

Cheminformatics **Microservice**: unifying access to open cheminformatics toolkits

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Abstract

In recent years, cheminformatics has experienced significant advancements through the development of new open-source software tools based on various cheminformatics programming toolkits. However, adopting these toolkits presents challenges, including proper installation, setup, deployment, and compatibility management. In this work, we present **the Cheminformatics Microservice**. This open-source solution provides a unified interface for accessing commonly used functionalities of multiple cheminformatics toolkits, namely RDKit, Chemistry Development Kit (CDK), and Open Babel. In addition, more advanced functionalities like structure generation and Optical Chemical Structure Recognition (OCSR) are made available through **the Cheminformatics Microservice** based on pre-existing tools. **The software service** also enables developers to extend the functionalities easily and **to** seamlessly integrate **them** with existing workflows and applications. It is built on FastAPI and containerized using Docker, making it highly scalable. An instance of the microservice is publicly available at <https://api.naturalproducts.net>. The source code is publicly accessible on GitHub, accompanied by comprehensive documentation, version control, and continuous integration and deployment workflows. All resources can be found at the following link: <https://github.com/Steinbeck-Lab/cheminformatics-microservice>.

Graphical abstract



Keywords

CDK, RDKit, Open Babel, cheminformatics, toolkits, microservice

Introduction

Open cheminformatics toolkits, large-scale chemical databases, and an increase in available computing power have led to significant advancements in the field of cheminformatics in recent years [1,2]. As a result, large amounts of chemical data can be handled and analysed efficiently, which in turn benefits research fields like chemistry, drug discovery, and material design. Multiple prominent open-source cheminformatics toolkits are available, which include RDKit [3], Open Babel [4], Chemistry Development Kit (CDK) [5,6], Indigo [7], and the recently developed Python-based Informatics Kit for Analysing CHemical Units (PIKACHU) [8]. A summary of their native programming language, latest version, and licence information is given in Table 1.

Table 1: Summary of widely used open-source cheminformatics toolkits.

Toolkit	Programming Language	Latest Version	Licence	Source code
Open Babel	C++	3.1.1	GNU General Public License (GPL)	https://github.com/openbabel/openbabel
CDK	Java	2.8.0	GNU Lesser General Public License v2.1	https://github.com/cdk/cdk
RDKit	C++, Python	2023.03.2	BSD 3-Clause License	https://github.com/rdkit/rdkit
PIKACHU	Python	1.0.13	MIT License	https://github.com/BTheDragonMaster/pikachu
Indigo	C/C++	1.11.0	Apache License 2.0	https://github.com/epam/Indigo

All cheminformatics toolkits mentioned above offer ready-to-use routines for common tasks like data format conversions, descriptor calculations, and structure editing. On top of these, every toolkit has an individual set of more advanced functionalities like coordinate generation, substructure analysis, or structure normalisation. For this reason, researchers often use multiple toolkits in their tools or workflows [9,10]. To do so, they have to familiarise themselves with the specific requirements, syntax, and algorithms of each employed toolkit. Being familiar with the underlying programming languages such as Python, Java, or C++ is required to achieve this most efficiently. It is also essential to have a thorough understanding of chemical concepts, molecular representations, and computational algorithms.

For developing cheminformatics workflows, machine learning models, or web applications, researchers and software developers need to set up a proper working environment for the toolkits in order to integrate them into their applications. These software tools can later become cumbersome to use and maintain if not set up properly or inadequately documented. Unfortunately, this is often the case due to the complexity of the setup, lack of documentation, and lack of good research data management practices [11]. Other challenges in developing cheminformatics software, databases, and web applications result from building on top of these toolkits due to factors such as various toolkit version management [12], dependencies management [13], and maintenance [14]:

- **Software Version Management:** The purpose of this process is to effectively manage the versions of software and toolkits throughout their development and maintenance cycle. The objective is to organise and track changes, facilitate collaboration, and ensure the stability and integrity of software projects, thus increasing productivity and streamlining development processes. This process can be time-consuming and requires careful planning and organisation.

- **Dependencies:** The majority of cheminformatics tools require several interdependent [third-party](#) libraries to function. Managing these dependencies can be challenging since developers must ensure that each dependency is installed correctly and compatible with the other dependencies. Otherwise, this can lead to conflicts between dependencies, which may cause the software to malfunction.
- **Maintenance:** It is challenging to maintain software and databases as they require regular updates and bug fixes to remain up-to-date and functional. In the special case of open-source software, this usually requires a large community of active and committed users and developers.

Most cheminformatics open-source programming toolkits have a rather high entrance barrier due to the [abovementioned aspects](#). Also, the quality of available documentation [and tutorials](#) varies. This is especially critical for young researchers new to the field who have to spend a lot of setup time before being able to work on their research projects. Therefore, online tools for cheminformatics are becoming increasingly popular due to their usual ease of use, adequate documentation, and the fact that no or only little programming knowledge is required [to use them](#) [15–18]. The use of web-based solutions or solutions that are driven by Application Programming Interfaces (APIs) [19] offers a [lower](#) entrance barrier. In addition, these services are platform-independent and can be easily integrated with software utilities, databases, repositories, and cheminformatics data management workflows [17].

[To overcome the challenging integration of third-party libraries like cheminformatics toolkits into application code](#), two common software development techniques can be used: containerization and microservices. Microservices [20], also referred to as microservice architecture, is a collection of small, autonomous services that can be deployed, scaled, and maintained individually [21]. By leveraging well-defined APIs, each microservice carries out a specific function and interacts with other microservices. These services are characterised by their granular nature and employ lightweight protocols [to enable](#) the independent execution of each service [22]. The native installation of such services on a system makes maintenance difficult in the long run. The service may not function as a result of Operating System (OS) level updates or [software environment](#) conflicts. In addition, in the event of a service failure, it is necessary to reboot the entire system. In order to address these issues, containerization can be used for the deployment of [software services and](#) applications. Containers are lightweight isolated environments that enable applications and their dependencies to run consistently across a variety of systems, independent of the OS [23]. In addition, [a container](#) provides a consistent and reproducible execution environment across development, testing, and production environments. In this work, containerization was achieved using Docker [24]. Software components can be containerized using Docker and distributed publicly via the Docker Hub [25], a cloud-based registry provided by Docker that allows developers to store, share, and distribute Docker images.

