PLOS ONE

RESEARCH ARTICLE

MMpI: A WideRange of Available Compounds of Matrix Metalloproteinase Inhibitors

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OPEN ACCESS

Citation: Muvva C, Patra S, Venkatesan S (2016) MMpI: A WideRange of Available Compounds of Matrix Metalloproteinase Inhibitors. PLoS ONE 11(8): e0159321. doi:10.1371/journal.pone.0159321

Editor: Qing-Xiang Amy Sang, Florida State University, UNITED STATES

Received: September 16, 2015

Accepted: June 30, 2016

Published: August 10, 2016

Data Availability Statement: The MMpI Database (http://clri.res.in/subramanian/databases/mmpi/) data are deposited in Figshare (http://figshare.com/) and the DOI: 10.6084/m9.figshare.2069767, URL: https://figshare.com/s/500d06c99085c06be2b7.

Funding: This work was supported by the Council of Scientific and Industrial Research (CSIR), (GENESIS, BSC0121 and OSDD projects) and Department of Biotechnology (DBT) NER-Twinning project (No. BT/272/NE/TBP/2011), New Delhi, India.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteinases involved in the regulation of the extracellular signaling and structural matrix environment of cells and tissues. MMPs are considered as promising targets for the treatment of many diseases. Therefore, creation of database on the inhibitors of MMP would definitely accelerate the research activities in this area due to its implication in above-mentioned diseases and associated limitations in the first and second generation inhibitors. In this communication, we report the development of a new MMpI database which provides resourceful information for all researchers working in this field. It is a web-accessible, unique resource that contains detailed information on the inhibitors of MMP including small molecules, peptides and MMP Drug Leads. The database contains entries of ~3000 inhibitors including ~72 MMP Drug Leads and ~73 peptide based inhibitors. This database provides the detailed molecular and structural details which are necessary for the drug discovery and development. The MMpI database contains physical properties, 2D and 3D structures (mol2 and pdb format files) of inhibitors of MMP. Other data fields are hyperlinked to PubChem, ChEMBL, BindingDB, DrugBank, PDB, MEROPS and PubMed. The database has extensive searching facility with MMpI ID, IUPAC name, chemical structure and with the title of research article. The MMP inhibitors provided in MMpI database are optimized using Python-based Hierarchical Environment for Integrated Xtallography (Phenix) software. MMpI Database is unique and it is the only public database that contains and provides the complete information on the inhibitors of MMP. Database URL: http://clri.res.in/subramanian/databases/mmpi/index.php.

Introduction

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases which are implicated in various diseases. MMPs belong to the metzincin superfamily and are found in plants, vertebrates and invertebrates [1, 2]. MMPs are important homeostatic protease regulators of extracellular signaling and structural matrix environment of cells and tissues [3]. More than four

Table 1. Classification of matrix metalloproteinase enzymes.

Collagenases	Gelatinases	Stromelysins	Membrane Type-MMP	Matrilysins	Enamelysin	Others	Metalloelastase
MMP-1	MMP-2	MMP-3	MMP-14	MMP-7	MMP-20	MMP-19	MMP-12
MMP-8	MMP-9	MMP-10	MMP-15	MMP-26		MMP-21	
MMP-13		MMP-11	MMP-16			MMP-23	
		MMP-27	MMP-17			MMP-28	
			MMP-24				
			MMP-25				

doi:10.1371/journal.pone.0159321.t001

decades ago, Gross and Lapierre [4] discovered MMP (type 1 collagenase). To date, 23 human MMPs have been reported (Table 1). On the basis of substrate specificity and homology, MMPs are classified into collagenases, gelatinases, stromelysins, membrane Type-MMP, matrilysins, enamelysin, metalloelastase and other MMPs [5, 6].

MMPs are considered as promising targets for the treatment of many diseases such as arthritis, cancer, atherosclerosis, nephritis, aneurysms, tissue ulcers, and fibrosis [7]. Different research groups and pharmaceutical companies have made several attempts to develop inhibitors of MMPs. The first generation MMP inhibitors are limited by the poor bioavailability [8] (e.g., batimastat, D-5410, and Galardin), second generation inhibitors have side-effects [9] (marimastat) and the third generation inhibitors have no zinc-binding group and depth of the S1'pocket in most metalloproteases [10]. The effectiveness of the MMP class inhibitors require (i) functional groups like hydroxamate, carboxylate, thiolate, phosphinyl etc and (ii) capable of chelating the zinc(II) binding group.

Overall the domain architectures of various MMPs are significantly different. However, the active site geometries of the catalytic domain of different MMPs are similar. Current approaches for developing inhibitors consider secondary binding sites (exosites). These are referred to as regulatory sites, unique exosites have been proposed to be present in all MMPs [11–13]. Attempts have been made to develop peptide based inhibitors which bind secondary binding sites (exosites) of MMPs [14].

