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Problem Solving Protocol

DenvInD: dengue virus inhibitors database for clinical and molecular research

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Abstract

Dengue virus (DENV) researchers often face challenges with the highly time-consuming process of collecting and curating information on known inhibitors during the standard drug discovery process. To this end, however, required collective information is not yet available on a single platform. Hence, we have developed the DenvInD database for experimentally validated DENV inhibitors against its known targets presently hosted at https://webs.iiitd.edu.in/raghava/denvind/. This database provides comprehensive information, i.e. PubChem IDs, SMILES, IC50, EC50, CC50, and wherever available Ki values of the 484 compounds *in vitro* validated as inhibitors against respective drug targets of DENV. Also, the DenvInD database has been linked to the user-friendly web-based interface and accessibility features, such as simple search, advanced search and data browsing. All the required data curation was conducted manually from the reported scientific literature and PubChem. The collected information was then organized into the DenvInD database using sequence query language under user interface by hypertext markup language. DenvInD is the first useful repository of its kind which would augment the DENV drug discovery research by providing essential information on known DENV inhibitors for molecular docking, computational screening, pharmacophore modeling and quantitative structure-activity relationship modeling.

Key words: Dengue virus; database; inhibitor; protease; methyltransferase; polymerase

Introduction

Dengue fever, caused by dengue virus (DENV), is a common health issue in the tropical countries with a high prevalence of mosquito-borne diseases, where more than 3.2 million cases were observed as per 2015 statistics of WHO. However, the unreported cases, especially in the middle-income countries and the rural areas, may add to this number [1]. A recent survey estimated that approximately 390 million DENV infections occur

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per year (95% CI) and 96 million of these infections are presenting clinically [2]. Also, 3.9 billion people, which represents almost half of the world's population, are projected at risk to dengue infection worldwide in 129 countries [3].

The Indian subcontinent and the Asia Pacific are more vulnerable to DENV infection because of respective climatic and other factors. The discovery and identification of DENV were reported by Ron Kimura and Susumu Hotta in 1943 while studying blood samples of patients during dengue epidemic in Nagasaki, Japan [4]. A year later, Albert B. Sabin and Walter Schlesinger independently isolated the DENV, which is now referred to as dengue virus 1 (DENV-1) [5]. The DENVs are members of the genus Flavivirus in the family Flaviviridae [6–7]. There are four serotypes of DENV, namely, DENV-1, DENV-2, DENV-3 and DENV-4 [6–7]. At the genomic level, these four serotypes share approximately 65% of their genomes [8–9]. Despite these variations, an infection caused by each dengue serotypes results in the same disease and similar clinical symptoms [6]. Transmission of DENV in humans takes place by the bite of *Aedes aegypti* or *Aedes albopictus* female mosquitoes [10–11]. Clinical manifestations of DENV infection include bleeding, low platelet count and leakage of blood plasma, commonly known as dengue hemorrhagic fever [12–14]. In other conditions, a massive increase in the systemic capillary permeability with consequent hypovolemia and dangerously low blood pressure were observed in the patients, defined as dengue shock syndrome, and eventually lead to death in some cases [15–16].

The DENV particle contains a single stranded, ~11 kb, positive-sense RNA encoding a single open reading frame which is translated into a long polyprotein that is later processed into 10 proteins by means of proteolytic cleavage [17]. Among these, seven proteins are known as non-structural proteins (NS), viz. NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5, and essentially required in the viral replication and assembly (Figure 1). Remaining three proteins, known as structural proteins, are used in the virus particle formation and marked as capsid [C], membrane [M] and envelope [E] proteins [18] (Figure 1). The structural protein C is crucial for nucleocapsid formation, which is the first step during DENV assembly. This nucleocapsid contains a viral genome and multiple copies of C protein. The nucleocapsid is surrounded by protein E derived from lipid bilayer of the host cells. Moreover, both protein E and M embedded in the viral envelope that spans through the lipid bilayer and form a protective outer layer to regulate the viral entry into human cells [19–20, 18].

