PubChemRDF: towards the semantic annotation of PubChem compound and substance databases

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Abstract

Background: PubChem is an open repository for chemical structures, biological activities and biomedical annotations. Semantic Web technologies are emerging as an increasingly important approach to distribute and integrate scientific data. Exposing PubChem data to Semantic Web services may help enable automated data integration and management, as well as facilitate interoperable web applications.

Description: This work, one of a series covering the PubChemRDF project, describes an approach to translate PubChem Substance and Compound information into Resource Description Framework (RDF) format. Basic examples are provided to demonstrate its use. The aim of this effort is to provide two new primary benefits to researchers in a cost-effective manner. Firstly, we aim to remove the inherent limitations of using the web-based resource PubChem by allowing a researcher to use readily available semantic technologies (namely, RDF triple stores and their corresponding SPARQL query engines) to query and analyze PubChem data on local computing resources. Secondly, this work intends to help improve data sharing, analysis, and integration of PubChem data to resources external to NCBI and across scientific domains, by means of the association of PubChem data to existing ontological frameworks, including CHEMical INFormation ontology, Semanticscience Integrated Ontology, and others.

Conclusions: With the goal of semantically describing information available in the PubChem archive, pre-existing ontological frameworks were used, rather than creating new ones. Semantic relationships between compounds and substances, chemical descriptors associated with compounds and substances, interrelationships between chemicals, as well as provenance and attribute metadata of substances are described.

Background

PubChem [1, 2] is an open repository for chemical substance description, biological activities and biomedical annotations. PubChem is organized as three distinct and interrelated primary databases: Substance, BioAssay, and Compound. The Substance database (accession SID) includes depositor-provided sample description information including chemical depictions, chemical names (synonyms), external registration identifiers, comments, and cross-links. The BioAssay database (accession AID) includes depositor-provided experimental result information, including experiment description, experiment protocol, and results for substance SIDs tested in a biological assay. The nature of the assay tests can be rather diverse, including phenotypic, against a defined target, high-throughput, dose–response, counter-screen, or physical property measurement. Contributors providing cross-links with their data help to integrate and cross-reference PubChem to other National Center for Biotechnology Information (NCBI) resources (like PubMed) and beyond (for example, other chemical biology resources and patent documents).

PubChem, as an archive, takes care to preserve the provenance of information. Each change to a contributed substance or assay made by the depositor is versioned. In addition, each PubChem depositor controls their own records. As such, there can be many providers of
information about a particular chemical substance (e.g., aspirin).

One of the key purposes of the Compound database is to help aggregate information from various PubChem contributors using the chemical structure as the key [2]. The Compound database (accession CID) contains the unique chemical structure abstracted from the Substance database. As a part of this, each substance record with chemical information is subjected to a validation and normalization procedure to ensure the chemical structure is well-defined (e.g., no variable or ill-defined information), makes chemical sense (e.g., it is very unlikely that five bonds are connected to a carbon atom in small molecules of pharmacological interest), and to provide a standard chemical representation (e.g., collapse functional group and tautomeric/resonance variation into an equivalent, single, canon form, as-is possible). Structures stored within PubChem Compound are cross-referenced and pre-clustered by identity and similarity group concepts [2]. In addition, PubChem Compound employs chemical name/structure consistency analysis [3]. This processing, and the aforementioned structure normalization, helps to reduce error proliferation by informing contributors of any potential issues found with in-coming data prior to it being loaded into PubChem, and by suppressing potentially anomalous depositor-provided information by default in PubChem Compound interfaces. In addition, for each Compound record, PubChem calculates 3-D coordinates [4], physical properties (e.g., molecular weight, XLogP3 [5]), and descriptors (e.g., InChI [6], SMILES [7, 8], IUPAC names [9]), as-is possible.

In order to facilitate data integration of public chemical information, more and more efforts have taken advantage of the common data format and representation backed by domain knowledge. The formalization of PubChem knowledge in a general, yet simple and flexible way. Each of PubChem contributors using the chemical structure as the key [2]. The Compound database (accession CID) contains the unique chemical structure abstracted from the Substance database. As a part of this, each substance record with chemical information is subjected to a validation and normalization procedure to ensure the chemical structure is well-defined (e.g., no variable or ill-defined information), makes chemical sense (e.g., it is very unlikely that five bonds are connected to a carbon atom in small molecules of pharmacological interest), and to provide a standard chemical representation (e.g., collapse functional group and tautomeric/resonance variation into an equivalent, single, canon form, as-is possible). Structures stored within PubChem Compound are cross-referenced and pre-clustered by identity and similarity group concepts [2]. In addition, PubChem Compound employs chemical name/structure consistency analysis [3]. This processing, and the aforementioned structure normalization, helps to reduce error proliferation by informing contributors of any potential issues found with in-coming data prior to it being loaded into PubChem, and by suppressing potentially anomalous depositor-provided information by default in PubChem Compound interfaces. In addition, for each Compound record, PubChem calculates 3-D coordinates [4], physical properties (e.g., molecular weight, XLogP3 [5]), and descriptors (e.g., InChI [6], SMILES [7, 8], IUPAC names [9]), as-is possible.

In order to facilitate data integration of public chemical information, more and more efforts have taken advantage of the common data format and representation backed by the controlled vocabularies with well-defined semantics [10, 11]. Linked Data [12] built for the Semantic Web (as a collection of technologies and standards) [13] offers an approach to share data using web technologies. Semantic Web technologies offer a well-defined syntax and semantics for the formal representation of and reasoning with domain knowledge. The formalization of PubChem knowledge provides clarity by defining the meaning of entity attributes and relations in a machine interpretable manner. Moreover, harnessing ontologies for knowledge description can promote the interoperability of PubChem data with other domain knowledge including systems biology [14], and translational medicine research [15], among others. The semantic annotation of PubChem databases can directly promote the interoperability between applications external to NCBI Entrez and PubChem interfaces.

Of key importance, Semantic Web technologies and standards include the trio of the Resource Description Framework (RDF), Web Ontology Language (OWL), and the RDF model can be expressed as a collection of triples. The semantics and syntax in a given RDF model defined in controlled vocabularies or ontologies, and OWL is widely used to create domain-specific ontologies with increased expressivity. It is worth noting that ontologies are not only vocabularies that define a set of common and shared terms in a hierarchical structure to describe domain knowledge, they are also computable by enabling first-order logical reasoning, i.e. the statements asserted to the parent classes can be inherited by the child classes. The logic-based inference can be used to derive new RDF statements that are not explicitly asserted, and logic rules can be used to identify conflict statements on behalf of consistency checking. Hence, ontologies designed for automated inference must be carefully formulated according to the semantics of the language and as such are distinct from informal knowledge organization systems such as taxonomy and thesaurus. SPARQL serves as an RDF query language and data access protocol for the Semantic Web with the ability to locate and retrieve specific information across widespread databases as well as generate query reports that can be directly analyzed by network visualization and data mining applications. SPARQL may be used to query relational databases [17, 18] as well as RDF databases (triple stores) [19, 20], and may increase in popularity in the near future with the rapidly increasing scalability of RDF databases. With all of this in mind, PubChem data described using existing ontology frameworks and published in RDF format could fulfill the equivalent need for a SQL-based database of PubChem. Once PubChem data in RDF format is loaded into an RDF triple store, it should be immediately usable to researchers for complex queries and data analysis in their own local compute environment, whether it is a desktop computer or a multi-server compute farm. The compressed RDF-formatted PubChem data is more compact than the equivalent PubChem SQL-based databases, helping to make data distribution more tractable. With RDF-formatted data, a documented SQL schema of PubChem data is no longer required, as the ontology linked to the data provides the necessary documentation. As long as the PubChemRDF data mapping is stable, development changes to PubChem internal
specialized systems can happen without impacting the PubChemRDF data. Therefore, in theory, Semantic Web technologies could provide the basis to replace the need for a SQL-based PubChem data system.

