

Chapter 2

How to Use the IUPHAR Receptor Database to Navigate Pharmacological Data

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Abstract

Today's data-intensive, interdisciplinary research challenges scientists to keep up to date with key experimental techniques and tools reported in the literature. The International Union of Basic and Clinical Pharmacology Database (IUPHAR-DB) goes some way to addressing this need by providing expert-curated information sourced from primary literature and displayed in a user-friendly manner online. The database provides a channel for the IUPHAR Nomenclature Committee (NC-IUPHAR) to provide recommendations on the nomenclature of receptors and ion channels, to document their properties and the ligands that are useful for receptor characterization. Here we describe IUPHAR-DB's main features and provide examples of techniques for navigating and exploring the information. The database is freely available online at <http://www.iuphar-db.org/>.

Key words: Drug target, Receptor, GPCR, Nuclear receptor, Ion channel, Pharmacology, Ligand, Experimental tool, Biocuration, Database

1. Introduction

Recent technological developments have led to an increase in the amount of information available to the laboratory research scientist. However, this information is often trapped in traditional forms of scientific publications and supplementary tables or, in the case of

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high-throughput campaigns (such as ligand screening, genomic, and proteomic datasets), in large data warehouses and repositories. To allow for effective navigation through these complex data, there is a necessity for well-curated, easy-to-access, focused, and trusted public-domain resources which identify, distil, standardize, integrate, and contextualize the essential information. For instance, such a resource would enable the novice researcher (or those conducting investigations into new areas) to identify pertinent literature, clarify nomenclature issues, categorize the available assays, and isolate the most useful experimental tools (including chemical tools, drugs, and radioligands) and procedures. In addition the resource would provide research leaders with a platform to offer clear recommendations to the scientific community on issues relating to their fields of expertise. Using the IUPHAR database (1) as an example, this chapter provides an illustration of how scientists could accelerate their research by taking advantage of online information from an expert-curated pharmacological database.

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 (2). Its mission is to provide recommendations for pharmacology, to extract 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. Its work is communicated through an online database, IUPHAR-DB, which is intended to provide free information on human drug targets to scientists anywhere in the world. 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).

IUPHAR-DB contains information on proteins from four superfamilies: G protein-coupled receptors (GPCRs), nuclear hormone receptors (NHRs), voltage-gated ion channels (VGICs), and ligand-gated ion channels (LGICs) ("drug targets") encoded by the human, mouse, and rat genomes (3). 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). Members of these protein families constitute the targets of at least a third of licensed therapeutic drugs, as well as several drugs of abuse (4). The data documented covers structural, functional, physiological, pathophysiological, and pharmacological aspects, with particular emphasis on reporting the activities of high-affinity and selective experimental tools frequently used to characterize protein targets in the laboratory.

NC-IUPHAR is committed to regularly updating the information, to increase the target coverage, and to issue further recommendations

on useful ligands with the ultimate aim of designing a “gold standard” set of experimental tools for benchmarking and ongoing use in the laboratory.

2. Materials

2.1. Receptor and Ion Channel Information

Presently, the database includes information on the protein products of over 600 human genes (and their rodent orthologues) including 351 GPCRs, 140 VGIC subunits, 70 LGIC subunits, and 48 NHRs, along with associated data on approximately 1,750 small molecules, 900 peptides, and 80 natural products. GPCRs, NHRs, and LGICs are grouped into families according to their endogenous ligands (5–7), whereas VGICs are grouped phylogenetically (8). Each family has an introductory chapter, lists of contributors and references, and individual data pages for each family member. Receptor and ion channel data pages contain the following information, where possible:

1. Approved IUPHAR nomenclature and alongside previous and alternative names found in the literature.
2. Genomic data including approved gene names linked to the HUGO Gene Nomenclature Committee (HGNC) (9), Mouse Genome Informatics (MGI) (10), and Rat Genome Databases (RGD) (11).
3. Links to other databases including RefSeq (12), Entrez Gene (13), OMIM (14), UniProt (15), Ensembl (16), and GeneCards (17).
4. Structural information including the identities of component subunits in heteromultimeric complexes and 3-dimensional X-ray crystal structures linked to the RCSB PDB (18).
5. Tissue distribution of gene expression at the levels of mRNA, protein, and radioligand binding.
6. Tissue function (physiological responses mediated by the receptor or ion channel).
7. Functional assays (whole tissue or isolated cell systems in which a pharmacological response can be firmly attributed to the function of a defined receptor or ion channel).
8. Physiological consequences of altering gene expression (e.g., in knockout and transgenic animals).
9. Functionally important receptor variants (e.g., polymorphisms, mutations, and splice variants, which have been demonstrated to alter receptor function).
10. Clinical relevance and disease association.