Furthermore, in DENV, NS1 protein is conserved N-linked non-structural glycoprotein (48 kDa) with six invariant intramolecular disulfide bonds, which are expressed on the cell surface and secreted into the extracellular space to perform the immune evasion activities [21–23]. The NS2A protein is one of the significant constituents of the DENV replication complex, which take part in the virion assembly and antagonizes the host immune response [24]. Likewise, the NS3 protein contains serine protease domain in complex with viral activator protein NS2B, and RNA helicase domain (Figure 1), which have multiple functional activities required for the viral RNA replication and viral assembly, respectively [25–27]. Whereas, the NS4A and the NS4B proteins are membrane-anchored proteins participated in the formation of DENV replication complex [28–30]. The NS5 protein is the largest and highly conserved DENV protein composed of 900 amino acid in the genus Flavivirus and contains two different domains, viz. the methyltransferase (MTase) domain and the RNA-dependent RNA polymerase (RdRp) domain (Figure 1). The MTase domain caps the DENV RNA genome, a step required for viral genome stability and translation into viral polyproteins using the host cell. Whereas, the RdRp domain synthesizes anti-genome and offspring genome [31–36].

Researchers working on DENV research, particularly in the drug discovery domain, frequently need information on various inhibitors and their targets, which is limited by time-consuming data curation and mining process from published literature and large unspecified databases. Hence, to address this problem, the present study presents the DenvInD as a collective database on known inhibitors against potential therapeutic targets of DENV to augment the ongoing research programs on DENV drug development.

Materials and methods

Data collection and compilation

To collect the potential compounds reported for anti-dengue activity, we searched on the PubMed, Scopus, Google Scholar and PubChem [37] for the DENV inhibitors information using several keywords, such as 'dengue virus inhibitors,' 'dengue virus NS3 inhibitor,' 'dengue virus NS3 protease inhibitor,' 'dengue virus helicase inhibitor,' 'dengue virus polymerase inhibitor,' 'dengue virus RNA dependent RNA polymerase inhibitor' and 'dengue virus methyltransferase inhibitor'. Following, the downloaded literature was catalogue to acquired the required information, i.e. compound name, information pertaining to *in vitro*/*in vivo* biological activity (IC50/EC50/CC50/Ki), the protein target as documented in the references along with its tracking number (PMID). Overall, DenvInD is divided into 12 columns: DenvInD ID (unique), IUPAC, PubChem ID, SID, AID, Smilies, IC50, Ki, EC50, CC50, PMID and protein name (Figure 2).

Database architecture and web interface

After all the required information was gathered, the data were integrated into the MySQL, an object-relational database management system, which supports the back end of the server. Following, the user-friendly web interface was developed using HTML5, CSS3, PHP (version 5.2.14) and JavaScript (version 1.7) as reported earlier [38–39] to access the designed DenvInD database from a variety of digital devices, such as laptops, mobiles and tablets.

Hosting and update provisions

DenvInD is freely available at https://webs.iiitd.edu.in/raghava/denvind/index.html. New data on the DENV inhibitors can be submitted in the database on request by providing the detail information about the compound, which would be further evaluated by our research team before publication in the DenvInD database. Request for data entry in the database can be sent by filling the online submission form available at https://webs.iiitd.edu.in/raghava/denvind/submit.php.

Results and discussion

DENV inhibitors data acquisition and database specifications

Extensive literature search and database mining results in a huge collection of potential inhibitors reported for target proteins in the DENV. Considering the suitable selection criteria and