Providing scientific data similar to that contained within PubChem in RDF format is not without precedent. Other RDF-based resources exist, such as European Bioinformatics Institute (EBI) RDF [21], Bio2RDF [22, 23], Linked Open Drug Data (LODD) [24], Chem2Bio2RDF [25], Open PHACTS [26], ChEMBL RDF [27], and others. The EBI RDF platform encompasses six public life science databases including ChEMBL, UniProt, Reactome, BioModels, BioSamples, and Expression Atlas. Bio2RDF serves as a mash-up system that integrates publicly available bioinformatics databases to provide interlinked life science data (~4 billion RDF triples). The LODD project, led by the World Wide Web Consortium (W3C) Health Care and Life Science Interest Group (HCLS IG), interlinks twelve open-access drug databases related to pharmaceutical research and development within the linked data cloud (~8 million triples). Chem2Bio2RDF is designed for integrated network analysis of heterogeneous datasets across the chemical and biological domains. It provides a computational tool for systems chemical biology and chemogenomics studies by aggregating multiple repositories cross-linked between Bio2RDF and LODD. Open PHACTS (Pharmacological Concept Triple Store) under the European Innovative Medicines Initiative (IMI) develops new solutions to create a public, integrated and sustainable Open Pharmacological Space (OPS) platform serving as an open source, open standard, open access infrastructure for drug discovery research. For example, standards are proposed on how to describe data sets and how to semantically link chemical compounds between databases [28].

With these precedents in mind, this work, one of a series covering the PubChemRDF project, describes how we translate PubChem substance and compound data into RDF format. Basic examples are provided to demonstrate its use. The aim of this effort is to provide two new primary benefits to researchers in a cost-effective manner. Firstly, the PubChemRDF project intends to remove the inherent limitations of using the web-based PubChem resource (such as limitations on query frequency or the inability to construct complicated queries using the available web-based interfaces) by allowing a researcher to use readily available semantic technologies (namely, RDF triple stores and their corresponding SPARQL query engines) to query and analyze PubChem data on local computing resources. Secondly, the PubChemRDF project intends to help improve data sharing, analysis, and integration of PubChem data to resources external to NCBI and across scientific domains by means of the association of PubChem data to existing ontological frameworks.

**Construction and content**

The PubChemRDF content covered in the scope of this paper includes the core chemical information archived in the PubChem Compound and Substance databases, the semantic relationships between compounds and substances, the chemical descriptors associated with compounds and substances, the interrelationships between compounds, and the provenance and attribution metadata of substances. The corresponding RDF statements to describe these will be demonstrated in the following sections. A set of standardized ontologies for enhanced data integration and interoperability were collected to define the domain-specific knowledge, including Chemical Entities of Biological Interest (ChEBI) [29–31], CHEMical INFormation ontology (CHEMINF) [32], Semanticscience Integrated Ontology (SIO) [33], Units of Measurement (UO) [34], Dublin Core Metadata Initiative (DCMI) Terms [35], Citation Typing Ontology (CiTO) [36], and Simple Knowledge Organization System (SKOS) [37]. The ontologies ChEBI, CHEMINF, SIO, and UO are interfaced by the NIH Roadmap National Center for Biomedical Ontology (NCBO) through its BioPortal [38], and comply with an evolving set of shared principles established by the Open Biomedical Ontologies (OBO) foundry [39]. Adoption of these core ontologies helps to ensure that the mapping of chemical information is compatible across multiple Semantic Web resources.

RDF statements described here are written in the Turtle syntax [40] with uniform resource identifier (URI) [41] references in relative form. The Turtle prefix directives for the namespaces of PubChem subdomains and the aforementioned ontologies are listed in Table 1, which can be used to resolve the base URIs relative to the fragment (local) identifiers. Both 303 URI (303 redirection) and hash URI were employed in the PubChemRDF project according to W3C recommendation [42]. Hash URI with a ‘#’ sign between the base URI and the fragment identifier was only used for PubChem vocabulary, which defines the types and relations of some PubChem-specific terms that cannot be identified in standardized ontologies. The 303 URI with a ‘:’ sign between the base URI and the fragment identifier was used for the other PubChemRDF subdomains (see Table 1). The fragment identifiers for PubChem Compound and Substance are constructed based on the CIDs and SIDs, respectively. The URIs for atorvastatin in PubChem Compound database [PubChem: CID60823] and Substance database [PubChem: SID103554720] are assigned as:
which can be represented in the relative form as compound:CID60823, and substance:SID103554720, respectively.

The fragment identifiers prefixed with the chemical descriptor namespace were constructed based on a combination of primary accession identifiers (CID or SID) and descriptor labels, except the depositor-provided synonyms. For instance, the URI for the molecular weight of CID60823 is represented as:

http://rdf.ncbi.nlm.nih.gov/pubchem/compound/CID60823

which can be abbreviated as descr:CID60823_Molecular_Weight. Given the fact that InChIKey is widely used to identify chemical structures and its value has a consistent pattern, which is good for URI construction, a separate namespace for the InChIKey subdomain has been created, which can be used to integrate chemical information from different RDF-based resources. The URI reference for the InChIKey is constructed based on its value as:

http://rdf.ncbi.nlm.nih.gov/pubchem/inchikey/XUKUURHRXDUEBC-KAYWLYCHSA-N

which can be abbreviated as inchikey: XUKUURHRXDUEBC—KAYWLYCHSA—N. Each SID may be associated with multiple depositor-provided synonyms, and vice versa. For instance, SID103554720 has three depositor-provided synonyms including atorvastatin, ChEMBL.