11. Tables of affinity data for selected agonists, antagonists, allosteric regulators, channel blockers, and gating inhibitors: These include endogenous ligands and selected experimental compounds including commonly and historically used chemical tools, approved drugs, and radiolabeled probes, linked to their ligand database pages.

2.2. Ligand Information

Ligand pages include the following information:

1. Commonly used names.
2. Systematic names including the International Union of Pure and Applied Chemistry (IUPAC) name.
3. Database links including to DrugBank (19), PubChem (20), and ChEMBL (21).
4. Tables of bioactivity data at receptors and ion channels in IUPHAR-DB (see Note 1).
5. Structural information and identifiers including InChIs, InChI keys, and SMILES.
6. Calculated (using the Chemistry Development Kit (CDK) (22)) physicochemical properties, including the Lipinski “drug-likeness” measures (23): polar surface area, predicted LogP, molecular weight, and number of hydrogen bond donors and acceptors; the number of rotatable bonds is also given (this confers an indication of molecular flexibility and complexity).
7. Lists of similar compounds on IUPHAR-DB, pre-clustered using Pipeline Pilot (Accelrys, San Diego, CA, USA).

2.3. Other Web Site Features

Other features of the Web site include downloadable lists of receptors, Hot Topics and Latest Pairings pages, which keep track of latest developments in the field, and comprehensive search tools. Users may perform database searches by keyword, for instance, receptor or ligand name, accession number, reference, or ligand structure (utilizing MarvinSketch editor (ChemAxon Kft., Budapest, Hungary) and Pinpoint cartridge (Dotmatics Limited, Bishops Cleeve, UK) for chemical substructure, similarity, and exact match searches).

2.4. Implementation and User Requirements

IUPHAR-DB is implemented as a PostgreSQL database (24) holding receptor information and an Oracle database (Oracle Corporation, Redwood Shores, CA, USA) holding ligand information. The public Web interface has been developed using Java technology (Oracle Corporation, Redwood Shores, CA, USA), incorporating Java Servlets, Java Server Pages, and JDBC. To view IUPHAR-DB Web pages as they were intended users require a modern Web browser, such as Mozilla Firefox 3 or higher, or

Internet Explorer 7 or higher (Microsoft Corporation, Redmond, WA, USA). To use the ligand structure editor users require a browser enabled with Java 1.5 or greater. Download of receptor data files in Microsoft Excel format would require a program capable of reading this type of file. Access to data in other formats may be obtained by contacting the database curators to discuss individual requirements.

Database development and data curation are overseen by NC-IUPHAR and its network of over 60 expert subcommittees, each committee being responsible for the nomenclature and data compilation for a receptor family. Where no relevant subcommittee exists, data are captured by the curators or individual experts and peer reviewed by at least two external expert referees. Data are sourced from and referenced to the primary literature (original articles in peer-reviewed publications rather than review articles), with links to citations in PubMed (25) and supported by more than one source where possible. After review by the curators to ensure accuracy and consistency with the rest of the information in the database, the data are added to the development server and transferred to the public database, after approval by NC-IUPHAR. Data are reviewed at regular intervals by subcommittees and other contributors and updated as necessary.

3. Methods

3.1. Nomenclature

Find the approved nomenclature for the receptor encoded by the *HTR1D* gene and what (if any) other names have been used in the literature.