Numerous compounds have been synthesized by various research groups and also by pharmaceutical companies. These compounds have been screened to develop inhibitors of MMPs [15]. To search MMP Drug Leads, small molecule inhibitors and peptide based inhibitors, we developed an online database MMpI (Matrix metalloproteinases Inhibitors). It provides information on physicochemical properties, biological activities (IC_{50} or K_i values) and hyperlinked to other databases. Overall, MMpI provides MMP Drug Leads, peptide, and small molecule inhibitors information.

Materials and Methods

Source of data

The primary data in the MMpI database are manually extracted from the full text of peer-reviewed scientific publications in various journals, such as *Journal of Medicinal Chemistry*, *Bioorganic and Medicinal Chemistry Letters*, *Organic Letters*, *Bioconjugate chemistry*, *European Journal of Medicinal Chemistry*, *Bioorganic and Medicinal Chemistry*, *Bioorganic Chemistry*, *The Journal of Biological Chemistry*, *Anti-Cancer Drugs*, *Journal of Enzyme Inhibition and Medicinal Chemistry*, *Nature Biotechnology*, *Biochimie*, *BioChemical Journal*, *Chemical and Pharmaceutical Bulletin*, *Journal of Agricultural and Food Chemistry*, *Matrix Biology*, *Biochemical Pharmacology*, *Bioconjugate Chemistry*, *Journal of Enzyme Inhibition and Medicinal Chemistry*. Although, the journals covered are not comprehensive, the selected volumes capture the high-quality information which is necessary for the development of database. From each

publication the details of the biological activity of tested compounds, target protein and physico-chemical information are abstracted.

Database architecture and web interface

MMpI is built on Apache HTTP server 2.4 with MySQL 5.6 at the back end, and the PHP 5.5 and JavaScript at the front end. Apache, MySQL, and PHP are preferred as these are open-source softwares and platform independent.

Results

Description of MMpI database

The MMpI database is openly accessible via a simple, user friendly interface at http://clri.res.in/subramanian/databases/mmpi/index.php. It is a web-based and platform-independent