### Table 1 The prefixes and corresponding namespaces of PubChem subdomains and standardized ontologies

| Prefixa | Namespaceb |
|---------|------------|
| PubChemRDF subdomains | http://rdf.ncbi.nlm.nih.gov/pubchem/compound/ |
| compound | http://rdf.ncbi.nlm.nih.gov/pubchem/substance/ |
| substance | http://rdf.ncbi.nlm.nih.gov/pubchem/descriptor/ |
| descr | http://rdf.ncbi.nlm.nih.gov/pubchem/inchikey/ |
| inchikey | http://rdf.ncbi.nlm.nih.gov/pubchem/synonym/ |
| syno | http://rdf.ncbi.nlm.nih.gov/pubchem/concept/ |
| concept | http://rdf.ncbi.nlm.nih.gov/pubchem/reference/ |
| reference | http://rdf.ncbi.nlm.nih.gov/pubchem/source/ |
| nbr | http://rdf.ncbi.nlm.nih.gov/pubchem/neighbor/ |
| source | http://rdf.ncbi.nlm.nih.gov/pubchem/vocabulary# |
| vocab | http://rdf.ncbi.nlm.nih.gov/pubchem/synonym/ |
| syno | http://rdf.ncbi.nlm.nih.gov/pubchem/concept/ |
| concept | http://rdf.ncbi.nlm.nih.gov/pubchem/reference/ |
| reference | http://rdf.ncbi.nlm.nih.gov/pubchem/source/ |
| vocab | http://rdf.ncbi.nlm.nih.gov/pubchem/vocabulary# |
| inchikey | http://rdf.ncbi.nlm.nih.gov/pubchem/inchikey/ |
| pdbr | http://rdf.wwpdb.org/pdb/ |
| mesh | http://id.nlm.nih.gov/mesh/ |
| chembl | http://rdf.ebi.ac.uk/resource/chembl/molecule/ |
| linkedchem | http://linkedchemistry.info/chembl/chemblid/ |

| Prefixa | Namespaceb | Vocabularies |
|---------|------------|--------------|
| rdfoptions | http://www.w3.org/2000/01/rdf-schema# | RDF schema [55] |
| rdf | http://www.w3.org/1999/02/22-rdf-syntax-ns# | RDF [56] |
| xsd | http://www.w3.org/2001/XMLSchema# | XML schema [57] |
| obo | http://purl.obolibrary.org/obo/ | ChEBI [29–31] and UO [34] |
| sio/cheminf | http://semanticscience.org/resource/b | CHEMINF [32] and SIO [33] |
| cito | http://purl.org/spar/cito/ | CiTO [36] |
| pdbo | http://rdf.wwpdb.org/schema/pdbx-v40.owl# | PDB ontology |
| skos | http://www.w3.org/2004/02/skos/core# | SKOS [37] |
| dcterms | http://purl.org/dc/terms/ | DCMI terms [35] |

* Prefix substitutes full URI namespace in the context of XML qualified name (QName).
* Namespaces can be associated with element and attribute names in URI references; SIO and CHEMINF share the same namespace.
identifier and ChEBI identifier; similarly, the chemical name atorvastatin has been associated with more than 70 different substances, including SID103554720, SID210282077, SID210279754, and so on. Moreover, the associations between the substances and synonyms are updated by depositors as a function of time. Hence, in order to disambiguate the URI references for the depositor-provided synonyms, an independent synonym subdomain was adopted to facilitate semantic integration based on chemical names. Since chemical names can be strangely long and may contain URL-encoding reserved characters, the MD5 hash values derived from the depositor-provided synonyms (one-to-one without clash) were used to construct URIs. For instance, the depositor-provided synonym of atorvastatin is represented as:

http://rdf.ncbi.nlm.nih.gov/pubchem/synonym/MD5_9a05646d461669f86de312d88ab5748a

which can be abbreviated as syno:MD5_9a05646d461669f86de312d88ab5748a. All of the depositor-provided synonyms were changed to lower case before generating MD5 hash values, so the synonym URIs are dereferenced in a case-insensitive manner.

**PubChem substance**

Every PubChem substance is attributed to one and only one depositor, and the provenance metadata is exposed by using the predicate dcterms:source (see Figures 1, 2):

```
substance:SID103554720 dcterms:source source:ChEMBL.
```

The RDF descriptions for ChEMBL are exposed in the data source subdomain. PubChem standardizes chemical structure representations for the purpose of aggregating substance-centric information. This standardization processing includes multiple validation and normalization steps. The validation steps are used to confirm the structural representation is chemically reasonable, being comprised of known atomic elements and with reasonable atomic valence. The normalization steps are used to produce a single chemical structure description from

![Figure 1](image_url) RDF diagram representing the attributes for substances SID103554720, SID43118161, SID26697365, SID822166, and compound CID60823, as well as the annotations for synonym and InChIKey instances.
a multitude of effectively equivalent chemical representations (at standard temperature and pressure). Often, the resulting canonical representation is a different tautomeric and resonance form than that originally provided by the PubChem Substance contributor. In most cases, this PubChem derived canonical representation can be considered an equivalent form to that provided by the depositor; however, it is possible that the depositor-provided tautomer is isolatable, more stable, and specifically intended. When standardization processing succeeds, there will be a PubChem Compound record associated to the corresponding substance record. If the standardization processing of a substance fails, for any reason, no compound record will be associated with the given substance record. The association between a PubChem substance and the corresponding PubChem compound is represented by using the predicate cheminf:CHEMINF_000477 (see Table 2):

```
substance:SID1UJ554/20 cheminf:CHEMINF_000477 compound:CID60823.
```

PubChem substances are associated with two kinds of attributes: versions and synonyms. The links between the substance and its attribute are exposed as (see Figures 1, 2):

```
substance:SID43118161 sio:has-attribute descr:SID43118161_Substance_Version.
substance:SID103554720 sio:has-attribute sync:MD5_b05d5ea6b2409bb280591ba5e374028c.
```

The types and values of the versions and synonyms are exposed in the descriptor and synonym subdomains.

If a PubChem Substance was deposited by ChEBI, it is represented as an instance of the corresponding ChEBI ontology class, by using the predicate rdf:type. If this substance has a standardized structure representation in PubChem Compound database, the corresponding compound and all of the other substances standardized to the same compound are exposed as instances of the same ChEBI ontology class. Such knowledge representation situates the PubChem Substance records within the context of the global linked open data project, and enables logic-based inference. For instance, a given ChEBI ontology class [obo:CHEBI_39548(atorvastatin)] has multiple instances sharing the same canonic structural representation, including substance:SID26697365, substance:SID43118161, substance:SID822166, substance:SID103554720, and compound:CID60823. Based on ChEBI ontological representation, we can infer the fact that all of those instances have pharmacological role: “hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor”. The inferred fact agrees well with the synonym annotation (concept:ATC_C10AA) defined by the World Health Organization (WHO) anatomical therapeutic chemical (ATC) (see Figure 1).

If a PubChem substance was deposited by Molecular Modeling Database (MMDM) [43], it is most likely co-crystallized with a macromolecule (protein, RNA, or DNA) in an experimental 3-D structure. If the Protein
Data Bank (PDB) cross reference for the given MMDB record is provided, a link between the PubChem substance and the PDB record is exposed:

If a PubChem substance was deposited by ChEMBL, it is cross-linked to EBI RDF [21] and ChEMBL RDF [27]:

substance:SID822166 pdbo:link_to_pdb pdrb:iHWK.

substance:SID103554720 skos:exactMatch chembl:CHEMBL1487.

If a PubChem depositor provided the PubMed references for a given substance, the literature mentioning of a given substance is exposed:

substance:SID1950 cito:isDiscussedBy reference:PMID11676470. where the calculated value, unit, and type of the given chemical descriptor are exposed in the descriptor subdomain (see Figure 3).