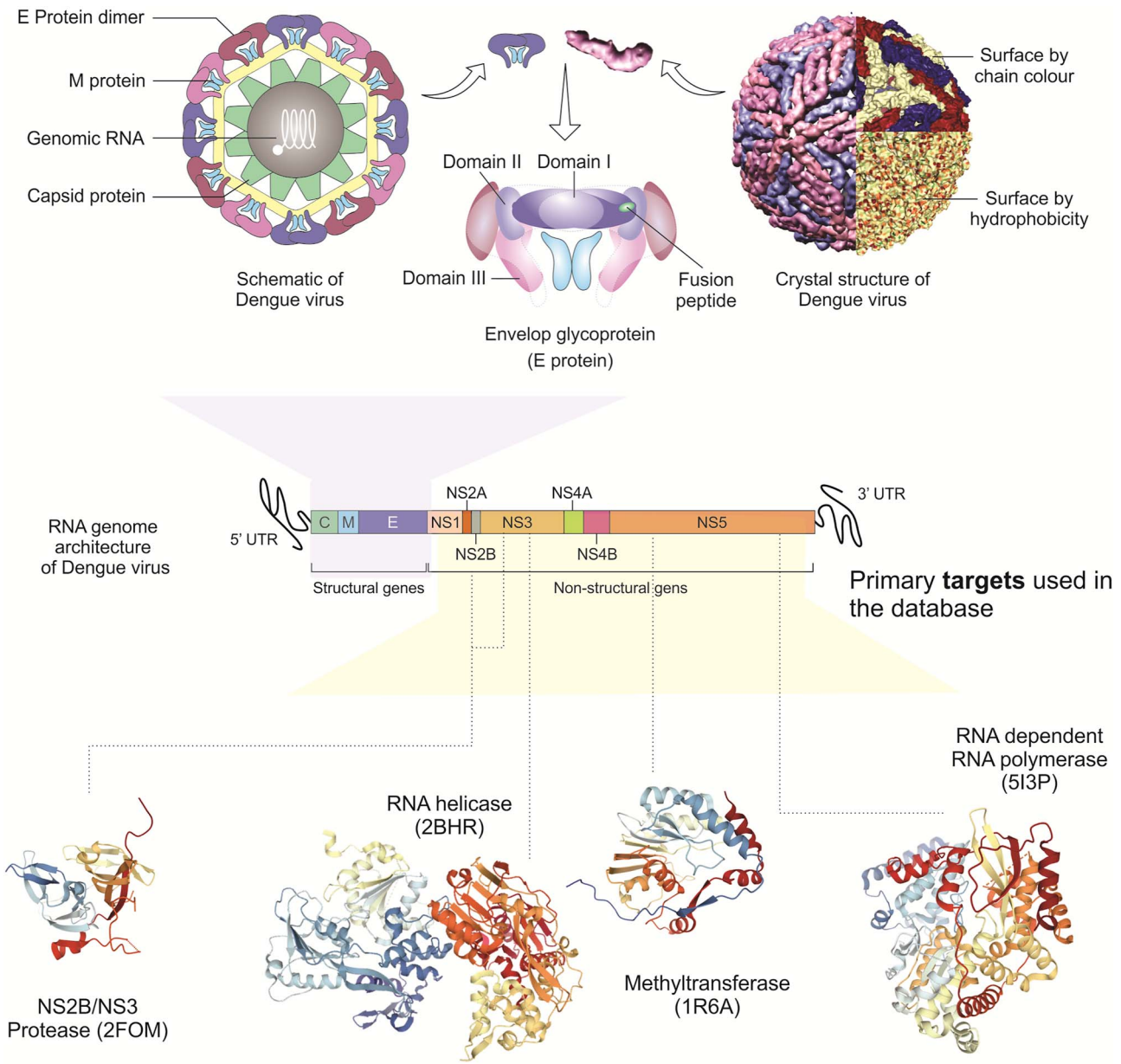


Figure 1. Overview of the dengue outer shell and genome structure. The upper panel represents schematic and crystal assembly of DENV (redrawn using PDB ID 1k4r) showing prominent structural components, including E protein dimer, M protein and capsid and various views of the surface, based on hydrophobicity and chain type. The lower panel represents the genome assembly of DENV organized into two distinct parts, structural and non-structural. The non-structural proteins considered as key targets for drug development, namely, NS2B/NS3 protease B(I)D 2FOM), RNA helicase (PDB ID 2BHR), MTase (PDB ID 1R6A) and RNA dependent RNA polymerase (5I3P).

removal of redundant data from scientific literature repositories like Pubmed, Scopus, Google Scholar and PubChem databases for 'dengue virus inhibitors' and related keywords as search parameters, a total of 484 inhibitors were identified at the time of manuscript preparation, which covered the respective complete information available on the public domains. Among the 484 compounds, NS3 protein inhibitors (64.4%) and NS5 MTase protein inhibitors (25.8%) constitute the largest part of the collected inhibitor data set. Moreover, 9.29% of the total inhibitors were logged for the NS5 polymerase inhibitor category, and only two inhibitors (Suramin and Novel benzoxazole) were recorded against NS3 helicase enzyme [40–41]. Although, the inhibitors list published in the DenvInD data is non-exhaustive and likely to be updated; it covers the best possible relevant information available at the time of manuscript submission (Figure 3A).