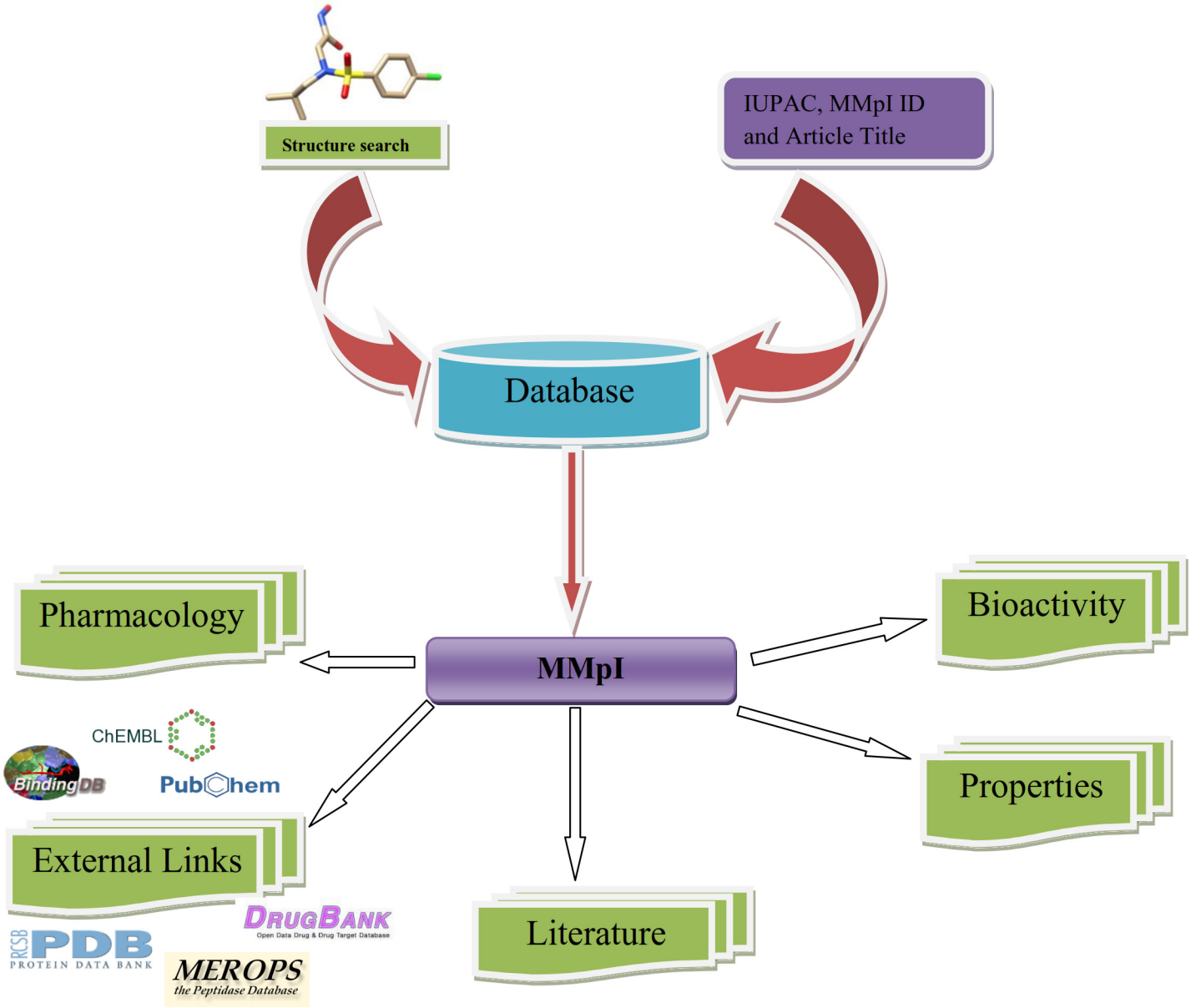


Fig 1. A schematic representation of the MMpI Pipeline.

doi:10.1371/journal.pone.0159321.g001

MMpI Database

A Database for Matrix Metalloproteinase Inhibitors

Home | Browse | Search | MMP Drug Leads | Peptide inhibitors | Download | Developers | Help

Search: Clear Submit

Welcome to MMpI

MMpI is a unique resource that contains detailed information on the MMP inhibitors inclusion small molecules and peptides and comprehensive list of MMP Drug Leads. The database contains 3000 inhibitors entries including 72 MMP Drug Leads and 73 peptide based inhibitors. MMpI is primarily engrossed on providing the detailed molecular and structural data needed to enable drug discovery and drug development.

About MMpI

The importance of matrix metalloprotease (MMP) in degradation of collagen and its relevance to arthritis and cancer have been well established. Therefore several attempts have been made to develop inhibitors for MMPs. However, there is no suitable database regarding the inhibitors for various MMPs. In this project, an attempt has been collect details about various inhibitors from previous studies to develop a comprehensive database.

MMP

Matrix metalloproteinases (MMPs) are a large family of calcium-dependent zinc-containing endopeptidases, which are responsible for the tissue remodeling and degradation of the extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan. They are regulated by hormones, growth factors, and cytokines, and are involved in ovarian functions.

Acknowledgements

The authors wish to thank the Council of Scientific and Industrial Research (CSIR), Department of Biotechnology (DBT) and GENESIS project New Delhi, India, for financial support.

Citation

MMpI Database

Fig 2. Home page of the MMpI database.

doi:10.1371/journal.pone.0159321.g002

database with ~3000 inhibitors including ~72 MMP Drug Leads and ~73 peptide based inhibitors. The pipeline of MMpI database is presented in Fig 1 and the home page of the MMpI database is shown in Fig 2. For example, user can retrieve potential compounds by employing a keyword search of the database using IUPAC name, derivative type, disease based, MMpI identifiers, and type of MMP and title of research article of interest.

The browser interface shows the classification of matrix metalloprotease. Using the interface, the investigator can derive the information (Fig 3). A table view of MMP Drug Lead molecules is also provided in MMP Drug Leads interface, with structure, MMpI ID, IUPAC name and

relevant binding protein (Fig 4). Users can go to compound record card to access further information, such as structure, bioactivity (IC_{50} or K_i values), and physico-chemical information.

This Database has a feature to search for a particular compound of interest and to retrieve information about the compound, or closely related compounds. The structure interface