PubChem chemical structure processing identifies structural overlaps and correlations under different circumstances. If a compound has more than one separate covalent unit, it is considered a mixture; if one of the covalent units can be considered to be a ‘parent’ compound (see below), it is considered to be a salt mixture. One or more component compounds are associated with the corresponding mixture. Beyond the chemical composition relationship, PubChem designates an identity grouping relationship between compounds, called a Compound Identity Group (CIG). This grouping information for related compounds is utilized to help associate various isotopic and stereo isomers provided by PubChem contributors. To implement this, several different levels of ‘sameness’ are considered: same-stereochemistry (isotope-form can vary), same-isotope (stereo-form can vary), and same-connectivity (isotope- and stereo-form can vary). In addition, the similarity neighboring between compounds are also incorporated in PubChem Compound based on different 2-D/3-D structural features [44]. The relations linking two compounds have been exposed as object properties in CHEMINF, with well-defined domain, range, and axioms. As an example, CID60823 is a component in over 400 mixture compounds. The chemical composition relations for one of these mixtures are expressed using predicate cheminf:CHEMINF_000480 (see Table 2) as follows (see Figure 3):

| CHEMINF term ID | Label | Definition |
|-----------------|-------|------------|
| CHEMINF_000477 | Has PubChem normalized counterpart | Non-symmetric predicate between substance as domain and compound as range |
| CHEMINF_000480 | Has component with uncharged counterpart | Non-symmetric predicate between a mixture compound as domain and its component as range |
| CHEMINF_000455 | Is isotopologue of | Symmetric predicate between two compounds (isotopomers) |
| CHEMINF_000461 | Is stereoisomer of | Symmetric predicate between two compounds (stereoisomers) |
| CHEMINF_000462 | Has same connectivity as | Symmetric predicate between two compounds with same connectivity |
| CHEMINF_000482 | Similar to by PubChem 2-D similarity algorithm | Symmetric predicate between two similar compounds according to 2-D Tanimoto score |
| CHEMINF_000483 | Similar to by PubChem 3-D similarity algorithm | Symmetric predicate between two similar compound according to 3-D Shape and Color Tanimoto scores |

* Non-symmetric means the subject and object in the triple are not interchangeable.
* Domain is the subject of triple.
* Range is the object of triple.
* The predicate is sub-property of CHEMINF_000462.
* Symmetric means the subject and object in the triple are interchangeable.
All components are acid/base neutralized as-is possible. If a component contains a super majority (≥70%) of all heavy (non-hydrogen) atoms across all unique components of a mixture and if that component has at least one carbon atom, it is designated as the parent component. In the above case, CID9919250 does not have a parent component. Another compound, CID23665101, has the parent component CID60823, and the other component CID5360545 is the salt counter-ion (non-parent component):

compound:CID9919250 vocab:has_parent
compound:CID60823; compound:CID9919251.

A compound is the parent of itself, its acid/base conjugates, and its salt-form variations. As such, the parent designation is helpful to aggregate the neutralized-form of a chemical structure with their salt-form or ionized-form variations, as is custom to do in bioactivity data analysis of organic chemicals, where the salt component is often assumed to not participate in the biological activity. Furthermore, according to the ontological representation:

vocab:has_parent rdfs:subPropertyOf
cheminf:CHEMINF_000480.

the following statement (inferred) is also true:

compound:CID23665101 vocab:has_parent
compound:CID60823.

Although the inferred statements are not explicitly stated in the dataset, they can be queried in the same way as the asserted statements when the RDF schema is recognized as the rule set by the reasoning engine.

Moreover, CID60823 is an isotopologue of CID10507504, and it is a stereoisomer of CID21029434. The CIG relations are expressed as follows (see Table 2; Figure 3):

compound:CID60823
cheminf:CHEMINF_000455 compound:CID10507504;
cheminf:CHEMINF_000461 compound:CID21029434.

again according to the ontological definition:

cheminf:CHEMINF_000455 rdfs:subPropertyOf cheminf:CHEMINF_000462.
cheminf:CHEMINF_000461 rdfs:subPropertyOf cheminf:CHEMINF_000462.
the following statements (inferred) are also true:

\[
\text{compoundCID60823}
\]
\[
\text{cheminfCHEMINF_000462 compoundCID10030610} ;
\text{cheminfCHEMINF_000462 compoundCID11330946}.
\]

Last but not least, CID60823 has over 800 structural similarity neighbors assigned by PubChem chemical structure processing. The similarity neighboring relations can be expressed using predicates
\[
\text{cheminfCHEMINF_000482} \quad \text{and}
\text{cheminfCHEMINF_UU0483} \quad \text{(see Table 2) as follows,}
\]
showing a single example for each of the two similarity types for CID60823 (see Figure 3):

\[
\text{compoundCID60823}
\]
\[
\text{cheminfCHEMINF_000482 compoundCID10030610} ;
\text{cheminfCHEMINF_000482 compoundCID11330946}.
\]

**Compound neighboring**

PubChem 2-D similarity neighbors are determined based on Tanimoto scores \( \geq 0.9 \), which are calculated using binary substructure fingerprints (881 bits in length) [45], PubChem 3-D similarity neighbors are determined based on two 3-D Tanimoto scores, calculated using 3-D conformers which are pre-computed for more than 90% of the PubChem compound records [46]. The two complementary 3-D Tanimoto scores are calculated for conformer neighbor pairs based on shape-optimized structural overlap and Gaussian-function aided volume integration: 3-D Shape Tanimoto (ST) and 3-D Color Tanimoto (CT) [44]. If two compounds have pharmacophore features (e.g., hydrogen bond acceptors), a threshold of ST \( \geq 0.80 \) and CT \( \geq 0.50 \) is used to determine the 3-D similarity neighboring; otherwise, a threshold of ST \( \geq 0.93 \) is used if neither compound has pharmacophore features. Although one RDF triple can be used to link two compounds according to their 2-D or 3-D similarity neighboring, the quantitative similarity scores cannot be expressed in the same triple. Hence, a set of triples were designed by instantiating similarity neighbor associations and score entities, in order to capture this knowledge (see Figure 4):

\[
\text{nbrCID60823_CID10030610_2DTanimotoScore}
\]
\[
\text{has-value}^\text{0.98''}^\text{xsd:double}
\]
\[
\text{rdf:type vocabPC2D_Fingerprint_TanimotoScore}.
\]

The 3-D structural similarity is evaluated using two complementary 3-D Tanimoto scores (see Figure 4) and is expressed as such:

\[
\text{nbrCID60823_CID11330946_3DSimilarity}
\]
\[
\text{has-value}^\text{0.59''}^\text{xsd:double}
\]
\[
\text{rdf:type vocabPC3D_Structural_Similarity}.
\]

The structural similarity is a subclass of
\[
\text{association}
\]
utilized to annotate the relation between two entities. This strategy for RDF n-ary representation of relational associations between two or more entities has been widely adopted. Gene-disease associations and protein–protein interactions have been successfully annotated in a similar manner, which were deposited in Nanopub.org [47]. The quantitative score assessing the structural similarity is expressed as:

\[
\text{nbrCID60823_CID11330946_3DSimilarity}
\]
\[
\text{has-measurement-value}
\]
\[
\text{scoreCID60823_CID11330946_3DFeatureTanimotoScore,}
\text{scoreCID60823_CID11330946_3DShapeTanimotoScore;}
\text{sio:refers-to}
\]
\[
\text{compoundCID11330946, compoundCID60823;}
\text{rdf:type vocabPC3D_Structural_Similarity,}
\text{nbrCID60823_CID11330946_3DFeatureTanimotoScore}
\]
\[
\text{has-value}^\text{0.88''}^\text{xsd:double}
\]
\[
\text{rdf:type vocabPC3D_Shape_TanimotoScore}.
\]

In addition to semantic annotation of the quantitative similarity scores between compounds, the provenance metadata of PubChem 2-D/3-D Tanimoto scores can also be expressed using object property
\[
\text{sio:is-output-of}
\]
(see Figure 4).