1. Enter the gene name into the “Quick text search” box on the left sidebar; click “Search the database” or press the Enter key (see Note 2).
2. The search results page should list the names of receptors that match the search query. Below the receptor name the matched database fields are listed; in this case these would be the human, rat, and mouse gene names, which all match the term “HTR1D” since the search is not case sensitive.
3. To access the receptor data page click on the receptor name, which is highlighted in blue to indicate a link.
4. On the receptor page, the NC-IUPHAR-approved nomenclature is indicated in large, bold letters at the top of the page (Fig. 1), in this case 5-HT_{1D} (26).
5. Other names used historically to refer to this receptor are listed under the heading “Previous and Unofficial Names” (Fig. 1);

5-HT_{1D}

Family: 5-Hydroxytryptamine receptors

Previous and Unofficial Names ?	
Names	References
5-HT _{1Dα}	86

Previous Gene Names		
Human	Rat	Mouse
HTRL	5HT1D	AI853647 Gpcr14 Htr1db

Fig. 1. Screenshot of part of the 5-HT_{1D} receptor data page showing the IUPHAR nomenclature at the top in *large bold letters*, previous and unofficial receptor names used in the literature, and previous names used to refer to the human, rat, and mouse genes.

in this case there is one name: 5-HT_{1Dα} and the reference where it was used.

- Another table, “Previous Gene Names” (Fig. 1), lists past names by which the gene was known in online databases.

3.2. Functional Heteromeric Receptors

Find out which combinations of subunits are known to form functional 5-HT₃ receptors in vivo and what in vitro assays are available to study them.

- Follow the link on the left sidebar for “Ion channel database.”
- Browse the “Ligand-gated ion channel” family list and click on “5-HT₃ receptors” (27).
- For families such as 5-HT₃ where subunits are known to combine in heteromeric receptors in vivo, the family page (Fig. 2) displays a list of subunits (5-HT3A to E) and a list of NC-IUPHAR-recognized in vivo receptors (5-HT₃AB and 5-HT₃A) (see Note 3).
- To access the database page for 5-HT₃AB click on the receptor’s name in the list.
- The “Subunits” table displays the names of subunits (linked to their database pages) which combine in the functional receptor.
- The “Functional Assays” table further down the page lists several expert-recommended in vitro assays that may be used for studying this receptor, with links to the literature for further information (see Note 4).

● Annotated and expert reviewed ● Annotated and awaiting review ● Awaiting annotation/under development ?

Voltage-gated ion channels

- Calcium-Activated Potassium Channels
- CatSper and Two-Pore Channels
- Cyclic Nucleotide-Regulated Channels
- Inwardly Rectifying Potassium Channels
- Transient Receptor Potential Channels
- Two-P Potassium Channels
- Voltage-Gated Calcium Channels
- Voltage-Gated Potassium Channels
- Voltage-Gated Sodium Channels

Ligand-gated ion channels

- **5-HT₃ receptors**
- GABA_A receptors
- Glycine receptors
- Ionotropic glutamate receptors
- Nicotinic acetylcholine receptors
- P2X receptors
- ZAC

5-HT₃ receptors

- Introduction
- Contributors
- References

Subunits

- 5-HT3A
- 5-HT3B
- 5-HT3C
- 5-HT3D
- 5-HT3E

Receptors

- 5-HT₃AB
- 5-HT₃A

To cite this receptor family data, please use the following:

John A. Peters, Sarah C. R. Lummis, Nicholas M. Barnes, Tim G. Hales, Beate Niesler.
 5-HT₃ receptors. Last modified on 2010-07-01. Accessed on 2011-03-29. IUPHAR database (IUPHAR-DB), <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=68>.

Fig. 2. A screenshot of an ion channel family page, showing the 5-HT₃ receptors. The family names shown on the *left* are each linked to their respective family pages. Family-specific information is displayed on the *right* of the page. Individual subunit and receptor pages can be accessed by clicking on their respective names. The key at the *top* of the page indicates the annotation and peer-review status of the information.

3.3. Variation and Clinical Relevance

Find out if there are any functionally relevant variants of the *KCNN3* gene and its protein product, KCa2.3, whether there is any disease association, and whether there are any animal models.