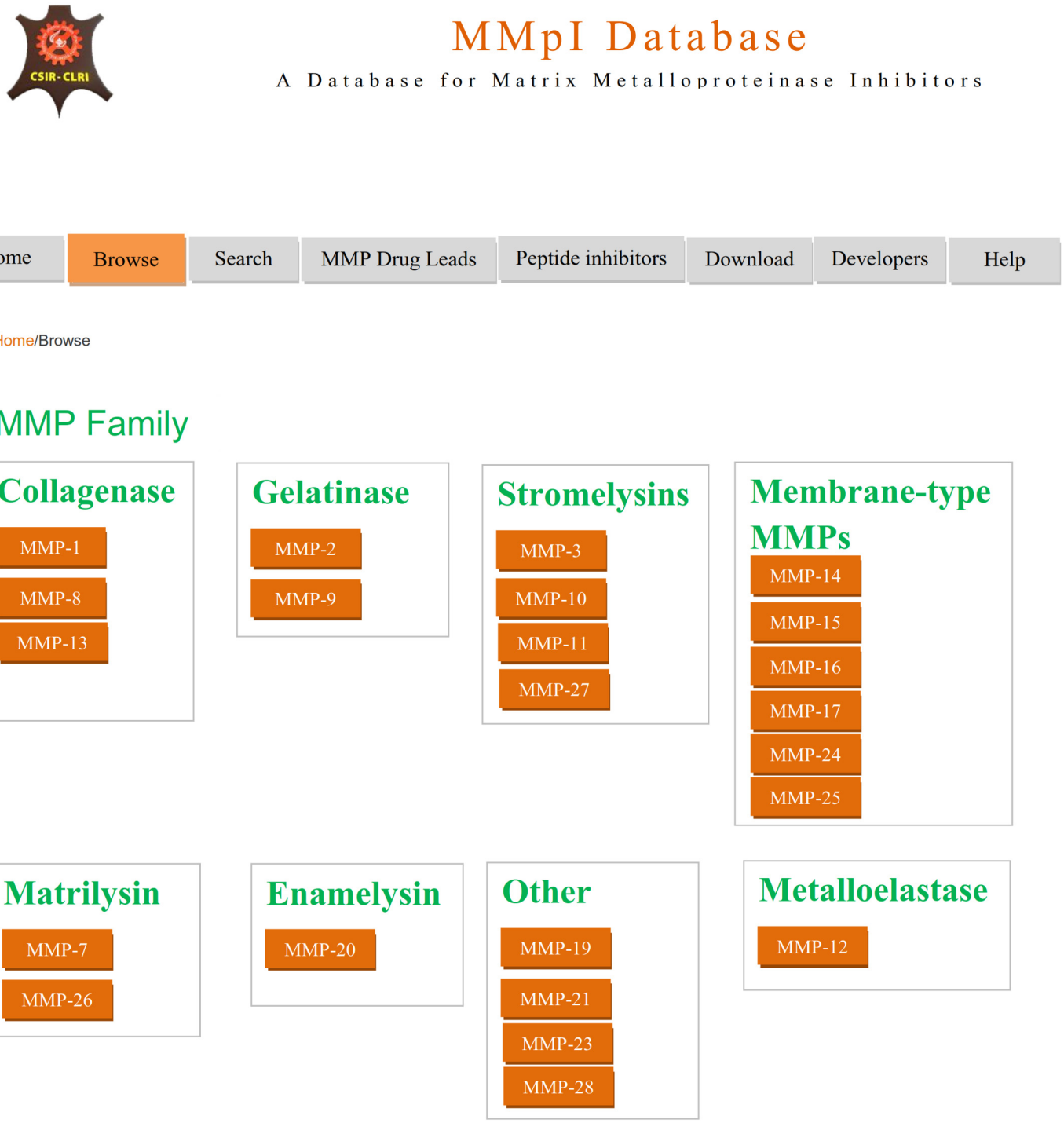


Fig 3. Interface of the MMpI database browser page.

doi:10.1371/journal.pone.0159321.g003

Home / mmp drug leads

MMP Drug Leads

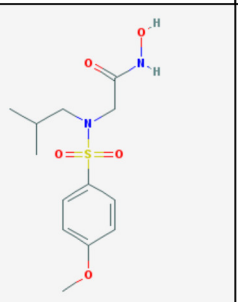
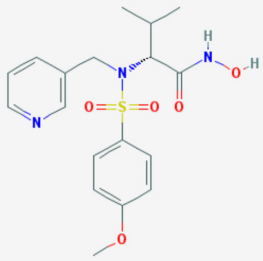
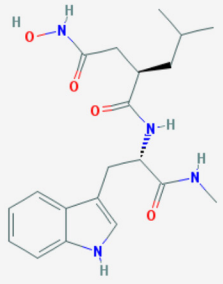
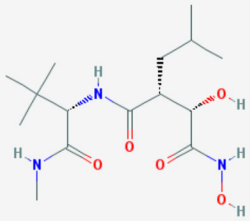
S.No.	Structure	ID	Name	Protein Binding
1		MMpI199701	N-hydroxy-2-[(4-methoxyphenyl)sulfonyl-(2-methylpropyl)amino]acetamide	MMP-3
2		MMpI199759	(2R)-N-hydroxy-2-[(4-methoxyphenyl)sulfonyl-(pyridin-3-ylmethyl)amino]-3-methylbutanamide	MMP-3
3		MMpI199829	(2R)-N'-hydroxy-N-[(2S)-3-(1H-indol-3-yl)-1-(methylamino)-1-oxopropan-2-yl]-2-(2-methylpropyl)butanediamide	MMP-1,MMP-2,MMP-3,MMP-9,MMP-14
4		MMpI199832	(2R,3S)-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-N',3-dihydroxy-2-(2-methylpropyl)butanediamide	MMP-1,MMP-2,MMP-3,MMP-9,MMP-14

Fig 4. Screenshot of the MMpI database showing MMP Drug Leads.

doi:10.1371/journal.pone.0159321.g004

provides the JME molecular editor drawing tool [16]. It is possible to sketch a structure of interest. A compound similarity search of the database can be carried out to retrieve inhibitor which is similar to the input structure (Fig 5).