This article presents [the Cheminformatics Microservice](#), an open-source solution for handling chemical data and performing various cheminformatics tasks by [employing](#) multiple

cheminformatics toolkits (CDK, RDKit, and Open Babel). These tasks include generating high-quality chemical structure depictions and 3D conformers, calculating molecular descriptors and IUPAC names, and converting SMILES representations of chemical structures into other machine-readable formats. The microservice can be accessed through a unified REST (REpresentational State Transfer) [26] interface, which is made available as a public server for anyone to access via api.naturalproducts.net. Alternatively, it can be [installed](#) locally or on a [private server](#) using the [provided](#) Docker image. It can also be deployed and [auto-scaled](#) on a [Kubernetes-managed private cluster in just a few steps via the Helm Charts provided](#) [27]. These deployment options are designed to be user-friendly [since they require](#) no prior knowledge of the underlying toolkits or their setup environment. They make [the presented software service](#) suitable for a wide range of applications in academic and industrial environments. The entire [Cheminformatics Microservice](#) source code is made available to the public on GitHub: <https://github.com/Steinbeck-Lab/cheminformatics-microservice>. Users and researchers are encouraged to submit feature requests and contribute to the microservice to ensure its continued growth.

Implementation

Cheminformatics [Microservice](#) is developed using FastAPI, a web framework for generating RESTful APIs [with](#) Python. FastAPI was chosen for this project due to its speed, efficiency, and suitability for building advanced APIs. It enables the [straightforward](#) creation of robust and scalable APIs. Docker is used for containerization, and semantic versioning principles are applied to track code changes and toolkit versions. In the [microservice](#) container, [the cheminformatics toolkits](#) RDKit and Open Babel are accessed natively using Python, while the Chemistry Development Kit (CDK) is integrated using JPytype [28]. [Cheminformatics Microservice](#) consists of five modules, namely *chem*, *convert*, *depict*, *ocsr*, and *tools*. Compliant with the OpenAPI [29] specification version 3.1.0, this work provides standard documentation, encourages interoperability, enables automatic code generation, simplifies validation, and integrates with a variety of tools and libraries to enhance the functionality of REST (REpresentational State Transfer) APIs. An overview of the [software architecture is given](#) in Figure 1.

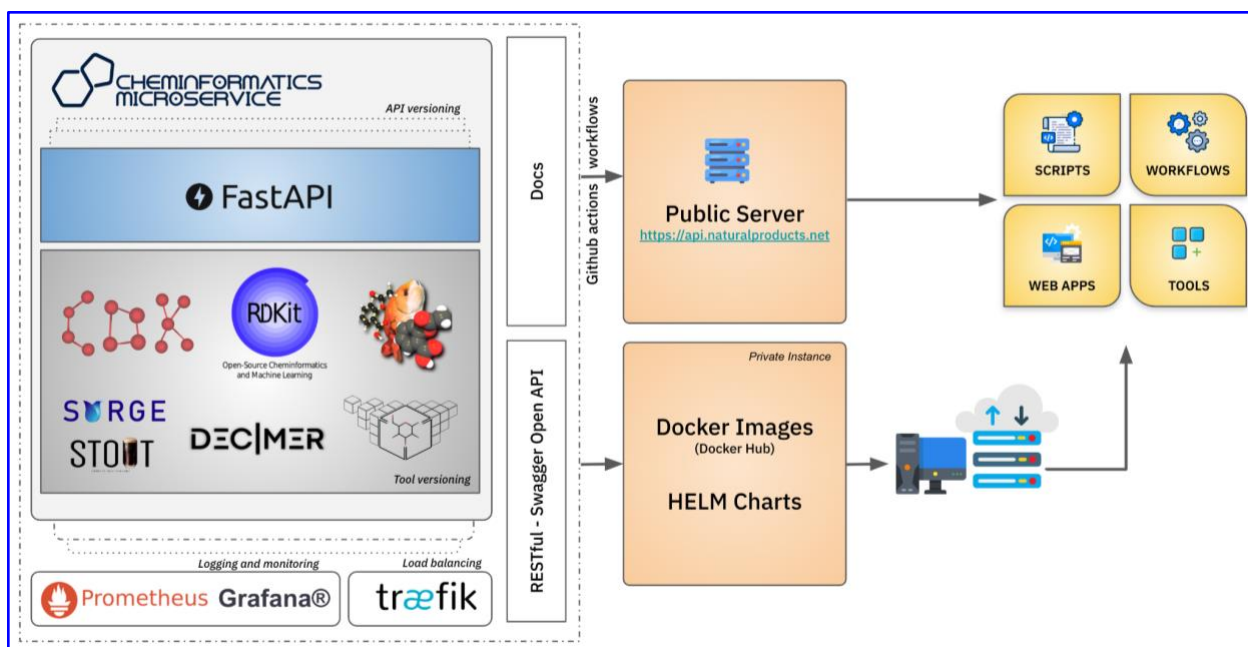


Figure 1: Overview of the Cheminformatics Microservice public server architecture. The public server can be accessed via <https://api.naturalproducts.net/latest/docs>.