1. Navigate to the database page for the calcium-activated potassium channel subunit KCa2.3 (28) by one of the methods described in Subheadings 3.1 and 3.2.
2. Four data tables (Fig. 3) towards the bottom of the page provide the sought information (see Note 5).
3. The “Clinically-Relevant Mutations” table provides information on disease-causing mutations and other disease associations where the protein might be a target for therapeutic intervention. General descriptions are provided of the disease role, available drugs, specific mutations, references, and links to the OMIM database (see Note 6).
4. The “Gene Expression and Pathophysiology” table presents data on relevance of changes in gene expression to human disease or animal models of human disease (see Note 7).
5. The “Biologically Significant Variants” table lists functionally relevant (see Note 6) splice variants and mRNA edited variants (see Note 8). The information includes the splice variant nomenclature, a general description of the functional effect, and, where possible, links to the entries in protein and mRNA sequence databases, preferably RefSeq (see Note 9).

Clinically-Relevant Mutations ?

Disease:Schizophrenia

OMIM:181500

Comments:The truncation has been found in one patient with schizophrenia. Expression of K_{Ca}2.3-1/285 causes dominant-negative suppression of K_{Ca}2.2 in Jurkat cells.

References:114-115

Click column headers to sort

Type	Species	Molecular location	Reference
Frameshift	Human	L283	114-115

Gene Expression and Pathophysiology ?

Increased expression in patients with myotonic muscular dystrophy.

Tissue or cell type:Patient muscle samples.

Pathophysiology:K_{Ca}2.3 is probably involved in hyperexcitability.

Species:Human

T

R

Biologically Significant Variants ?

Alternative splicing leads to the inclusion if an additional 15aa in the outer pore region. The channel, known as hSK3-ex4, is a functional channel whose message is expressed at 0-2% of hK_{Ca}2.3 levels. The channel is insensitive to apamin, scyllatoxin and tubocurarine.

Amino acids:746

Type:Splice variant

Species:Human

References:101

Isoform a

Nucleotide accession:NM_002249

Protein accession:NP_002240

Amin

Type:

Spec

Refer

Phenotypes, Alleles and Disease Models ?

Mouse data from MGI

[Click here to show/hide data](#)

Allele	Composition & genetic background	Accession	Phenotype Id	Phenotype	Reference
Kcnn3 ^{tm1.3pad}	Kcnn3 ^{tm1.3pad} /Kcnn3 ^{tm1.3pad} involves: 129S4/SvJae * C57BL/6	MGI:2153183	MP:0005572	abnormal breathing frequency	PMID: 10988076

Fig. 3. Sections of database tables for the ion channel subunit K_{Ca}2.3, displaying information on clinical relevance, disease association, biologically significant variants, and animal models.

6. Lastly, the “Phenotypes, Alleles and Disease Models” table lists additional data on mouse strains with induced and spontaneous genetic mutations and their phenotypes obtained from and linked to MGI (see Note 10).

3.4. Pharmacological Data

Access receptor and ion channel pharmacological data.

1. Ligands are categorized according to their pharmacological actions on protein targets into agonists, antagonists, pore blockers, gating inhibitors, and allosteric regulators and organized








Agonists							
Key to terms and symbols		View all chemical structures			Click column headers to sort		
Ligand		Sp.	Action	Affinity	Units	Reference	
[¹²⁵I]DOI	 	Rn	Full agonist	9.1	pK _d	62	
(+)-[³H]DOB		Hs	Full agonist	9.1	pK _d	183-184	
5-HT	 	Hs	Full agonist	8.9	pK _d	184	
ORG-5222		Hs	Full agonist	9.6	pK _i	65	
LSD		Hs	Full agonist	9.4	pK _i	189	

Fig. 4. A screenshot of an agonist database table displaying a selected list of compounds along with their affinity data; the endogenous ligand 5-HT (serotonin) and two radiolabeled compounds are *highlighted*.

into separate tables on the appropriate receptor pages (Fig. 4).