The interface for peptide inhibitors and triple helical peptide inhibitors show the classification of matrix metalloprotease. Based on this, the researchers can view the database and

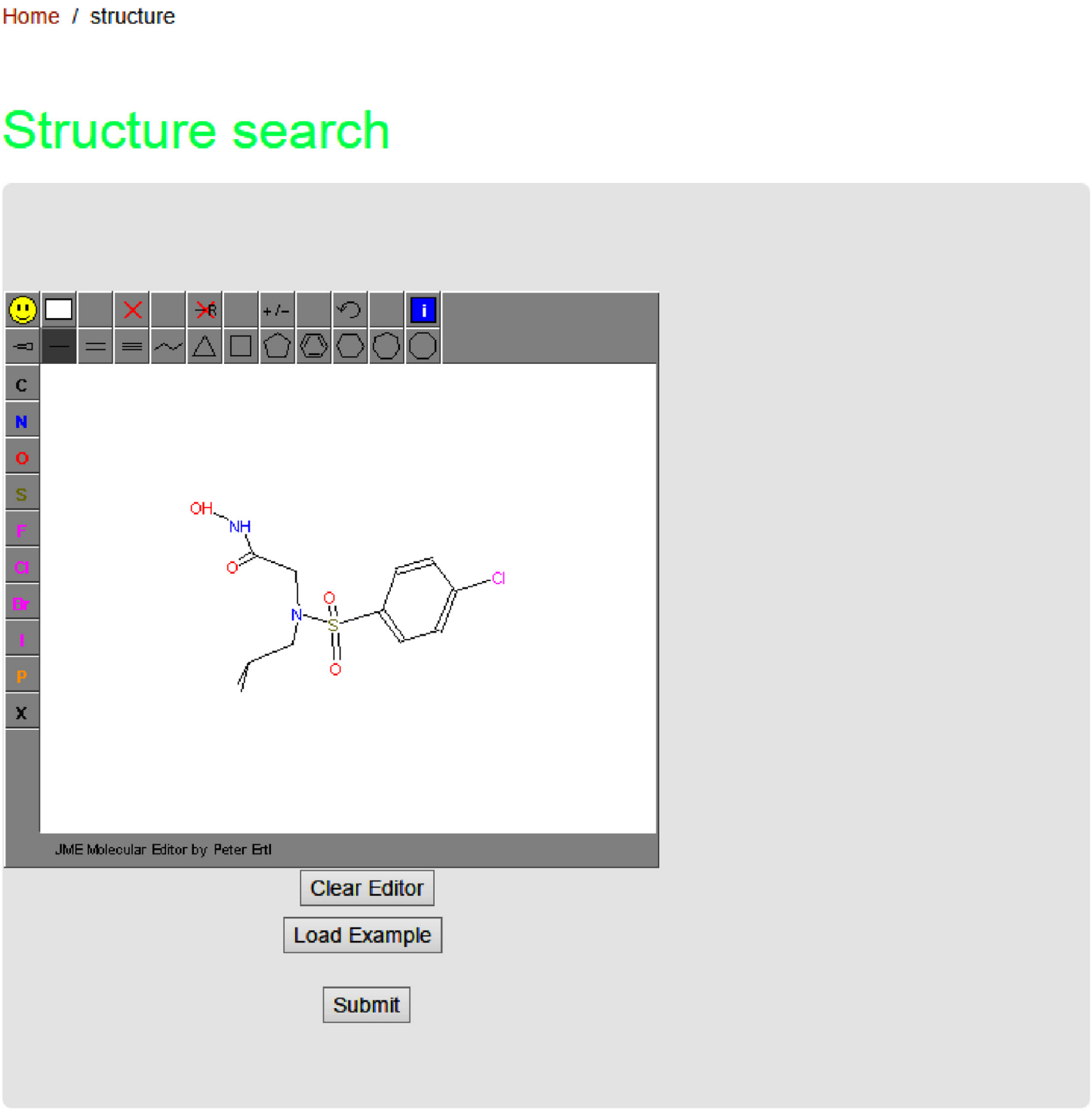


Fig 5. Choice of sketchers allows the user to draw a structure of interest and search the database for similar compounds.

doi:10.1371/journal.pone.0159321.g005

retrieve information on the peptide inhibitors (Fig 6). This interface provides the MMpI database unique id for peptide inhibitor, type of MMP, peptide sequence, bioactivity (IC_{50} or K_i values) and journal information.

