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
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, ename lyns, 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 metalloproteinase Inhibitors). It provides information on physicochemical properties, biological activities (IC50 or Ki 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
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
### MMP Drug Leads

| S.No. | Structure | ID       | Name                                                                 | Protein Binding                  |
|-------|-----------|----------|----------------------------------------------------------------------|----------------------------------|
| 1     | ![Structure 1](image1) | MMp199701 | N-hydroxy-2-[(4-methoxyphenyl)sulfonyl-(2-methylpropyl)amino]acetamide | MMP-3                            |
| 2     | ![Structure 2](image2) | MMp199759 | (2R)-N-hydroxy-2-[(4-methoxyphenyl)sulfonyl-(pyridin-3-ylmethyl)amino]-3-methylbutanamide | MMP-3                            |
| 3     | ![Structure 3](image3) | MMp199829 | (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     | ![Structure 4](image4) | MMp199832 | (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.

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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.

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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.

**MMP Peptide Inhibitors**

**Collagenase**
- MMP-1
- MMP-8
- MMP-13

**Gelatinase**
- MMP-2
- MMP-9

**Stromelysins**
- MMP-3
- MMP-10
- MMP-11
- MMP-27

**Membrane-type MMPs**
- MMP-14
- MMP-15
- MMP-16
- MMP-17
- MMP-24
- MMP-25

**Matrilysin**
- MMP-7
- MMP-26

**Enamelysin**
- MMP-20

**Other**
- MMP-19
- MMP-21
- MMP-23
- MMP-28

**Metalloelastase**
- MMP-12

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

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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$_{v}$ values), physico-chemical properties and pharmacological information. In addition, record card page provides cross-references to other resources like Pubchem [19], ChEMBL [20],
MMpI Compound Search Results:

| S.No. | Structure | ID      | Name                                                                 | Protein Binding |
|-------|-----------|---------|----------------------------------------------------------------------|-----------------|
| 1     | ![](structure1.png) | MMpI199701 | N-hydroxy-2-[(4-methoxyphenyl)sulfonyl]-(2-methylpropylamino)acetamide | MMP-13          |

**Compound Record Card**

![Compound Record Card](compound_record_card.png)

**Bioactivity**
- MMP: Not Available
- C119: Not Available
- A100: Not Available
- A100: Not Available
- A100: Not Available
- A100: Not Available
- A100: Not Available
- A100: Not Available
- A100: Not Available
- A100: Not Available

**Properties**
- Molecular Formula: C15H16NO13
- Molecular Weight: 325.27 g/mol
- H-Bond Donor: 2
- H-Bond Acceptor: 6
- LogP: 1.2
- Rotatable Bond Count: 7

**Pharmacology**
- Indications: Not Available
- Pharmacodynamics: Not Available
- Mechanism of action: Not Available
- Absorption: Not Available
- Metabolism: Not Available
- Excretion: Not Available
- Half-life (in vivo): Not Available
- Elimination: Not Available

**Chemical/Links**
- PubChem: CPD0042
- CIDs: 5475
- Śląsk: 3290
- DrugBank: DB0071
- CAS: 111-13-5
- VIP: VIP-3

**Literature**
- Title: Understanding of COX-1/COX-2 interactions, novel potent, selective and orally active aromatase inhibitors and cyclooxygenase-2 inhibitors in rodents
- Journal: Journal of Medicinal Chemistry
- PubMed: 21457028

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**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

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

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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).
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.