The *chem* module offers various functions such as descriptor calculation, stereoisomer enumeration, HOSE code [30] generation, NPLikeness score calculation [31], ClassyFire classification [32], molecular structure standardisation [33], and a preprocessing pipeline for the upcoming version of the COCONUT database as explained in the results section below. The *convert* module provides conversions from SMILES [34] to other molecular string representations such as InChI [35,36], InChIKey [36], canonical SMILES [37], CXSMILES [38], SELFIES [39,40], and IUPAC names. The latter is achieved via the Smiles TO iUpac Translator (STOUT) version 2.0 toolkit [41]. Additionally, MOL files can be generated with 2D and 3D coordinates from SMILES input. Using the *depict* module, one can generate 2D depictions of chemical structures with various settings, including an option to generate 2D representations with stereochemical annotations following the Cahn–Ingold–Prelog [42] (CIP) sequence rules. RDKit or CDK can be used to generate 2D representations. The depictions are generated in an SVG format and may be scaled to fit the needs of the user. It is also possible to generate a 3D depiction [43] using this module, which is useful as a chemical structure display option for databases or as a teaching aid. The underlying 3D conformer is generated using RDKit. The *ocsr* module incorporates Deep Iearning for Chemical Image Recognition (DECIMER) modules [44,45] for translating images of chemical structures into machine-readable SMILES representations. These can be accessed via HTTP POST requests. Finally, the *tools* module is designated as a miscellaneous collection of advanced cheminformatics tools. It offers a function to generate chemical structures from a molecular formula given as input using the surge chemical graph generator [46]. Other functions of the *tools* module can be used to identify glycosidic moieties in input molecules and to remove them in order to generate the aglycone structure. These routines are implemented based on the Sugar Removal Utility (SRU) [47].

The functionalities offered by each main module described above can also be implemented via independent Python functions, enabling users to access [Cheminformatics Microservice](#) natively without the REST interface. Users can import and [use it](#) like any other package directly in their own Python code. Individual toolkit wrapper modules provide access to the three cheminformatics toolkits RDKit, CDK, and Open Babel. RDKit and Open Babel are natively accessible, while CDK, a Java library, has functionalities ported to Python using JPy. It is possible to extend the functionalities provided by cheminformatics toolkits in the future by [using](#) these wrapper modules. Separating them into individual modules is necessary to achieve granular control over the functions. This also ensures that the entire system will not be broken if one module is affected [by potential software failures](#). The Python functions are documented separately, and the documentation can be accessed via: <https://cheminformatics-microservice.readthedocs.io/en/latest/>.

To ensure [reproducibility](#), a [consistent](#) versioning system is essential. Best practices for research data management [48,49] recommend documenting software and component versions separately, especially for tools like [the presented microservice](#) with multiple dependencies. [Cheminformatics Microservice](#) uses multi-level versioning to record API and software dependencies. The codebase undergoes bi-annual major releases, with corresponding documentation provided for the underlying toolkits, tools, and environment dependencies for each release. The API [version updates](#) are released only when significant changes to the API endpoints have been made. It is possible to update the underlying cheminformatics toolkits whenever new releases are published without having to update the entire code base since the REST API remains unchanged. The [API usage](#) can be logged, monitored, and visualised using Prometheus [50] and Grafana [51] in a standalone or distributed environment. [Cheminformatics Microservice](#) can also be deployed using a Continuous Integration and Continuous Deployment (CI/CD) pipeline via GitHub Actions [52]. [Code](#) integration, testing, and application deployment are automated [using CI/CD](#), which fosters collaboration, minimises [manual](#) tasks, and enables timely feedback.

Results and Discussion

The [presented Cheminformatics Microservice](#) provides straightforward access to [the](#) open-source cheminformatics toolkits RDKit, CDK, and OpenBabel, as well as deep learning-[based tools such as](#) Deep Iearning for Chemical Image Recognition (DECIMER) [for OCSR](#) and Smiles TO iUpac Translator (STOUT). [Building on top of these tools and toolkits, it makes](#) a diverse selection of important functionalities needed by cheminformaticians on a daily basis accessible via a RESTful interface. Additionally, [Cheminformatics Microservice](#) includes a number of widely used packages, [like](#) the ChEMBL [53] curation pipeline [33], CDK-based sugar removal [functionalities](#) [47], and the open-source structure generator surge [46]. [The presented microservice is intended to facilitate the handling of large amounts of chemical structural data to](#) enable the development of adaptable, scalable, and [maintainable](#) cheminformatics applications.

The main modules of [Cheminformatics Microservice](#) are well-documented and can be accessed via the following link: <https://api.naturalproducts.net/>. In order to obtain the [output](#) generated by the microservice, each [API](#) module uses either a *GET* or a *POST* HTTP request method [54].

Most of the services provided by the *chem*, *convert*, and *depict* modules can be accessed using SMILES as an input format for molecular structures. Where a specific functionality provided by the microservice can be achieved in a similar manner with RDKit, CDK, or Open Babel, the user has the option of employing the toolkit of their choice via an additional parameter. The *chem* module offers routines for structure manipulation and standardisation, descriptor calculation, and chemical classification. The *standardize* functionality is used via a *POST* method for the purpose of standardising molecules represented by MOL format tables through the ChEMBL structure curation pipeline. The *convert* module enables users to convert SMILES representations into other formats of their choice, using the *GET* method. Meanwhile, the *depict* module allows users to generate customised 2D depictions of molecular structures, offering options for coloured or black and white output images. The stereochemical annotations on the 2D depictions are generated using the Cahn-Ingold-Prelog (CIP) priority rules. To accomplish this, the Java package *centres* [55,56] is used in conjunction with CDK. Additionally, the *depict* module is able to produce interactive 3D models of input structures. Figure 2 A, B illustrates the application of the depict module to generate a 2D depiction with CIP annotations in colour on a scale of 512 x 512 pixels and with a 52° rotation. The depicted image with CIP annotations can be generated directly by using this call to the API:

[https://api.naturalproducts.net/latest/depict/2D?smiles=C\[C@\]12CC\[C@H\]3\[C@H\]\(\[C@@H\]1CC\[C@@H\]2O\)CCC4=CC\(=O\)CC\[C@\]34C&width=512&height=512&rotate=52&&CIP=true&unicolor=false&toolkit=cdk](https://api.naturalproducts.net/latest/depict/2D?smiles=C[C@]12CC[C@H]3[C@H]([C@@H]1CC[C@@H]2O)CCC4=CC(=O)CC[C@]34C&width=512&height=512&rotate=52&&CIP=true&unicolor=false&toolkit=cdk)

2D representations are produced in the form of SVG images, whereas 3D representations are returned as HTML files containing embedded JSMol objects [57,58].