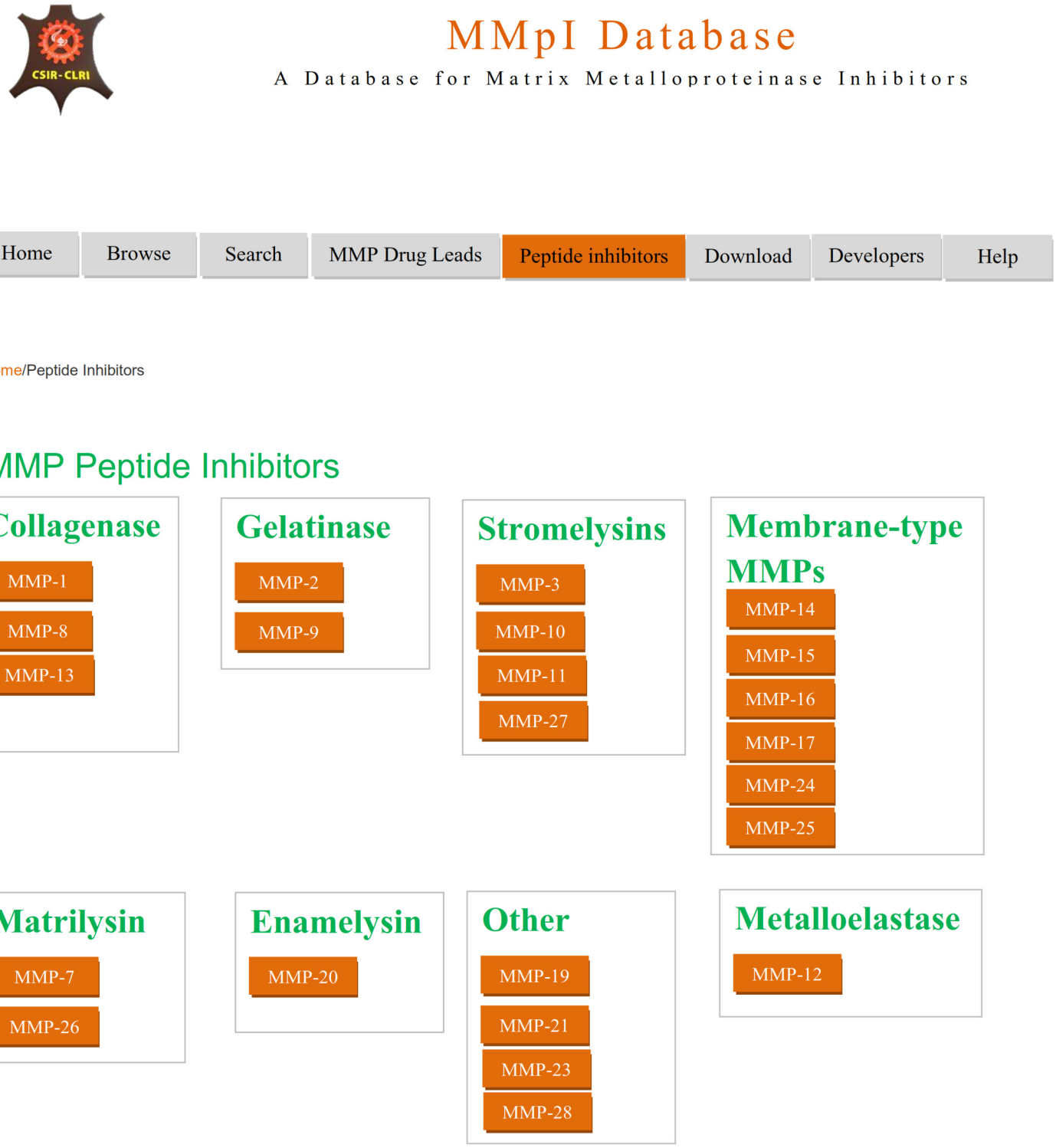


Fig 6. Screenshot of the MMpI database showing MMP peptide inhibitors.