**Descriptor, InChIKey, and synonym**

The chemical descriptor representation consists of triples specifying the type, value, and unit associated with the chemical descriptor, as is appropriate. The following RDF statements in turtle syntax represent the description of molecular weight as a property for CID60823 (see Figure 3):

\[
\text{descrCID60823_Molecular_Weight}
\]
\[
\text{has-value CHEMINF_000334;}
\text{has-unituo UO_0000055.}
\]
where the descriptor value conforms to the data types defined in XML schema [48]. A list of calculated chemical descriptors exposed in PubChemRDF statements is found in Table 3, and each of them is formally typed using the CHEMINF vocabulary. Representing properties in a central vocabulary such as CHEMINF enables comparison between chemical properties arising from different databases in a standardized fashion. The software used by PubChem for calculating descriptor values is also defined in CHEMINF, as shown in Table 4.

Calculated InChIKey and depositor-provided synonyms were exposed in separate subdomains. The associated CIDs of a given InChIKey and synonym are linked through predicate sio:is-attribute-of (see Figure 1) within their subdomains:

It is noteworthy that although depositor-provided synonyms are attributes of both PubChem substances and compounds, not all of the synonyms of a given substance are automatically assigned as the synonyms of the corresponding compound. A crowdsourcing-based voting mechanism is implemented to filter out anomalous name/structure associations and to resolve conflicts of name/structure associations from various data sources. So if the majority votes as per the algorithm agree on a given name/structure association, there would be two triples
specifying the link between the synonym and substance (in the substance subdomain), as well as the link between the synonym and compound (in the synonym subdomain). Otherwise, only one triple would be available, linking the synonym and substance (in the substance subdomain).

The type and value of a given synonym are exposed as well (see Figure 1). In order to maximally leverage metadata for chemical name searches, different subtypes of synonyms were specified, including the chemical abstract service (CAS) registry number, unique ingredient identifiers (UNIIs), drug trade names, international nonproprietary names (INNs), and so on (see Table 5). The subtypes of the depositor-provided identifiers as a substance-centric descriptor were also specified to some extent. Since there are hundreds of types of depositor-provided identifiers and many of these are not frequently used, it would be unrealistic to annotate all of them. Therefore, only several subtypes of depositor-provided identifiers have been explicitly distinguished, and the rest of them were typed as validated chemical database identifiers (CHEMINF_000467) (see Table 5). Annotating the types of synonyms and identifiers allows data items to be grouped at a semantic level rather than only at a syntactic level.

In addition, whenever an InChIKey or a synonym represents a chemical structure that belongs to a Medical Subject Headings (MeSH) concept or an ATC concept, its major topic is annotated using predicate `dcterms:subject` (see Figure 1):

\[
\text{dcterms:subject mesh:} \text{M0179294.}
\]

### Table 3 Calculated chemical descriptor and the corresponding ontology term ID

| Property name         | Term ID          | Software library |
|-----------------------|------------------|------------------|
| Molecular weight      | CHEMINF_000334   | PubChem          |
| Molecular formula     | CHEMINF_000335   |                  |
| Total formal charge   | CHEMINF_000336   |                  |
| Mono isotopic weight  | CHEMINF_000337   |                  |
| Exact mass            | CHEMINF_000338   |                  |
| Compound identifier   | CHEMINF_000140   |                  |
| Covalent unit count   | CHEMINF_000369   |                  |
| Defined atom stereocenter count | CHEMINF_000370 |                  |
| Defined bond stereocenter count | CHEMINF_000371 |                  |
| Isotope atom count    | CHEMINF_000372   |                  |
| Heavy atom count      | CHEMINF_000373   |                  |
| Undefined atom stereocenter count | CHEMINF_000374 |                  |
| Undefined bond stereocenter count | CHEMINF_000375 |                  |
| Canonical SMILES      | CHEMINF_000376   | OEChem           |
| Isomeric SMILES       | CHEMINF_000379   |                  |
| Preferred IUPAC name  | CHEMINF_000382   | LexiChem         |
| Hydrogen bond donor count | CHEMINF_000387   | Cactvs           |
| Hydrogen bond acceptor count | CHEMINF_000388 |                  |
| Rotatable bond count  | CHEMINF_000389   |                  |
| Structure complexity  | CHEMINF_000390   |                  |
| Tautomer count        | CHEMINF_000391   |                  |
| TPSA                  | CHEMINF_000392   |                  |
| XLogP3                | CHEMINF_000395   | XLogP3           |
| IUPAC InChI           | CHEMINF_000396   | InChI            |
| IUPAC InChIKey        | CHEMINF_000399   |                  |

The software library used by PubChem to calculate property values are associated with each chemical property.

### Table 4 Name, version, and corresponding CHEMINF term ID for software libraries used to calculate chemical properties of PubChem compound

| Name                  | Version | CHEMINF term ID |
|-----------------------|---------|-----------------|
| PubChem               | 2.1     | CHEMINF_000333  |
| OEChem                | 1.9.0   | CHEMINF_000429  |
| LexiChem              | 2.2.0   | CHEMINF_000384  |
| Cactvs                | 3.408   | CHEMINF_000386  |
| XLogP3                | 3.0     | CHEMINF_000394  |
| InChI                 | 1.0.4   | CHEMINF_000398  |

* Please note that these versions will change as a function of software updates.

### Table 5 The types and corresponding CHEMINF term ID of the depositor-provided synonyms and identifiers

| Database identifier                        | CHEMINF term ID |
|--------------------------------------------|-----------------|
| ChEMBL identifier                          | CHEMINF_000412  |
| KEGG identifier                            | CHEMINF_000409  |
| Human Metabolome Database identifier       | CHEMINF_000408  |
| ChemSpider identifier                      | CHEMINF_000405  |
| ChEBI identifier                           | CHEMINF_000407  |
| DrugBank identifier                        | CHEMINF_000406  |
| CAS registry number                        | CHEMINF_000446  |
| EC numbera                                 | CHEMINF_000447  |
| RTECS numberb                              | CHEMINF_000566  |
| LipidMaps identifier                       | CHEMINF_000564  |
| National service center number             | CHEMINF_000565  |
| Unique ingredient identifier               | CHEMINF_000563  |
| Validated chemical database identifierc     | CHEMINF_000467  |
| Drug trade name                            | CHEMINF_000561  |
| International nonproprietary name          | CHEMINF_000562  |
| PubChem depositor-supplied name            | CHEMINF_000339  |

* A seven-digit identifier for chemical substances for regulatory purposes within the European Union.