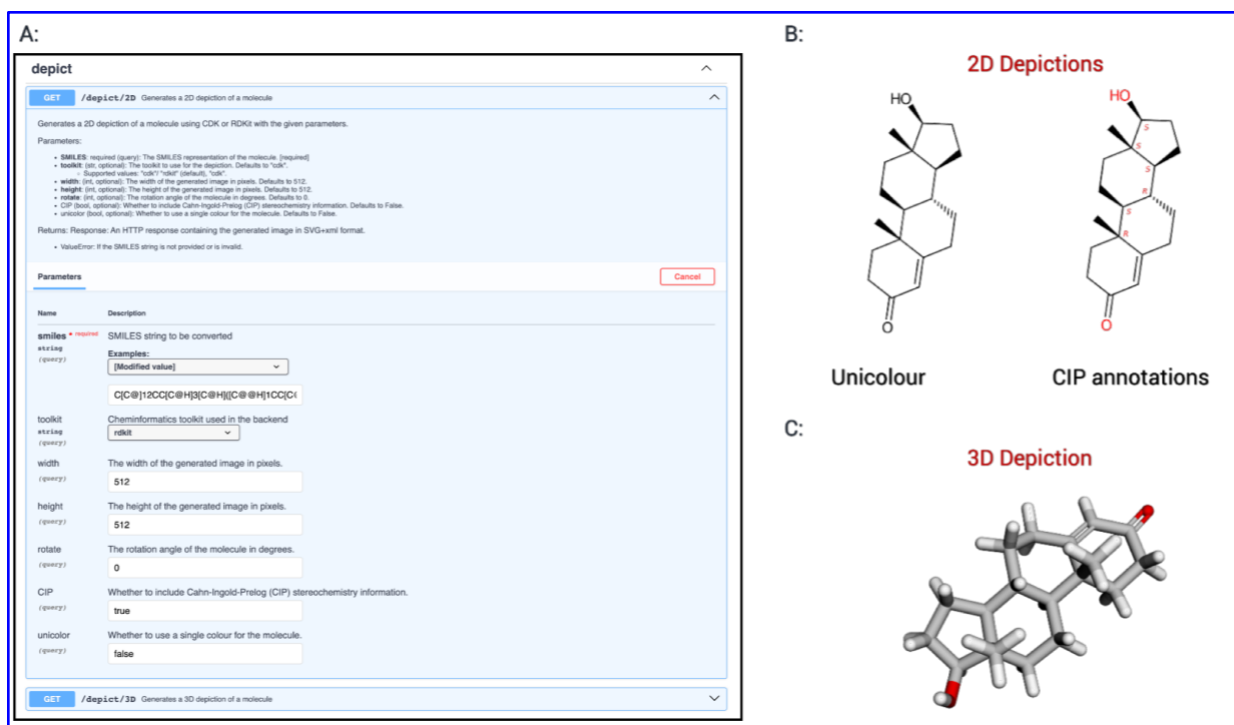


Figure 2: A: The screenshot showcases the output of the *depict* module, displaying the depiction options for the input molecule Testosterone given as a SMILES string. B: The output of the *depict* module with *unicolor* and CIP annotations for 2D depictions, and C: the interactive 3D depiction [59].

Through REST API calls, the *tools* and *ocsr* modules offer convenient access to the underlying functionalities of the integrated tools. For example, the *tools* module allows users to employ the open-source chemical structure generator surge to generate chemically valid structures based on a provided molecular formula. The generated structures are returned as a list of SMILES representations. In order to address the resource-intensive nature of the chemical structure generation process, a maximum limit of 10 heavy atoms in the given molecular formula has been imposed. This restriction applies exclusively to the public instance. The *tools* module also allows users to access the Sugar Removal Utility (SRU) to detect and remove linear and circular sugar moieties in/from input structures. Users can access the DECIMER toolkit through the *ocsr* module, which enables identification, segmentation, and translation into machine-readable representations of chemical structure depictions from the scientific literature.

Currently, *Cheminformatics Microservice* is available to the public via <https://api.naturalproducts.net/latest/docs> and in the back end, the container is running on a compute server with the processor Intel(R) Xeon(R) Gold 6226R CPU @ 2.90GHz and 16GB of RAM.

Use of Cheminformatics Microservice in the COCONUT database

Cheminformatics Microservice is extensively employed in the upcoming version of the COCONUT (COLleCtion of Open Natural prodUCtS) database that is currently under development. With the *depict* module, it becomes feasible to present all the natural product structure data entries within COCONUT in both 2D and 3D formats (Figure 3). The microservice also includes the generation of molecular descriptors and further preprocessing steps for data submission to the COCONUT database.

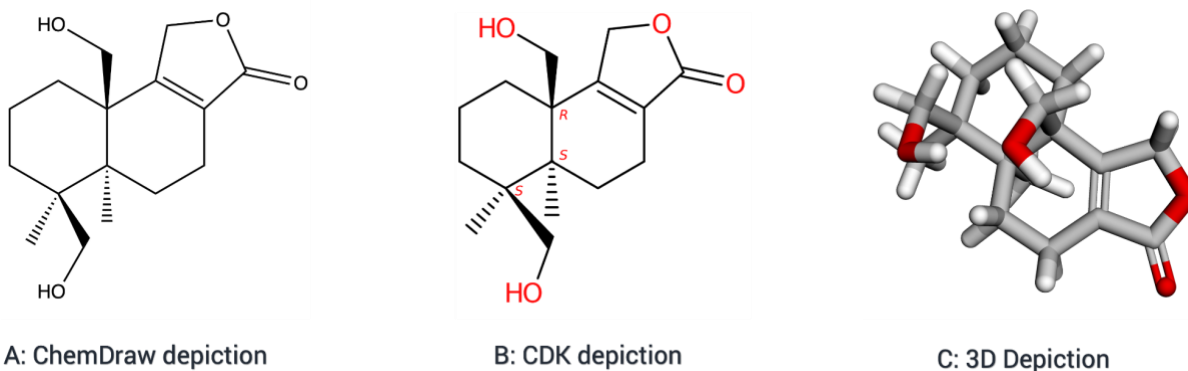


Figure 3: The molecule [Astellolide W](#) [60] was extracted from the referenced article using DECIMER. The structure is depicted using ChemDraw (A) and CDK (B) for 2D representations, while the 3D depiction (C) was created using [the presented microservice](#).