- All ligands are listed along with their pharmacological actions (e.g., full, partial, reverse agonist) and activity data represented as pK_i, pK_d, pIC₅₀, and pEC₅₀ values (as appropriate).
- Each ligand is augmented with an aromatic symbol (six-carbon ring) to indicate availability of 2D structural information.
- Endogenous ligands are highlighted with an icon (a blue square containing the letter E).
- Where additional data are available about a ligand's selectivity at different targets (on a per species basis), these are aggregated in a specific table accessible via a link indicated by a green circle containing the letter S.
- Radiolabeled analogues are highlighted using a yellow radioactive hazard symbol.
- All ligands in each category can be viewed in a structure–activity relationship (SAR) grid (Fig. 5) showing the 2D structure, name, and list of targets for each compound (to access click on “View all chemical structures” at the top of the table). This allows users to quickly visualize the structure–activity profiles of active ligand sets and appreciate the inter-receptor promiscuity profiles of the compounds, which could be useful when selecting chemical tools to use in experimental work.

3.5. Ligands and Chemical Search Tools

Use the chemical search tools to find ligands, examine their properties, and investigate their target profiles.

- Follow links to the “Ligand search” page on the left sidebar.
- Search the database by using ligand common name, specific database chemical identifier (e.g., CAS Registry Number or

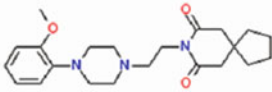
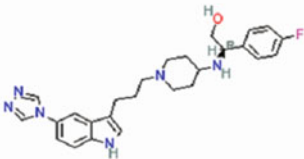
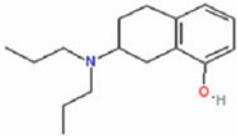
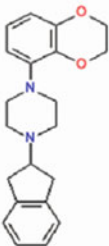
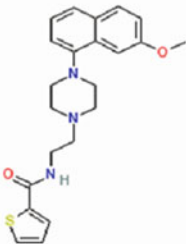
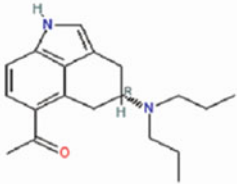
Available chemical structures for 5-HT _{1A} agonists		
 <p>Name: BMY-7378 Targets: 5-HT_{1A}, α_{1A}-adrenoceptor, α_{1B}-adrenoceptor, α_{1D}-adrenoceptor</p> <p>Use in search</p>	 <p>Name: L-772,405 Targets: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}</p> <p>Use in search</p>	 <p>Name: [³H]8-OH-OPAT Targets: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}</p> <p>Use in search</p>
 <p>Name: [³H]S-15535 Targets: 5-HT_{1A}</p> <p>Use in search</p>	 <p>Name: S-14671 Targets: 5-HT_{1A}</p> <p>Use in search</p>	 <p>Name: LY293284 Targets: 5-HT_{1A}</p> <p>Use in search</p>

Fig. 5. Section of a SAR grid showing a selected list of 5HT_{1A} agonists and their target profiles. The images and ligand names link to ligand pages and target names to their receptor pages.

PubChem Compound ID), or the chemical structure search tool.

- The chemical structure search tool allows users to draw in and modify chemical structures or substructures (Fig. 6) and to use these as queries to retrieve exact matching ligands, similar ligands, or those containing related superstructures from the database (see Note 11).
- The hits are displayed as a listing of the 2D images of the compounds along with their associated biological target(s) (Fig. 7).
- Each 2D image can be clicked to retrieve the ligand page (Fig. 8), containing calculated physicochemical parameters, a “Summary” tab (with systematic names, synonyms, and links to other online resources), “Biological activity” tab, “References” tab, a “Structure” tab with various electronic structure formats