Features of various inhibitors

Based on clinical and molecular research requirements, various features of the reported inhibitors were collected as discussed in the respective methodologies. A total of 12 features were framed for the designed database where some of the features were collected from the public repositories or reported literature. During DenvInD database assignment for collected features, 8 out of 12 identifiers, i.e. DenvInd ID, IUPAC name, PubChem ID, SID, AID, PMID, protein name and SMILES notation were determined for all

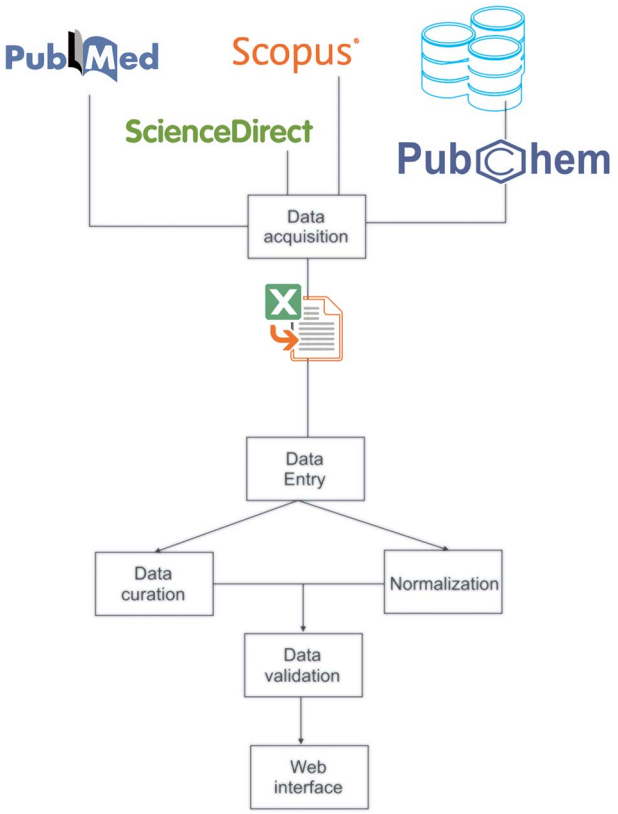


Figure 2. Methodology pipeline representing various sources of data collected for the development of the database and overview of the process followed for the development of web-interface.

the inhibitors. DenvInD ID is an unique identifier for each record in the database. However, for four identifiers, viz. IC50, Ki, EC50 and CC50 at least one or more identifier values were assigned to the inhibitors in the data set. Only a few had all the known identifiers which remain a common drawback of the database and likely to be updated in the future (Figure 3B).

Features of interface and database architecture

In order to keep the interface user-friendly and simple, we have kept some useful features such as a simple menu for search and browse, and basic description about the DenvInD database on the home page (Figure 4A). The search page has a query submission form where user can easily choose the option to search the inhibitors based on various criteria included in the 12 fields during the database preparation (Figure 4B). On searching with the specific keyword, the intermediate page has been developed to reflect the results hyperlinks to detailed page (Figure 4C). The detailed page contains complete information in the printable format with all the values assigned to different identifiers in the database (Figure 4D). In order to keep the result page light, we have not included the extensive graphics and structural images of the inhibitors, which makes it user-friendly on a mobile platform. Nevertheless, structure and associated literature can be easily accessed through various identifiers such as CID, SID or can be rendered on the standalone software using SMILES notations.

Interestingly, a number of previous studies and systematic reviews have identified the number of DENV inhibitors and have been widely used; this database compiled most of the information in user-friendly platform. Some of the notable reviews on the inhibitors that were used to extract information included [42].

Besides this literature, several successful attempts have been reported by researchers and computational biologists to simplified access on the essential information for clinicians and researchers in the forms of distinct databases. The database of DENV integrated information including genome and proteome [43], DENV drug targets database (http://www.bioinformatics.org/dengueDTDB/Pages/main.htm), DenvInt, a database for protein–protein interactions between DENV and its hosts were developed [44]. A database on DENV virus antibody which systematically links the serotype specificity with epitope mapping in DENV, developed by Sidhartha Chaudhury *et al.* [45], DENVirDB: a web portal of DENV genome sequence information on Asian isolates developed by Anet *et al.* [46] has some significant contributions in the DENV drug discovery domain.

In additional to primary databases, some of the other databases contained information related to dengue as a subset, such as DENV variation database as AVPDb, a database of antiviral peptides developed by OSDD consortium [47], and a subset of NCBI's genome database has been remarkable and highly accessed [48]. Despite the available resources, collective information about the inhibitors of various proteins of DENV remains largely scattered across the various literature and database, which was accomplished in this database and expected to bridge the current gap.