doi:10.1371/journal.pone.0159321.g006

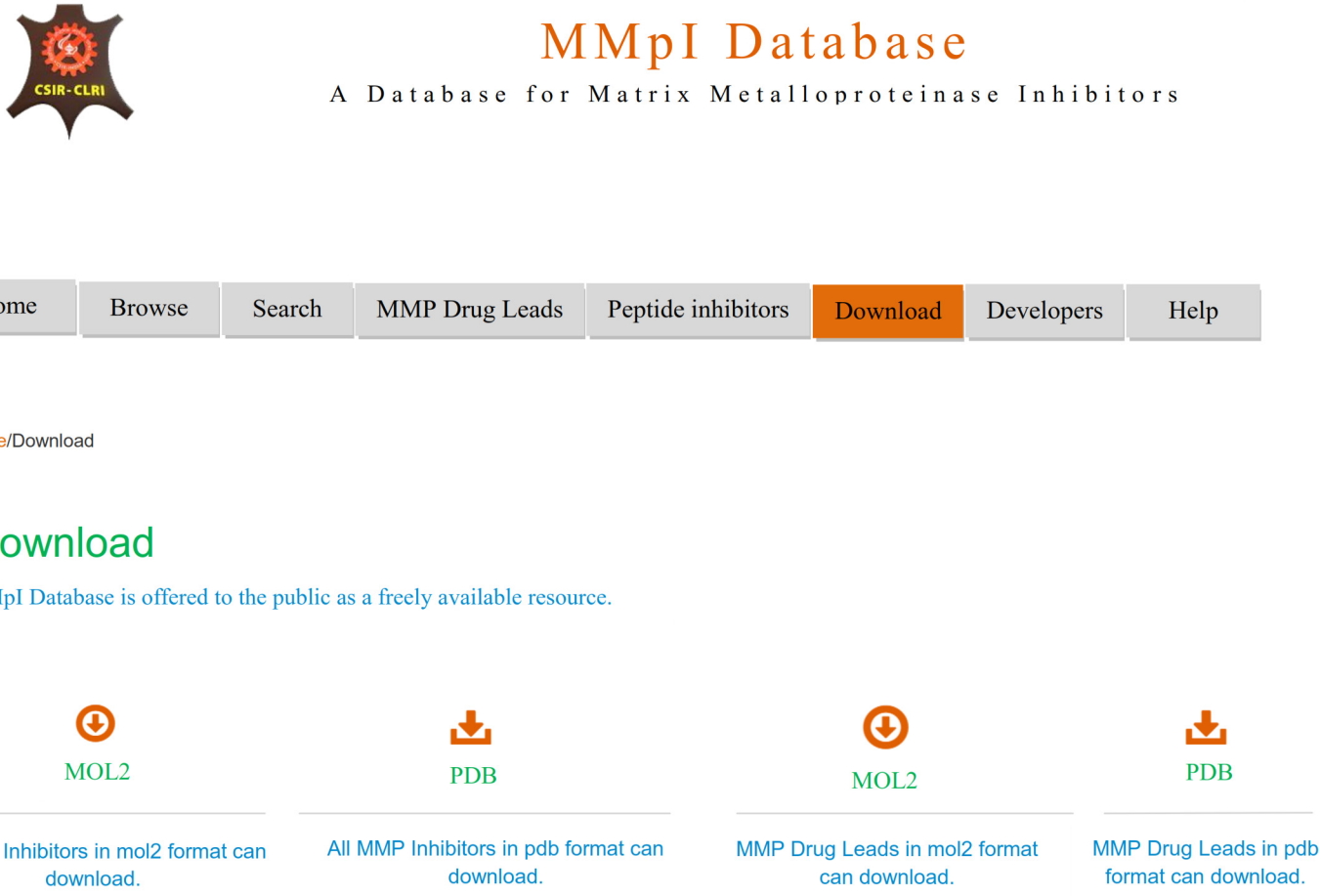


Fig 7. Interface of the MMpI database download page.

doi:10.1371/journal.pone.0159321.g007

The download interface allows the investigator to download the MMP inhibitors and MMP Drug Leads in pdb and mol2 formats (Fig 7). The MMP inhibitor and drug lead files in pdb and mol2 formats were optimized using Python-based Hierarchical Environment for Integrated Xtallography (Phenix) software [17]. This optimized compound can be used for drug design, docking or screening studies.

Example

It is expected that researchers look for essential and specific small molecule inhibitors or peptide inhibitors or triple helical peptides for MMP. As an example, to get the structure or analogs of hydroxamic acid inhibitors of stromelysins, one can search via search box or can sketch using JME tool which is incorporated in this database (Fig 5). Upon submission, the MMpI compound search results in a page with suitable structures. Then the researcher can select the compound of interest and the page will redirect to MMpI, compound record card page. This page provide further details about MMpI ID, IUPAC name, type of inhibitor and structures (2D and 3D) visualization in 2D and 3D using Jmol [18]. In addition, it is also possible to download the 3D structure in pdb and mol2 formats. The compound record card also covers bioactivity (IC_{50} or K_i values), physico-chemical properties and pharmacological information. In addition, record card page provides cross-references to other resources like Pubchem [19], ChEMBL [20],