Documentation

Cheminformatics Microservice offers detailed documentation alongside its source code, ensuring that users can easily access and navigate it without a high entry barrier. The documentation provides clear guidance on how to effectively [use](#), [deploy](#), and [install the software](#). Figure 4 offers a glimpse of the documentation that is deployed using GitHub Pages and can be accessed at the following URL:

<https://docs.api.naturalproducts.net>.

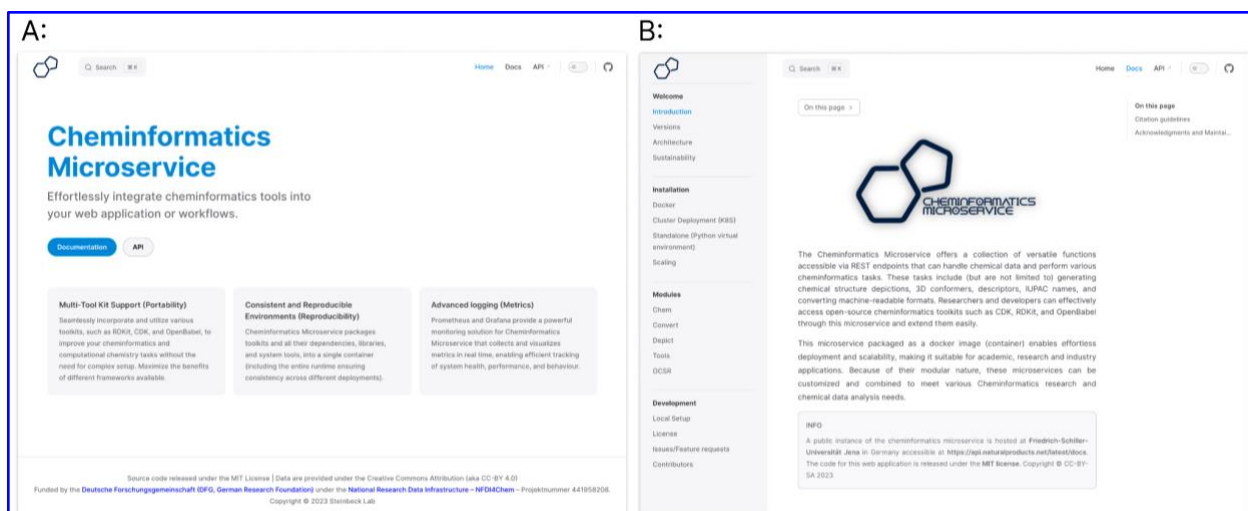


Figure 4: Screenshots of the [Cheminformatics Microservice](#) landing page (A) and detailed documentation (B)

Performance and scalability

Scaling is particularly important for those who plan to use the API endpoints for database generation, large-scale descriptor calculation, or automated literature mining since it considerably reduces the overall computation time required. Cheminformatics Microservice is specifically designed to scale at large, in a local deployment as well as an orchestrated cluster. It can be configured to run on multiple workers when deployed independently. If deployed through Docker Compose or over a Kubernetes cluster, the microservice can be auto-scaled infinitely to handle incoming requests. Helm Chart or the Docker Compose file provided in the codebase enable scaling without any additional setup. Prometheus and Grafana are used to monitor the request count over time. These logs and other performance indicators will facilitate the scaling of Cheminformatics Microservice workers based on user demand in the future.

To determine scalability, stress testing was performed using Vegeta [61]. To determine the maximum throughput Cheminformatics Microservice can handle when deployed on a machine with Intel(R) Xeon(R) Gold 6226R CPU @ 2.90GHz and 16GB of RAM, requests in small increments were added using Vegeta and the delivered throughput was measured until a limit was reached (Figure 5). This stress test indicated that the service reached its maximum capacity when handling approximately 2500 requests per second for echo requests, after which the success rate began to decline. When queried with the task to generate 2D coordinates for a molecular structure given as a SMILES string using RDKit, Figure 5 clearly demonstrates that the microservice can effectively handle a wide range of requests, ranging from 50 to 500 per second. With an increase in the input molecule size and number of requests per second, this rate starts to deteriorate. A detailed description of the stress test can be found in the supplementary information.