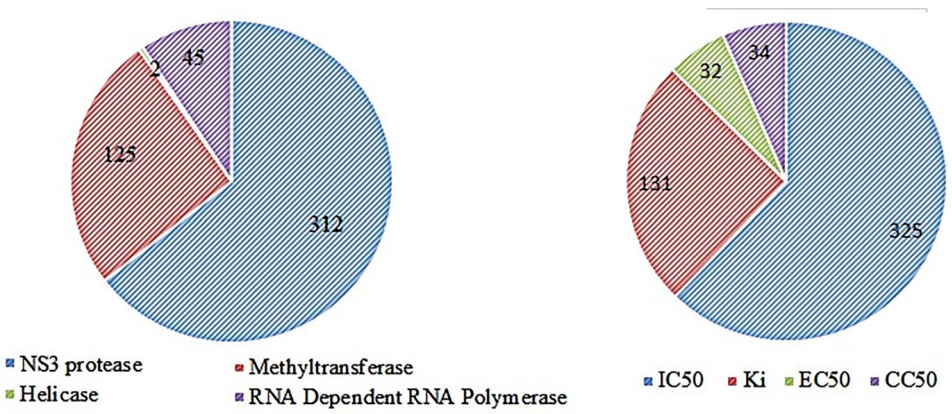
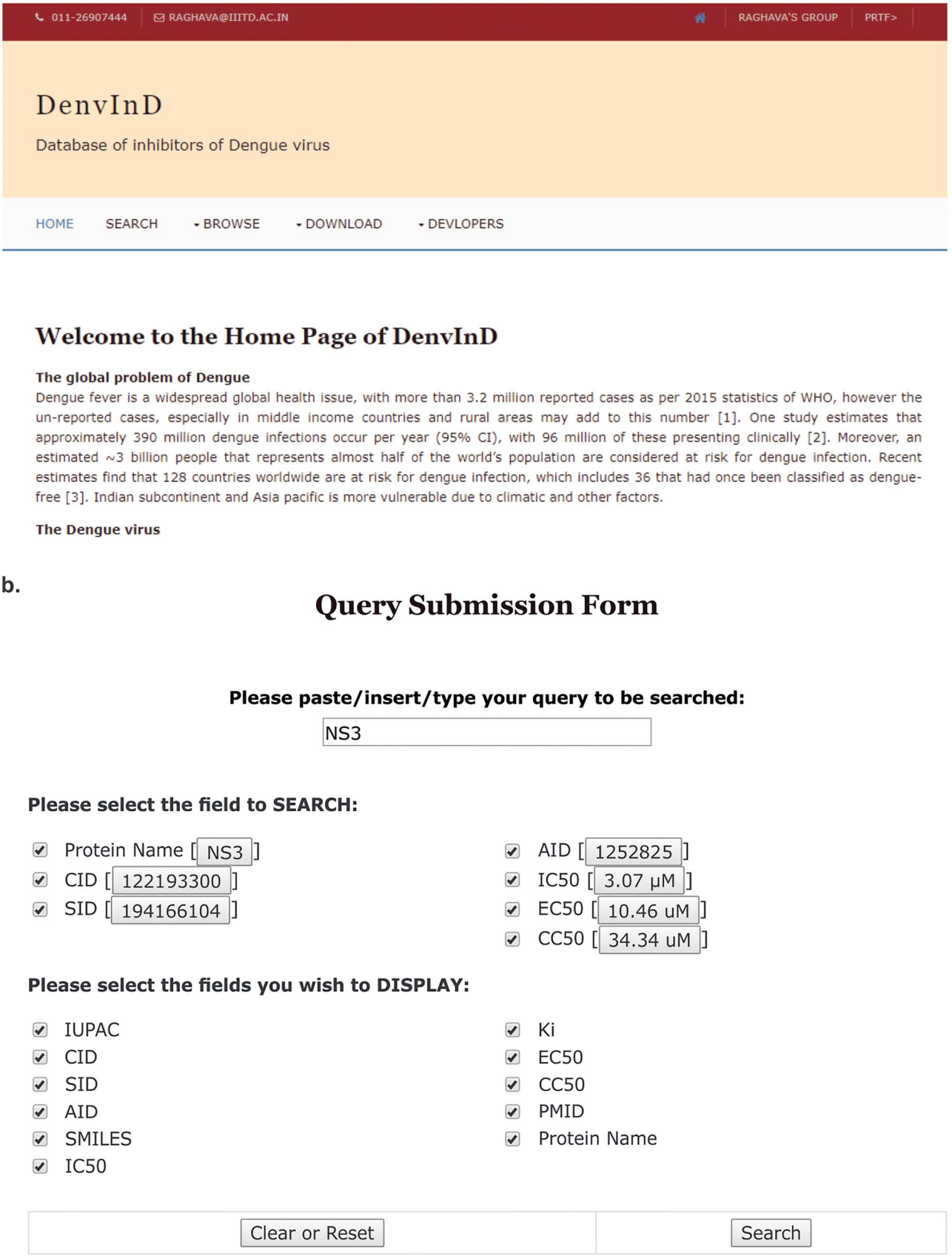