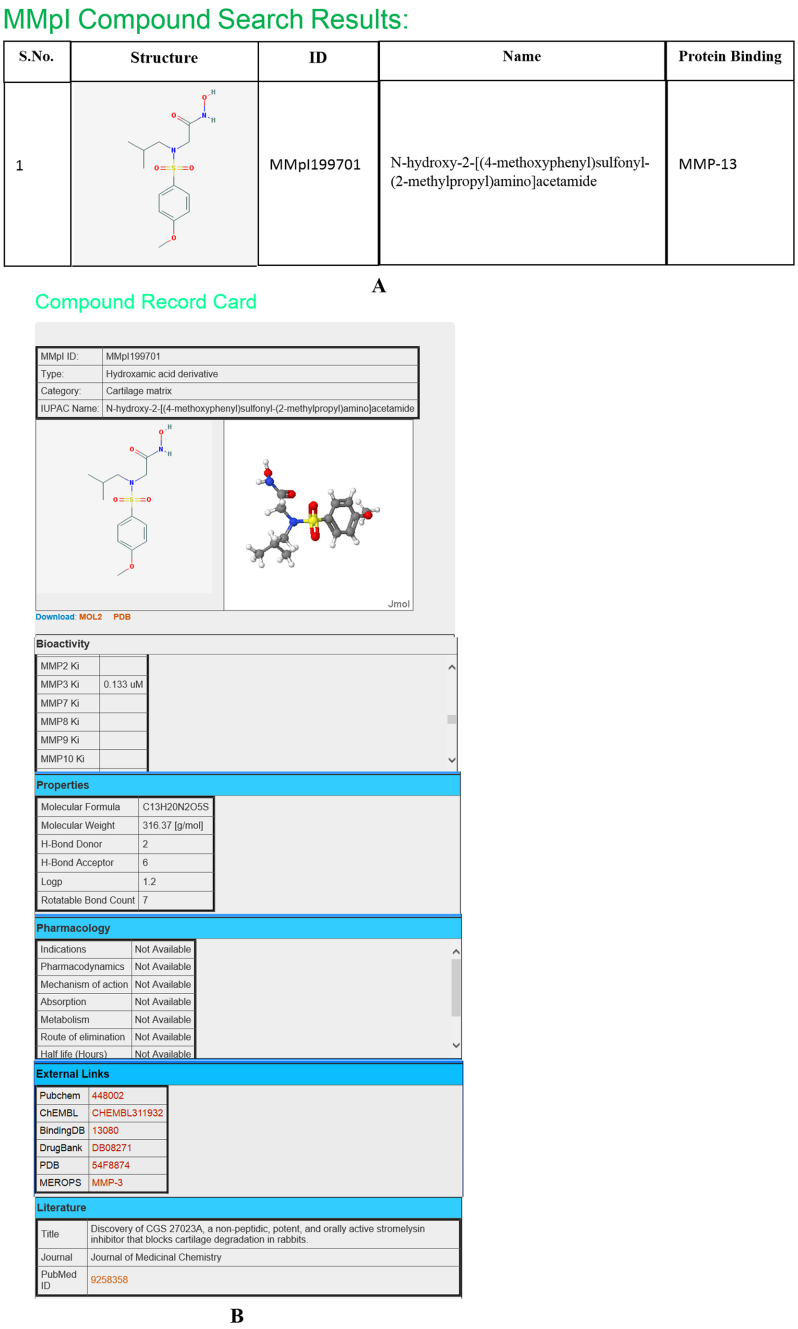


Fig 8. A screenshot montage of the MMpI database showing. (A) Compound search results. (B) MMP compound record card.

doi:10.1371/journal.pone.0159321.g008

Binding DB [21], DrugBank [22] PDB [23] and MEROPS [24]. Finally the report card contains a link to the source of the journal from where the information is retrieved (Fig 8A and 8B).

Discussion

MMpI is a web-accessible database that offers quantitative chemical, physical, pharmaceutical and biological data about thousands of well-studied drug leads, inhibitors and peptide

inhibitors of MMP. MMpI is primarily focused on providing detailed molecular data needed to facilitate drug discovery and development. MMpI is unique, not only in the type of data but also in the level of integration and depth of coverage. In addition to its extensive coverage of small molecules and drugs, it is the only public database that provides information on the inhibitors of matrix metalloproteinases. MMpI also supports an extensive array of visualizing, querying and search options. It is hoped that MMpI will serve as a useful resource to research community.

Further development

We will try to incorporate the new releases as soon as they will be available in the public domain.

Acknowledgments

The authors thank Mr. Vishal Pandya and Ms. Priscilla Preethi for their help in the collection of data. We thank Mr. S. Srikanth, Computer Centre, CSIR-CLRI, for his help in hosting the database.

Author Contributions

Conceived and designed the experiments: CM SV.

Performed the experiments: CM SP.

Analyzed the data: CM SV.

Contributed reagents/materials/analysis tools: CM.

Wrote the paper: CM SP SV.

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