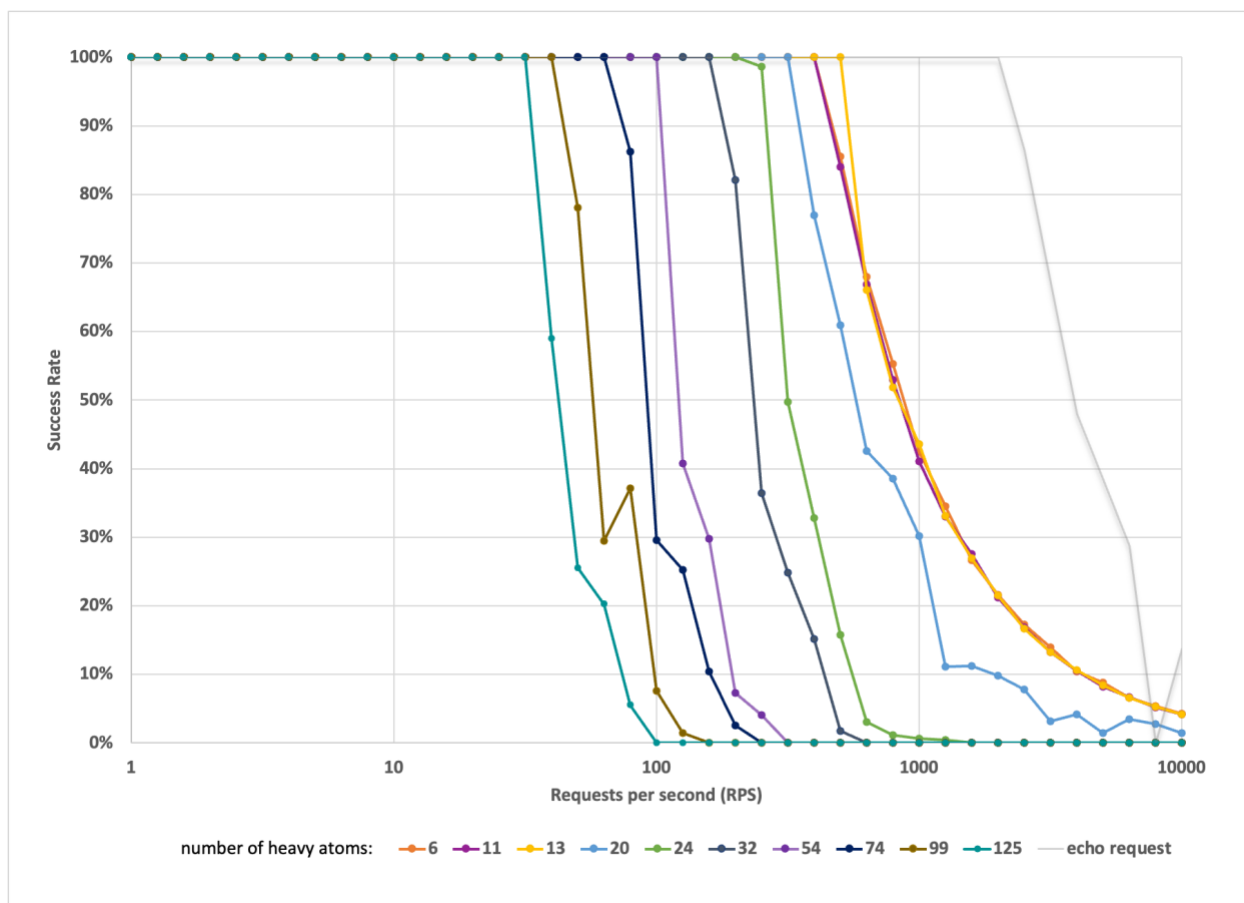


Figure 5: A snapshot of performance comparing the success rate with an increase in the number of requests per second as well as with an increase in the number of heavy atoms in the input. The grey line represents the maximum number of requests the server could process (echo request).

Nevertheless, the default configuration of [Cheminformatics Microservice](#) ensures excellent stability in handling user requests and effectively manages to [execute](#) the computation required.

However, limitations are imposed on [the](#) public instance [for some specific](#) tools and routines. For example, restrictions are imposed in the structure generator [surge](#) when dealing with molecules containing more than ten heavy atoms, as this service demands significant computational resources. Access to mass mining through the DECIMER endpoint is also restricted. [These](#) restrictions might be reconsidered in the future, depending on the user demand and computation resource availability.

Conclusion

The [presented Cheminformatics Microservice](#) is a self-contained, web-based service that operates independently of the operating system. This can be used by researchers with no or

limited programming experience to perform daily cheminformatics tasks effortlessly via the API hosted at <https://api.naturalproducts.net>. This service allows a diverse range of open-source cheminformatics toolkits to be accessed without requiring any software installation or environment setups. To the best of our knowledge, it is currently the sole **microservice in the field of cheminformatics** offering users the ability to access multiple toolkits, as well as additional tools such as the open-source structure generator surge, Sugar Removal Utility (SRU), and the DECIMER OCSR tools. **Cheminformatics Microservice** is designed to be user-friendly, easily extendable, deployable, and scalable. It can be accessed through the public API or hosted on private clusters or single machines.

The integration of multiple cheminformatics toolkits in a centralised platform enhances user accessibility to cheminformatics utilities. By using industry-standard monitoring, deployment, documentation, and code quality standards, this project demonstrates software development in a user-focused manner. By making the source code and the documentation completely open and public, we aim to make valuable contributions to the scientific community while also enabling the submission of feature requests for future enhancements. **Cheminformatics Microservice is anticipated to become** an invaluable asset for cheminformaticians due to its inherent expandability. It follows a clear semantic versioning system, receives bi-annual updates, and includes comprehensive documentation. These characteristics significantly facilitate data reproduction and reuse for researchers, thereby fostering better collaboration among peers.

List of abbreviations

2D - Two Dimensional

3D - Three Dimensional

APIs - Application Programming Interfaces

BSD - Berkeley Software Distribution

CC - Creative Commons

CDK - Chemistry Development Kit

CI/CD - Continuous Integration and Continuous Deployment

CIP - Cahn–Ingold–Prelog

COCONUT - COLleCtion of Open Natural prodUcTs

CPU - Central Processing Unit

CXSMILES - Chemaxon Extended Simplified Molecular Input Line Entry Specification

DECIMER - Deep IEarning for Chemical Image Recognition

GB - Gigabyte

GHz - Gigahertz

GNU - GNU's Not Unix

GPL - General Public License

HOSE - Hierarchically Ordered Spherical Environment

HTTP - Hypertext Transfer Protocol

HTML - [Hypertext Markup Language](#)

InChI - International Chemical Identifier

IUPAC - International Union of Pure and Applied Chemistry

JDK - Java Development Kit
JPyPe - Java for Python
JSMol - JavaScript Molecular viewer
MIT - Massachusetts Institute of Technology
NPLikeness - Natural Product Likeness
OCSR - Optical Chemical Structure Recognition
OS - Operating System
PC - Personal Computer
PIKACHU - Python-based Informatics Kit for Analysing CHemical Units
RAM - Random Access Memory
REST - REpresentational State Transfer
SELFIES - SELF-referencing Embedded Strings
SMILES - Simplified Molecular Input Line Entry Specification
SRU - Sugar Removal Utility
STOUT - SMILES-TO-IUPAC-name translator
SVG - Scalable Vector Graphics