* Identifying numbers used in the Registry of Toxic Effects of Chemical Substances (RTECS) database of toxicity information.

* Identifying descriptor is the superclass of other identifier types in the table.
Data sources
PubChem substance contents are provided by a variety of data sources. Exposing provenance and attribution metadata is helpful to evaluate the reliability and creditability of data sources, as well as to integrate the diverse information from them. The provenance for SID103554720 is described as follows:

```
substance:SID103554720 dcterms:source
  source:ChEMBL.
```

where `source:ChEMBL` is represented as an instance of `dcterms:Dataset`, and the title and alternative names (if possible) for the dataset was exposed through predicate `dcterms:title` and `dcterms:alternative`.

In order to guide better navigation through data sources, PubChem allows depositors to categorize the type of information they provide or that their resource contains. This is exposed as the "substance categorization classification". The categories may be either topic-related such as biological properties, chemical reactions, metabolic pathways, physical properties, protein 3D structures, theoretical properties, and toxicology; or depositor identity-related such as imaging agents, journal publishers, molecular libraries screening center network, NIH substance repository, and substance vendors [49]. A single data source may be attributed to multiple categories. The predicate `dcterms:subject` can be used to tag a data source with a specific topic, subsequently, to classify the data source into corresponding categories. The dataset topic in each category is an instance of `skos:concept`, and is in a concept scheme named Substance Categorization Classification. The corresponding RDF graph describing data provenance is depicted in Figure 2.

Utility and discussion
The semantic relations between PubChem Compound and Substance provide a way to aggregate and interlink information from different data sources based on the same canonical representation of a chemical structure. For instance, CID60823 (atorvastatin) refers to a standardized chemical structure derived from several Substance records including: SID26697365 deposited by ChEBI, which can be related to the structure-based classification according to the ChEBI ontology; SID51091801 deposited by Kyoto Encyclopedia of Genes and Genomes (KEGG), which contains information on biological pathways and biomolecular interactions; SID822166 deposited by Molecular Modeling Database (MMDB), which has protein-bound 3D structure information; SID135019185 deposited by ChemIDplus, which correlates toxicology and safety references to the given chemical structure; and SID103554720 deposited by ChEMBL, which associates bioactivity profiles to the given chemical structure. As a result, the resources across chemical, biological, and life science domain can be interlinked for CID60823. If the RDF statements were loaded into a triple store with SPARQL query interface, the following SPARQL query can be used to retrieve all of the substances and data sources associated with CID60823:

```
SELECT DISTINCT ?substance ?source
WHERE {
  ?substance sio:CHEMINF_000477 compound:CID60823.
  ?substance dcterms:source ?source.
}
```

Once integrated, the domain knowledge can be shared across data sources. For instance, the pharmacological roles defined in ChEBI ontology can be used to annotate a given chemical found in PDB crystal structure [PDB:1HWK]:

```
PREFIX obov: <http://purl.obolibrary.org/obo#> 
SELECT DISTINCT ?rolelabel
WHERE {
  ?substance pobo:link_to_pdb pdbr:1HWK.
  ?substance rdf:type ?chebi.
  ?chebi rdfs:subClassOf [a owl:Restriction; 
      owl:onProperty obov:has_role; 
      owl:someValuesFrom ?role].
  ?role rdfs:label ?rolelabel.
}
```

The query returned two different pharmacological roles, which are “antilipemic drug” and “hydroxymethylglutaryl-CoA reductase inhibitor”. In order to perform the query in the local computing resources, both PubChemRDF data and ChEBI ontology should be loaded into the same RDF store.

The chemical descriptors serve as quantified attributes to describe PubChem Compound and Substance records. The PubChemRDF design utilizes object properties `sio:has-attribute` and `sio:has-value` to specify the relations between the chemical entities and the associated descriptors. SIO is developed to support knowledge representation and reasoning in the scientific research, and the same design pattern has been implemented in the Bio2RDF mash-up system [22, 23] and the Semantic Automated Discovery and Integration (SADI) [50, 51] web service. Re-use of such design patterns across multiple Semantic Web offerings reduces the effort it takes to construct federated queries. The data consumers can refine a collection of PubChem Compound or Substance records according to the values of a given chemical descriptor. For instance, a PubChemRDF user can search for the PubChem compounds that belong to non-steroidal
anti-inflammatory drugs (NSAIDs) defined in ChEBI, and have molecular weight less than 200:

```sql
PREFIX obo: <http://purl.obolibrary.org/obo#>
SELECT distinct ?compound
WHERE {
  ?compound rdfs:type ?chebi.
  ?chebi rdfs:subClassOf [ a owl:Restriction;
    owl:onProperty obov:has_role; 
    owl:someValuesFrom obo:CHEBI_35475].
  ?comp sio:has-attribute ?mW.
  ?mW rdf:type sio:CHEMINF_000334.
  ?mW sio:has-value ?mWValue.
  FILTER(?mWValue < 200)
}
```

The SPARQL query returned 72 different compounds listed in Additional file 1: Table S1.

In order to bridge RDF data publishing and RDF data consumption, a variety of semantic data models have been proposed for the provenance and attribution metadata. These include Nanopublication [52], Bio2RDF [53], and Open PHACTS [54] dataset provenance models. The PubChemRDF project also provides provenance and attribution metadata for various data sources, and the provenance descriptions originate and augment the Open PHACTS dataset descriptions. Since the topics used to categorize data sources in PubChem are highly domain-specific, we assigned skos:Concept URIs to attempt to precisely capture the categorization of PubChem data sources. These metadata can be very helpful for information retrieval and refinement. For instance, a PubChemRDF user can collect a set of PubChem substances that belong to NSAIDs defined in ChEBI and come from data sources providing protein 3-D structures:

```sql
PREFIX obov: <http://purl.obolibrary.org/obo#>
SELECT DISTINCT ?substance ?source
WHERE {
  ?substance dcterms:source ?source.
  ?source dcterms:subject concept:Protein_3D_Structures.
  ?substance rdfs:type ?chebi.
  ?chebi rdfs:subClassOf [ a owl:Restriction;
    owl:onProperty obov:has_role; 
    owl:someValuesFrom obo:CHEBI_35475].
}
```

The query return 115 different substances associated with their data sources, most of which were deposited by the Molecular Modeling Database (MMDB). The complete list is available in Additional file 1: Table S2.

