druggable genome. *Nature Rev. 1*, 727–730.

(13) UniProt Consortium. (2011) Ongoing and future developments at the Universal Protein Resource. *Nucleic Acids Res. 39*, D214–219.

(14) Flicek, P., Amode, M. R., Barrell, D., Beal, K., Brent, S., Chen, Y., Clapham, P., Coates, G., Fairley, S., Fitzgerald, S., Gordon, L., Hendrix, M., Hourlier, T., Johnson, N., Kahari, A., Keefe, D., Keenan, S., Kinsella, R., Kokocinski, F., Kulesha, E., Larsson, P., Longden, I., McLaren, W., Overduin, B., Pritchard, B., Riat, H. S., Rios, D., Ritchie, G. R., Ruffier, M., Schuster, M., Sobral, D., Spudich, G., Tang, Y. A., Trevanion, S., Vandrovcova, J., Vilella, A. J., White, S., Wilder, S. P., Zadissa, A., Zamora, J., Aken, B. L., Birney, E., Cunningham, F., Dunham, I., Durbin, R., Fernandez-Suarez, X. M., Herrero, J., Hubbard, T. J., Parker, A., Proctor, G., Vogel, J., and Searle, S. M. (2011) Ensembl 2011. *Nucleic Acids Res. 39*, D800–806.

(15) Sayers, E. W., Barrett, T., Benson, D. A., Bolton, E., Bryant, S. H., Canese, K., Chetvernin, V., Church, D. M., Dicuccio, M., Federhen, S., Feolo, M., Geer, L. Y., Helmberg, W., Kapustin, Y., Landsman, D., Lipman, D. J., Lu, Z., Madden, T. L., Madej, T., Maglott, D. R., Marchler-Bauer, A., Miller, V., Mizrachi, I., Ostell, J., Panchenko, A., Pruitt, K. D., Schuler, G. D., Sequeira, E., Sherry, S. T., Shumway, M., Sirotkin, K., Slotta, D., Souvorov, A., Starchenko, G., Tatusova, T. A., Wagner, L., Wang, Y., John Wilbur, W., Yaschenko, E., and Ye, J. (2010) Database resources of the National Center for Biotechnology Information. *Nucleic Acids Res. 38*, D5–16.

(16) Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/omim.

(17) Lipinski, C. A., Lombardo, F., Dominy, B. W., and Feeney, P. J. (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev. 46*, 3–26.

(18) Wishart, D. S., Knox, C., Guo, A. C., Cheng, D., Shrivastava, S., Tzur, D., Gautam, B., and Hassanali, M. (2008) DrugBank: a knowledgebase for drugs, drug actions and drug targets. *Nucleic Acids Res. 36*, D901–906.

(19) Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., and Bourne, P. E. (2000) The Protein Data Bank. *Nucleic Acids Res. 28*, 235–242.