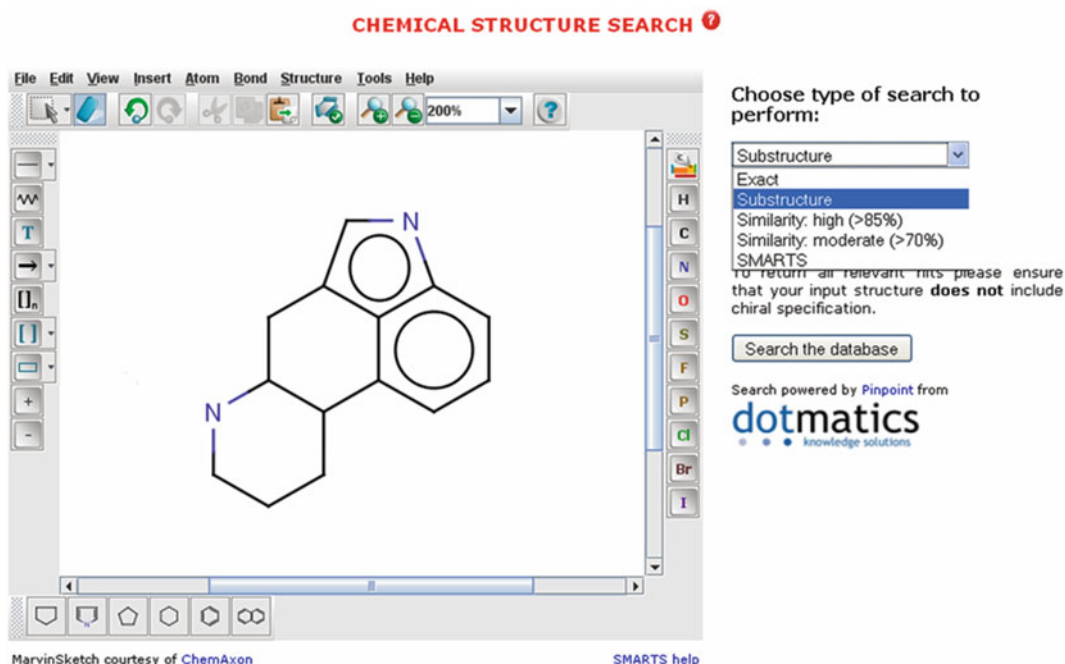


Fig. 6. The chemical editor and structure search tool, illustrating how the ergoline core may be used as a substructure query.

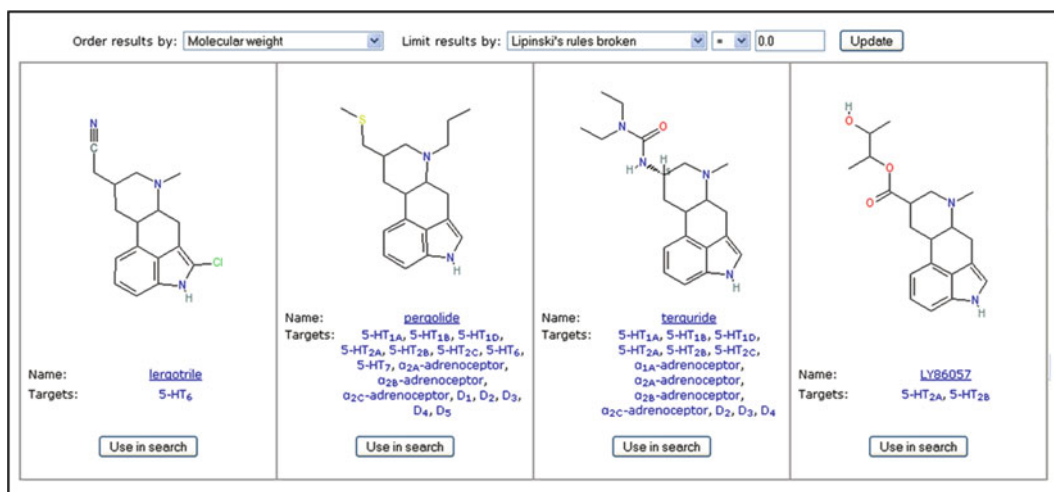


Fig. 7. Results from the ergoline substructure query. Ligand names (*underlined*) and target names link to ligand and protein target pages, respectively.

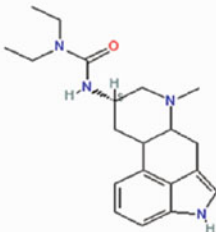
of the ligand (see Note 12), and sets of structurally similar compounds available via the “Similar ligands” tab.

- Finally, the 2D image on the ligand page can be clicked on to launch the structure editor, the structure modified, and used as the basis of a new ligand structure query (Fig. 6).