The PubChemRDF project allows maximal flexibility to cross-reference a PubChem Substance record with other data sources. For instance, SID103554720 is interchangeable to an external RDF-based resource, and the fact is declared as a RDF triple:

```
substance:SID103554720
skos:exactMatch linkedchem:CHEMBL1487.
```

where the predicate skos:exactMatch was also employed by the Open PHACTS project for cross-referencing. Cross-linking to other RDF-based resources entails federated queries over other remote SPARQL endpoints. For instance, the following federated query can be used to search the Uppsala SPARQL endpoint for ChEMBL RDF triples [27] related to SID103554720:

```sql
PREFIX onto: <http://rdf.farmbio.uu.se/chembl/onto#>
SELECT DISTINCT ?rel ?value ?unit ?label
WHERE {
  substance:SID103554720 skos:exactMatch ?chembl.
  SERVICE < http://rdf.farmbio.uu.se/chembl/sparql >
  WHERE {
    ?chembl owl:equivalentClass ?mol.
    ?act onto:forMolecule ?mol.
    ?act onto:relation ?rel.
    ?act onto:standardValue ?value.
    ?act onto:standardUnits ?unit.
    ?act onto:type ?type.
    ?act onto:onAssay ?assay.
    ?assay rdfs:label ?label.
  }
}
```

The query returned 97 different bioactivities associated with corresponding ChEMBL assays. The complete list of query results is available in Additional file 1: Table S3.

**Conclusion**

As described above, with the goal of semantically describing the information available in the PubChem archive, pre-existing ontological frameworks were used, rather than creating new ones. Semantic relationships between compounds and substances, chemical descriptors associated with compounds and substances, interrelationships between chemicals, as well as provenance and...
attribute metadata of substances were described. Future PubChemRDF papers will cover the semantic description of additional PubChem information such as bioactivity data and cross-references to proteins, genes, patents, or biomedical literature, among others.

PubChemRDF exposes data content that may not be available in any of currently existing RDF-based cheminformatics and bioinformatics resources, and it is designed to be highly compatible and consistent with them by incorporating the commonly used ontologies and vocabularies. All of the PubChemRDF URIs are dereferencable, once the exposed URIs are cross-linked by other RDF-based resources, the semantic integration should be fairly easy for end users. When considered in a wider context, there may be many promising benefits to integrating a semantic description of the PubChem chemical knowledgebase with other semantically described biological and life science domain knowledge bases. Semantic annotation of the PubChem Compound and Substance data systems works towards a machine-understandable knowledge representation, and helps pave the way to more automated and holistic data integration of scientific information. Given a collection of RDF statements describing the types and relations based on a set of formal ontologies, it is feasible to expose PubChem chemical resources to cross-domain queries, and more cross-site interoperable web applications. In addition, PubChemRDF provides a new ability for researchers to utilize schema-less data systems and so-called RDF-triple stores with SPARQL query engines to analyze data available within PubChem using local computing resources.

Availability
The dataset is publically available without license restrictions, and it can be either accessed through REST interface (documented at: https://pubchem.ncbi.nlm.nih.gov/rdf/) or downloaded at: ftp://ftp.ncbi.nlm.nih.gov/pubchem/RDF.

Additional file

Additional file 1. The supporting information for the paper entitled: PubChemRDF: towards the semantic annotation of PubChem compound and substance databases.

Abbreviations
CHEBI: Chemical Entities of Biological Interest; CHEMINF: Chemical Information Ontology; CID: PubChem compound identifier; EBI: European Bioinformatics Institute; INN: International nonproprietary names; NCBI: National Center for Biotechnology Information; OWL: Web Ontology Language; RDF: Resource Description Framework; SID: PubChem substance identifier; SIO: semantic-Biotechnology Information; URI: uniform resource identifier; UNII: unique ingredient identifier; XML: eXtenstible markup language.

Authors’ contributions
GF and EB implemented the semantic annotations; CB, MD, JH, and EW contributed to the RDF modeling and the alignment of the existing ontological framework with the PubChem specific knowledge base. All of the authors contributed to the manuscript drafting and editing. All authors read and approved the final manuscript.

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Acknowledgements
This research was supported (in part) by the Intramural Research Program of the National Library of Medicine, NIH. Many thanks to the PubChem team (including Paul Thiessen, Lianyi Han, Jane He, Siqian He) who provided database API functions to retrieve data from Compound and Substance databases.

Compliance with ethical guidelines
Competing interests
The authors declare that they have no competing interests.