Figure 3. **(A)** Statistics and features of DenvInD. **(B)** Completeness of identifiers across the database.

a.



b.

Figure 4a. Screenshots and appearance of the DenvInD interface. (**A**) Home page; (**B**)user query page; (**C**) intermediate search results page; (**D**) detailed search result page.

c.

Welcome to Search Module Result Page of DenvInD

ID	IUPAC
DenvInD_1	tert-butyl N-[(2S)-4-methylsulfanyl-1-[(2S)-2-[(4-nitrophenyl)carbamoyl]pyrrolidin-1-yl]-1-oxobutan-2-yl]carbamate
DenvInD_2	N-[(2S)-1-[[(2S)-6-amino-1-[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-1-oxohexan-2-yl]amino]-3-(3-carbamimidoylphenyl)-1-oxopropan-2-yl]benzamide
DenvInD_3	4-amino-N-[(2S)-1-[[(2S)-6-amino-1-[[(1S)-2-amino-2-oxo-1-phenylethyl]amino]-1-oxohexan-2-yl]amino]-3-(4-carbamimidoylphenyl)-1-oxopropan-2-yl]benzamide
DenvInD_4	(2S)-6-amino-N-[(1S)-2-amino-2-oxo-1-phenylethyl]-2-[[(2S)-3-[4-(diaminomethylideneamino)phenyl]-2-(3-phenylpropanoylamino)propanoyl]amino]hexanamide

d.

Detailed description page of DenvInD

This page provides detail information of Selected ID DenvInD_1

Primary information	
ID	DenvInD_1
IUPAC	tert-butyl N-[(2S)-4-methylsulfanyl-1-[(2S)-2-[(4-nitrophenyl)carbamoyl]pyrrolidin-1-yl]-1-oxobutan-2-yl]carbamate
CID	72723356
SID	194166104
AID	1059448
SMILES	CC(C)(C)OC(=O)NC(CCSC)C(=O)N1CCCC1C(=O)NC2=CC=C(C=C2)[N+](=O)[O-]
IC50	10.5 μM
Ki	NA
EC50	NA
CC50	NA
PMID	24268549
Protein Name	NS3 Protease

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Figure 4b. Continued.

A major limitation of this database is the incomplete information on selected features for the complied DENV inhibitors. However, these fields are supposed to be discovered in future studies and, hence, regular updates of the DenvInD database remain a major concern. Although, the designed database is only useful for the dengue research community which again appears as a potential limitation, but it has an advantage to the dengue research community in terms of saving time and efforts in their ongoing research. Moreover, we have also included the data submission form for the researchers, who

is actively working in the domain and, therefore, can submit the data directly into the portal. However, the creation shall be performed under expert supervision in a blinded manner, and after final approval, the data would be included in the database to keep the database non-redundant and usable for a long period of time. In future upgrades, this database may also include the information on potential vaccine candidates as they are currently being explored, and the number remains significantly low. Moreover, the access controls and interface improvement are the additional features which could be manipulated with the advent of technology and operating systems.

Key Points

- Dengue represents one of the most devastating viral infection in tropical countries, with approximately 3.2 million reported cases as per 2015 statistics of WHO.
- Scattered availability of information on DENV and its inhibitors remains a challenge for most drug developers and researchers.
- DenvInd provides comprehensive information about the DENV inhibitor mainly NS3 and NS5.
- DenvInd is divided into 12 columns with DenvInd ID and four other identifiers (SID, AID, Smilies, PMID) and various quantitative parameters (IC50, Ki, EC50, CC50).
- At present, the database remains limited value to the dengue research community, which again appears as a potential limitation but also an advantage to the dengue research community, which can save time and efforts in their ongoing research.

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Conflict of Interest statement

Authors declare no conflict of interest.

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