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Author Contributions
Conceived and designed the experiments: CM SV.
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References
1. Brinckerhoff CE, Matrisian LM. Matrix metalloproteinases: a tail of a frog that became a prince. Nature Rev. Mol. Cell Biol, 2002; 3: 207–214.
2. Gomis-Rüth FX. Structural aspects of the metzincin clan of metalloendopeptidases. Mol Biotechnol, 2003; 24: 157–202. PMID: 12746556
3. Eckhard U, Huesgen PF, Schilling O, Bellac CL, Butler GS, et al. Active site specificity profiling of the matrix metalloproteinase family: Proteomic identification of 4300 cleavage sites by nine MMPs explored with structural and synthetic peptide cleavage analyses. Matrix Biol. 2016; 49:37–60. doi:10.1016/j.matbio.2015.09.003 PMID: 26407638
4. Gross J, Lapiere CM. Collagenolytic activity in amphibian tissues: a tissue culture assay. Proc Natl Acad Sci USA. 1962; 48: 1014–1022. PMID: 13902219
5. Whittaker M, Floyd CD, Brown P, Gearing AJ. Design and Therapeutic Application of Matrix Metalloproteinase Inhibitors. Chemical Reviews. 1999; 99: 2735–2776. PMID: 11749499
6. Overall CM. and López-Otín C. Strategies for MMP inhibition in cancer: innovations for the post-trial era. Nat Rev Cancer. 2002; 2: 657–672. PMID: 12209155
7. Keeling J, Herrera GA. Human matrix metalloproteinases: characteristics and pathologic role in altering mesangial homeostasis. Microsc Res Tech. 2008; 71:371–9. doi: 10.1002/jemt.20565 PMID: 18300288
8. Bachmann LH, Stephens J, Richey CM, Hook EW 3rd. Measured versus self-reported compliance with doxycycline therapy for chlamydia-associated syndromes: high therapeutic success rates despite poor compliance. Sex Transm Dis. 1999; 26: 272–278. PMID: 10333280
9. Renkiewicz R, Qiu L, Lesch C, Sun X, Devalaraja R, et al. Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rat. Arthritis Rheum. 2003; 48: 1742–1749. PMID: 12794843
10. Devel L, Czarny B, Beau F, Georgiadis D, Stura E, Dive V. Third generation of matrix metalloprotease inhibitors: Gain in selectivity by targeting the depth of the S1’ cavity. Biochimie. 2010; 92:1501–1508. doi: 10.1016/j.biochi.2010.07.017 PMID: 20696203

11. Morrison CJ, Butler GS, Rodríguez D, Overall CM. Matrix metalloproteinase proteomics: Substrates, targets, and therapy. Curr. Opin. Cell Biol. 2009; 21: 645–653. doi: 10.1016/j.ceb.2009.06.006 PMID: 19616423

12. Sela-Passwell N, Trahtenherts A, Krüger A, Sagi I. New opportunities in drug design of metalloproteinase inhibitors: Combination between structure-function experimental approaches and systems biology. Expert Opin. Drug Discov. 2011; 6: 527–542. doi: 10.1517/17460441.2011.560936 PMID: 22646077

13. Sela-Passwell N, Rosenblum G, Shoham T, Sagi I. Structural and functional bases for allosteric control of MMP activities: Can it pave the path for selective inhibition? Biochim. Biophys. Acta. 2010; 1803: 29–38. doi: 10.1016/j.bbamcr.2009.04.010 PMID: 19406173

14. Ndinguri MW, Bhowmick M, Tokmina-Roszyk D, Robichaud TK, Fields GB. Peptide-based selective inhibitors of matrix metalloproteinase-mediated activities. Molecules. 2012; 17:14230–48. doi: 10.3390/molecules171214230 PMID: 23201642

15. Peterson JT. Matrix metalloproteinase inhibitor development and the remodeling of drug discovery. Heart Fail Rev. 2004; 9: 63–79. PMID: 14739769

16. Ertl Peter. Molecular structure input on the web. J.Cheminform. 2010; 2: 1–9. doi: 10.1186/1758-2946-2-1 PMID: 20298528

17. Adams PD, Afonine PV, Bunkóczi G, Chen VB, Davis IW, et al. PHENIX: a comprehensive Python-based system for macromolecular structure solution. Acta Crystallogr D Biol Crystallogr. 2010; 66: 213–221. doi: 10.1107/S0907444909052925 PMID: 20124702

18. Jmol: an open-source Java viewer for chemical structures in 3D. Available: http://www.jmol.org/.

19. Bolton E, Wang Y, Thiessen PA, Bryant SH. Chapter 12 PubChem: Integrated Platform of Small Molecules and Biological Activities. Annual Reports in Computational Chemistry. 2008; 4: 217–240.

20. Bento AP, Gaulton A, Hersey A, Bellis LJ, Chambers J, et al. The ChEMBL bioactivity database: an update. Nucl. Acids Res. 2014; 42: D1083–D1090. doi: 10.1093/nar/gkt1031 PMID: 24214965

21. Liu T, Lin Y, Wen X, Jorissen RN, Gilson MK. Binding DB: a web-accessible database of experimentally determined protein-ligand binding affinities. Nucl. Acids Res. 2007; 35: D198–D201. PMID: 17145705

22. Law V, Knox C, Djoumbou Y, Jewison T, Guo AC, et al. DrugBank 4.0: shedding new light on drug metabolism. Nucleic Acids Res. 2014; 42: D1089–D1097. doi: 10.1093/nar/gkt1068 PMID: 24203711

23. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, et al. The Protein Data Bank. 2000; 28: 235–242.

24. Rawlings ND, Barrett AJ, Finn RD. Twenty years of the MEROPS database of proteolytic enzymes, their substrates and inhibitors. Nucleic Acids Res. 2016; 44: D343–D350. doi: 10.1093/nar/gkv1118 PMID: 26357717