Received: 2 February 2015 Accepted: 22 June 2015
Published online: 14 July 2015

References
1. PubChem. http://pubchem.ncbi.nlm.nih.gov. Accessed 8 July 2015
2. Bolton EE, Wang Y, Thiessen PA, Bryant SH (2008) Chapter 12 PubChem: integrated platform of small molecules and biological activities. In: Ralph AW, David CS (eds) Annual reports in computational chemistry, vol 4. Elsevier, USA, pp 217–241
3. Bolton EE, Kim S, Geer LY, Yu B, Bryant SH, He J PubChem synonym filtering process using crowdsourcing. In preparation
4. Bolton E, Kim S, Bryant S (2011) PubChem3D: conformer generation. J Cheminform 3(1):1
5. Cheng T, Zhao Y, Li X, Lin F, Xu Y, Zhang X et al (2007) Computation of octanol-water partition coefficients by guiding an additive model with knowledge. J Chem Inf Model 47(6):2140–2148
6. Heller S, McNaught A, Stein S, Tschekhovskoi D, Pettree I (2013) InChI—the worldwide chemical structure identification standard. J Cheminform 5(1):7
7. OECD Toolkit for SMILES. http://www.eyesopen.com/docs/toolkits/current/html/OECChem_TK-c-+/-SMILES.html. Accessed 8 July 2015
8. James CA (2012) OpenSMILES specification. http://www.opensmiles.org/opensmiles.html. Accessed 8 July 2015
9. Lexichem Toolkit for IU/PAC. http://www.eyesopen.com/docs/toolkits/current/html/Lexichem_TK-c-+/-index.html. Accessed 8 July 2015
10. Phadungsuwan K, Kraft M, Townsend JA, Murray-Rust P (2012) The semantics of Chemical Markup Language (CML) for computational chemistry: CompChem. J Cheminform 4(1):15
11. Chepelev LL, Dumontier M (2011) Chemical entity semantic specification: knowledge representation for efficient semantic cheminformatics and facile data integration. J Cheminform 3(1):20
12. W3C Linkeddata. http://www.w3.org/wiki/LinkedData. Accessed 8 July 2015
13. W3C Semantic Web. http://www.w3.org/2001/sw/. Accessed 8 July 2015
14. Wild DJ, Ding Y, Sheth AP, Harland L, Gifford EM, Lajiness MS (2012) Systems chemical biology and the Semantic Web: what they mean for the future of drug discovery research. Drug Discov Today 17(9–10):469–474
15. Luciano JS, Andersson B, Batchelor C, Bodenreider O, Clark T, Denney CK et al (2011) The Translational Medicine Ontology and Knowledge Base:
driving personalized medicine by bridging the gap between bench and bedside. J Biomed Semantics 2(Suppl 2):S1
16. Yu L (2011) A developers guide to the semantic web: Springer Publishing Company, Incorporated
17. ontop: a platform to query databases as Virtual RDF Graphs using SPARQL. http://ontop.inf.unibz.it/. Accessed 8 July 2015
18. D2R: Accessing relational databases as virtual RDF graphs. http://d2rq.org/. Accessed 8 July 2015
19. Virtuoso. http://virtuoso.openlinksw.com/. Accessed 8 July 2015
20. OWLIM. http://www.ontotext.com/owlim. Accessed 8 July 2015
21. Jupp S, Malone J, Bolleman J, Brandizzi M, Davies M, Garcia L et al (2014) The EBI RDF platform: linked open data for the life sciences. Bioinformat- ics 30(9):1338–1339
22. Belloeuf F, Nolin MA, Tourigny N, Rigault P, Morissette J (2008) Bio2RDF: towards a mashup to build bioinformatics knowledge systems. J Biomed Inform 41(5):706–716
23. Callahan A, Cruz-Toledo J, Ansell P, Dumontier M (2013) Bio2RDF Release 2: improved coverage, interoperability and provenance of life science linked data. In: Cimiano P, Coelho O, Presutti V, Hollink L, Rudolph S (eds) The semantic web: semantics and big data, vol 7882. Springer Berlin Heidelberg, pp 200–212
24. Samwald M, Jentzsch A, Bouton C, Kalleioso CS, Willighagen E, Hajagos J et al (2011) Linked open drug data for pharmaceutical research and development. J Cheminform 3(1):19
25. Chen B, Dong X, Jiao D, Wang H, Zhu Q, Ding Y et al (2010) ChemZi- o2RDF: a semantic framework for linking and data mining chemog- enomic and systems chemical biology data. BMC Bioinformatics 11:255
26. Williams AJ, Harland L, Groth P, Pettifer S, Chichester C, Willighagen EL et al (2012) Open PHACTS: semantic interoperability for drug discovery. Drug Discov Today 17(21–22):1188–1198
27. Willighagen EL, Waagmeester A, Spjuth O, Ansell P, Williams AJ, Tkachenko V et al (2013) The ChEMBL database as linked open data. J Cheminform 5(1):23
28. Brenninkmeijer C, Evelo C, Gobble C, Gray AJG, Groth P, Pettifer S et al (2012) Scientific lenses over linked data: an approach to support task specific views of the data. A vision. In: Proceedings of 2nd international workshop on linked science 2012—Tackling Big Data
29. Deytysarenko K, de Matos P, Ennis M, Hastings J, Zbinden M, McNaught A et al (2008) CheBI: a database and ontology for chemical entities of biological interest. Nucleic Acids Res 36(Database issue):D344–D350
30. de Matos P, Aicantar A, Dekker A, Ennis M, Hastings J, Haug K et al (2010) Chemical entities of biological interest: an update. Nucleic Acids Res 38(Database issue):D249–D254
31. Hastings J, de Matos P, Dekker A, Ennis M, Harsha B, Kale N et al (2013) The CheBI reference database and ontology for biologically relevant chemistry: enhancements for 2013. Nucleic Acids Res 41(Database issue):D456–D463
32. Hastings J, Chepelev L, Willighagen E, Adams N, Steinbeck C, Dumontier M (2011) The chemical information ontology: provenance and disam- biguation for chemical data on the biological semantic web. PLoS One 6(10):e25513
33. Semanticscience Integrated Ontology (SIO). http://code.google.com/p/ semanticscience/wiki/SIO. Accessed 8 July 2015
34. Gkoutos GV, Schofield PN, Hoehndorf R (2012) The units ontology: a tool for integrating units of measurement in science. Database (Oxford) 2012-ba033
35. DCMI (2012) DCMI terms. In: DCMI recommendation. http://dublincore.org/documents/dcmi-terms/. Accessed 8 July 2015
36. Shotton D (2010) CiTO, the citation typing ontology. J Biomed Semantics 1(Suppl 1):56
37. Miles A, Bechhofer S (2009) SKOS simple knowledge organization system. In: W3C recommendation. http://www.w3.org/TR/skos-reference/. Accessed 8 July 2015
38. Whetzel PL, Noy NF, Shah NH, Alexander PR, Nyulas C, Tudorache T et al (2011) BioPortal: enhanced functionality via new Web services from the National Center for Biomedical Ontology to access and use ontologies in software applications. Nucleic Acids Res 39(Web Server issue):W541–W545
39. Smith B, Ashburner M, Rosse C, Bard J, Bug W, Ceusters W et al (2007) The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration. Nat Biotechnol 25(11):1251–1255
40. Beckett D, Berners-Lee T (2011) Turtle—RDF Triple Language. In: W3C team submission. http://www.w3.org/TeamSubmission/turtle/. Accessed 8 July 2015
41. Berners-Lee T. Uniform resource identifier (URI): generic syntax. In: Request for Comments: 3986. http://www.ietf.org/rfc/rfc3986.txt. Accessed 8 July 2015
42. Cool URIs for the semantic web. http://www.w3.org/TR/ cooluris/#solutions. Accessed 8 July 2015
43. Madje T, Lanczycki CJ, Zhang D, Thiessen PA, Geer RC, Marchler- Bauer A et al (2014) MMDB and VAST+: tracking structural similarities between macromolecular complexes. Nucleic Acids Res 42(Database issue)D297–D303
44. Bolton EE, Kim S, Bryant SH (2011) PubChem3D: similar conformers. J Cheminform 3:13
45. PubChem Fingerprints. ftp://ftp.ncbi.nlm.nih.gov/pubchem/specifications/pubchem_fingerprints.txt. Accessed 8 July 2015
46. Bolton EE, Chen J, Kim S, Han L, He S, Shi W et al (2011) PubChem3D: a new resource for scientists. J Cheminform 3(1):32
47. Nanopub. http://nanopub.org/wordpress/. Accessed 8 July 2015
48. Biron PV, Permanente K, Malhotra A (2004) XML schema part 2: datatypes and evolution. In: W3C recommendation. http://www.w3.org/TR/ xmlschema-2/
49. Substance categorization classification. http://pubchem.ncbi.nlm.nih.gov/docs/subcmpd_summary_page_help.html#Clasification/Substance Categorization. Accessed 8 July 2015
50. Chepelev LL, Dumontier M (2011) Semantic web integration of cheminformatics resources with the SADI framework. J Cheminform 3:16
51. Wilkinson M, Vanderlak B, McCarthy L (2011) The semantic automated discovery and integration (SADI) web service design-pattern, API and reference implementation. J Biomed Semantics 2(1):8
52. Groth P, Gibson A, Velterop J (2010) The anatomy of a nanopublication. Inform Serv Use 30(1):51–56
53. Bio2RDF Dataset Provenance. https://github.com/bio2rdf/bio2rdf-scripts/ wiki/Bio2RDF-Dataset-Provenance. Accessed 8 July 2015
54. Nanopub. http://nanopub.org/wordpress/. Accessed 8 July 2015
55. Groth P, Gibson A, Velterop J (2010) The anatomy of a nanopublication. Inform Serv Use 30(1):51–56
56. Malona F, Miller E (2004) RDF schema primer. In: W3C recommendation. http:// www.w3.org/TR/rdf-schema/. Accessed 8 July 2015
57. Sperberg-McQueen CM, Thompson H (2000) XML schema. In: W3C recommendation. http://www.w3.org/XML/Schema. Accessed 8 July 2015