IUPHAR-DB Ligand: 56

Ligand name
terguride

2D Structure



Calculated Physical-Chemical Properties

Hydrogen bond acceptors	5
Hydrogen bond donors	2
Rotatable bonds	5
Topological polar surface area	47.61
Molecular weight	340.23
XLogP	2.52
No. Lipinski's rules broken	0

Molecular properties generated using the [CDK](#)

Summary

Biological activity

References

Structure

Similar ligands

Classification

Compound class	Synthetic organic
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IUPAC Name

3,3-diethyl-1-[(4S)-6-methyl-6,11-diazatetracyclohexadeca-1(16),9,12,14-tetraen-4-yl]urea

Synonyms

1,1-diethyl-3-[(8a)-6-methylergolin-8-yl]urea

Database Links

ChEMBL Ligand	217385 , 421252
PubChem CID	37816
Search on ChemSpider	JOAHPSVPXZTVEP-NXVRBGIVSA-N
Wikipedia	Terguride

Please note: some links may refer to related isomers. For more details please contact: curators@iuphar-db.org

Fig. 8. Part of a ligand page, showing the “Summary” tab. The “Biological activity,” “References,” “Structure,” and “Similar ligands” tabs link to further data.

4. Notes

1. The method of data collection (one subcommittee per receptor family) has left gaps in the knowledge of target activity spectra for a few ligands. Data collection for ligand cross-reactivity profiles (including targets not yet covered by IUPHAR-DB) is under way.
2. If preferred, the database will also accept gene and protein accession numbers such as the HGNC ID or the Entrez Gene ID. To access this functionality click on “Receptor search” on the left sidebar beneath the “Quick text search” box and navigate

to the section entitled “Search by database identifier.” Here, enter the accession number, select the source database from the drop-down menu, and begin the search.

3. One of NC-IUPHAR’s missions is to assess the evidence for in vivo existence of functional heteromeric receptors and provide guidance on their nomenclature (29). This requires stringent criteria for the recognition of protein complexes with physiological or pharmacological relevance. Thus, IUPHAR-DB does not justify the inclusion of suggested heteromeric receptors whose biological relevance has not been confirmed.
4. Further information on functional assays used to study ligand binding may be found in the comments sections of the “Agonists” and “Antagonists” tables. Recorded ligand activities can vary depending on the type of assay used, so database users are encouraged to always read the original publications, which are linked from the tables. In future versions of the database there will be more detailed annotation of individual ligand binding and functional assays, which will allow users to more easily compare and assess the pharmacological data.
5. Variations in the type and level of detail of information on individual receptors or ion channels arise due to a number of factors, including the extent to which the receptor has been studied, the scope of the published literature, the existence or otherwise of an NC-IUPHAR subcommittee, the priorities and interests of individual subcommittee members, and when the receptor was added to the database. Clinical relevance and variant data were two areas prioritized by the VGIC subcommittees.
6. Only details on demonstrable functionally important variants are included in IUPHAR-DB. There may be other variants reported in the literature or sequence databases whose existence and/or functional relevance may be unconfirmed.
7. Information on model organism gene knockouts and other artificially induced changes in gene expression and protein activity is generally included in the table “Physiological Consequences of Altering Gene Expression.”
8. In addition to splice and mRNA edited variants, this table may also include non-synonymous single-nucleotide polymorphisms (SNPs) with functional relevance.
9. The variants described in the literature are not always to be found in protein or nucleotide databases.
10. This information was downloaded from the MGI database and has not been checked by NC-IUPHAR experts or IUPHAR-DB curators.
11. The Pinpoint search algorithm (Dotmatics Limited, Bishops Stortford, UK) uses linear bit-strings encoded as internal fingerprints to recover compounds similar to query molecules.

12. Various representations of the ligand 2D molecular structure, generated using Open Babel (30), are made available for users to download. These include the following:
 - (a) Simplified Molecular Input Line Entry Specification (SMILES), which allows for unambiguous specification of chemical structures using short ASCII strings. Here, we use the terms “canonical SMILES” to represent 2D structures without chiral or isotopic information and “isomeric SMILES” to mean canonical smiles which include chiral specification.
 - (b) Standard InChI (IUPAC International Chemical Identifier) is a nonproprietary, standard, textual identifier for chemical substances designed to facilitate linking of information and database searching.
 - (c) InChI Keys are a simplified version of a full InChI, designed for easy Web searching.
 - (d) Work currently underway aims to provide further structural information and formats for polypeptide ligands, including amino acid sequences and details on posttranslational or chemical group modifications.

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