Availability and requirements

- **Project name:** Cheminformatics Microservice
- **Project home page:** <https://github.com/Steinbeck-Lab/cheminformatics-microservice>
- **Docker Image:** <https://hub.docker.com/r/nfdi4chem/cheminformatics-microservice>
- **Helm Chart repo :** <https://nfdi4chem.github.io/repo-helm-charts/>
- **Helm Chart GitHub:** <https://github.com/NFDI4Chem/repo-helm-charts>
- **Current version:** v1.6.0
- **DOI of archived current release:** <https://doi.org/10.5281/zenodo.7745987>
- **Operating system(s):** Independent
- **Programming language:** Python 3, HTML
- **Requirements:**
 - API calls:
 - Internet connection and command line interface or a web browser
 - Run locally:
 - Docker - To use [Cheminformatics Microservice](#) as a Docker container.
 - Conda environment - to use [Cheminformatics Microservice](#) natively without Docker.
 - Dependencies (managed by Docker/Conda):
 - Python packages: uvicorn>=0.15.0,<0.16.0, fastapi>=0.80.0, fastapi-pagination==0.10.0, fastapi-versioning>=0.10.0, prometheus-fastapi-instrumentator, jpype1==1.4.1, jinja2, pandas, chembl_structure_pipeline, HOSE_code_generator @ [git+https://github.com/Ratsemaat/HOSE_code_generator](https://github.com/Ratsemaat/HOSE_code_generator), websockets==10.4, pillow==9.4.0, opencv-python==4.7.0.68, matplotlib==3.4.3, scikit-image, pdf2image==1.16.2, IPython, pystow>=0.4.9, unicodedata2==15.0.0, efficientnet, tensorflow==2.12.0,

- pillow-heif==0.10.0, selfies>=2.1.1, httpx>=0.24.1,
keras_preprocessing==1.1.2, decimer-segmentation>=1.1.2, STOUT-
pypi>=2.0.5 and decimer>=2.2.0
 - Java: OpenJDK for Java 11
 - Java Libraries: CDK 2.8.0 , SRU 1.3.2 and Centres 1.0
- **Licence:** MIT
- **Documentation:**
 - Home page: <https://docs.api.naturalproducts.net/>
 - API: <https://api.naturalproducts.net/latest/docs>
 - Python **Documentation:** <https://cheminformatics-microservice.readthedocs.io/en/latest/>
- **Any restrictions to use by non-academics:** None.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

The authors have given their consent for the work to be published.

Competing interests

The authors do not have any competing interests to declare.

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Authors' contributions

VC and KR initiated the project and developed the software. NS developed, automated, and documented the work. JS helped with Java porting. KR designed the logo. VC, JS, and KR wrote the paper together. KR and CS supervised the study. All authors read and approved the final manuscript.

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References

1. Ambure, P.; Aher, R.B.; Roy, K. Recent Advances in the Open Access Cheminformatics Toolkits, Software Tools, Workflow Environments, and Databases. In *Methods in Pharmacology and Toxicology*; Methods in pharmacology and toxicology; Springer New York: New York, NY, 2014; pp. 257–296 ISBN 9781493935192.
2. Wegner, J.K.; Sterling, A.; Guha, R.; Bender, A.; Faulon, J.-L.; Hastings, J.; O'Boyle, N.; Overington, J.; Van Vlijmen, H.; Willighagen, E. Cheminformatics. *Commun. ACM* **2012**, *55*, 65–75, doi:10.1145/2366316.2366334.
3. Landrum, G.; Others RDKit: Open-Source Cheminformatics Software.(2016). URL <http://www.rdkit.org/>, <https://github.com/rdkit/rdkit> **2016**.
4. O'Boyle, N.M.; Banck, M.; James, C.A.; Morley, C.; Vandermeersch, T.; Hutchison, G.R. Open Babel: An Open Chemical Toolbox. *J. Cheminform.* **2011**, *3*, 33, doi:10.1186/1758-2946-3-33.
5. Willighagen, E.L.; Mayfield, J.W.; Alvarsson, J.; Berg, A.; Carlsson, L.; Jeliaskova, N.; Kuhn, S.; Pluskal, T.; Rojas-Chertó, M.; Spjuth, O.; et al. The Chemistry Development Kit (CDK) v2.0: Atom Typing, Depiction, Molecular Formulas, and Substructure Searching. *Journal of Cheminformatics* **2017**, *9*. doi: 10.1186/s13321-017-0220-4
6. Steinbeck, C.; Han, Y.; Kuhn, S.; Horlacher, O.; Luttmann, E.; Willighagen, E. The Chemistry Development Kit (CDK): An Open-Source Java Library for Chemo- and Bioinformatics. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 493–500, doi:10.1021/ci025584y.
7. Indigo Toolkit Available online: <https://lifescience.opensource.epam.com/indigo/> (accessed on 25 June 2020).
8. Terlouw, B.R.; Vromans, S.P.J.M.; Medema, M.H. PIKACHU: A Python-Based Informatics Kit for Analysing Chemical Units. *J. Cheminform.* **2022**, *14*, 34, doi:10.1186/s13321-022-00616-5.
9. Brinkhaus, H.O.; Rajan, K.; Zielesny, A.; Steinbeck, C. RanDepict: Random Chemical Structure Depiction Generator. *J. Cheminform.* **2022**, *14*, 31, doi:10.1186/s13321-022-00609-4.
10. Zulfiqar, M.; Gadelha, L.; Steinbeck, C.; Sorokina, M.; Peters, K. MAW: The Reproducible Metabolome Annotation Workflow for Untargeted Tandem Mass Spectrometry. *J. Cheminform.* **2023**, *15*, 32, doi:10.1186/s13321-023-00695-y.
11. Ashiq, M.; Usmani, M.H.; Naeem, M. A Systematic Literature Review on Research Data

Management Practices and Services. *Glob. Knowl. Mem. Commun.* **2022**, 71, 649–671, doi:10.1108/gkmc-07-2020-0103.

12. Van Gurp, J.; Prehofer, C. Version Management Tools as a Basis for Integrating Product Derivation and Software Product Families. In Proceedings of the Proceedings of the Workshop on Variability Management-Working with Variability Mechanisms at SPLC; 2006; pp. 48–58.
13. Esparrachiari, S.; Reilly, T.; Rentz, A. Tracking and Controlling Microservice Dependencies. *ACM Queue* **2018**, 16, 44–65, doi:10.1145/3277539.3277541.
14. Canfora, G.; Cimitile, A. SOFTWARE MAINTENANCE. In *Handbook of Software Engineering and Knowledge Engineering*; World Scientific Publishing Company, 2001; pp. 91–120 ISBN 9789810249731.
15. Huang, Y.-C.; Tremouilhac, P.; Nguyen, A.; Jung, N.; Bräse, S. ChemSpectra: A Web-Based Spectra Editor for Analytical Data. *J. Cheminform.* **2021**, 13, 8, doi:10.1186/s13321-020-00481-0.
16. Jablonka, K.M.; Moosavi, S.M.; Asgari, M.; Ireland, C.; Patiny, L.; Smit, B. A Data-Driven Perspective on the Colours of Metal-Organic Frameworks. *Chem. Sci.* **2020**, 12, 3587–3598, doi:10.1039/d0sc05337f.
17. Patiny, L.; Borel, A. ChemCalc: A Building Block for Tomorrow's Chemical Infrastructure. *J. Chem. Inf. Model.* **2013**, 53, 1223–1228, doi:10.1021/ci300563h.
18. Patiny, L.; Zasso, M.; Kostro, D.; Bernal, A.; Castillo, A.M.; Bolaños, A.; Asencio, M.A.; Pellet, N.; Todd, M.; Schloerer, N.; et al. The C6H6 NMR Repository: An Integral Solution to Control the Flow of Your Data from the Magnet to the Public. *Magn. Reson. Chem.* **2018**, 56, 520–528, doi:10.1002/mrc.4669.
19. Ofoeda, J.; Boateng, R.; Effah, J. Application programming interface (API) research. *Int. J. Enterp. Inf. Syst.* **2019**, 15, 76–95, doi:10.4018/ijeis.2019070105.
20. Newman, S. *Building Microservices*; O'Reilly Media, 2015; ISBN 9781491950357.
21. Wolff, E. *Microservices: Flexible Software Architecture*; Addison-Wesley, 2017; ISBN 9780134602417.
22. Chen, L. Microservices: Architecting for Continuous Delivery and DevOps. In Proceedings of the 2018 IEEE International Conference on Software Architecture (ICSA); April 2018; pp. 39–397.
23. Containerization Explained Available online: <https://www.ibm.com/topics/containerization> (accessed on 22 June 2023).
24. Turnbull, J. *The Docker Book: Containerization Is the New Virtualization*; James Turnbull, 2014; ISBN 9780988820203.
25. Cook, J. Docker Hub. In *Docker for Data Science: Building Scalable and Extensible Data Infrastructure Around the Jupyter Notebook Server*; Cook, J., Ed.; Apress: Berkeley, CA,

2017; pp. 103–118 ISBN 9781484230121.

26. Sohan, S.M.; Maurer, F.; Anslow, C.; Robillard, M.P. A Study of the Effectiveness of Usage Examples in REST API Documentation. In Proceedings of the 2017 IEEE Symposium on Visual Languages and Human-Centric Computing (VL/HCC); October 2017; pp. 53–61.
27. Gokhale, S.; Poosarla, R.; Tikar, S.; Gunjawate, S.; Hajare, A.; Deshpande, S.; Gupta, S.; Karve, K. Creating Helm Charts to Ease Deployment of Enterprise Application and Its Related Services in Kubernetes. In Proceedings of the 2021 International Conference on Computing, Communication and Green Engineering (CCGE); September 2021; pp. 1–5.
28. Nelson, K.E.; Scherer, M.K.; Others *JPytype*; Lawrence Livermore National Lab.(LLNL), Livermore, CA (United States), 2020.
29. Initiative, O. Openapi Initiative, 2021. . [org/web/20210210172220/https://www. openapis. Org](https://web/20210210172220/https://www.openapis.Org).
30. Bremser, W. Hose — a Novel Substructure Code. *Anal. Chim. Acta* **1978**, *103*, 355–365, doi:10.1016/S0003-2670(01)83100-7.
31. Ertl, P.; Roggo, S.; Schuffenhauer, A. Natural Product-Likeness Score and Its Application for Prioritization of Compound Libraries. *J. Chem. Inf. Model.* **2008**, *48*, 68–74, doi:10.1021/ci700286x.
32. Djoumbou Feunang, Y.; Eisner, R.; Knox, C.; Chepelev, L.; Hastings, J.; Owen, G.; Fahy, E.; Steinbeck, C.; Subramanian, S.; Bolton, E.; et al. ClassyFire: Automated Chemical Classification with a Comprehensive, Computable Taxonomy. *J. Cheminform.* **2016**, *8*, 61, doi:10.1186/s13321-016-0174-y.
33. Bento, A.P.; Hersey, A.; Félix, E.; Landrum, G.; Gaulton, A.; Atkinson, F.; Bellis, L.J.; De Veij, M.; Leach, A.R. An Open Source Chemical Structure Curation Pipeline Using RDKit. *J. Cheminform.* **2020**, *12*, 51, doi:10.1186/s13321-020-00456-1.
34. Weininger, D. SMILES, a Chemical Language and Information System. 1. Introduction to Methodology and Encoding Rules. *J. Chem. Inf. Comput. Sci.* **1988**, *28*, 31–36, doi:10.1021/ci00057a005.
35. Heller, S.R.; McNaught, A.; Pletnev, I.; Stein, S.; Tchekhovskoi, D. InChI, the IUPAC International Chemical Identifier. *J. Cheminform.* **2015**, *7*, 23, doi:10.1186/s13321-015-0068-4.
36. The IUPAC International Chemical Identifier (InChI). *Chemistry International -- Newsmagazine for IUPAC* **2009**, *31*, 7–9, doi:10.1515/ci.2009.31.1.7.
37. Weininger, D.; Weininger, A.; Weininger, J.L. SMILES. 2. Algorithm for Generation of Unique SMILES Notation. *J. Chem. Inf. Comput. Sci.* **1989**, *29*, 97–101, doi:10.1021/ci00062a008.
38. Chemaxon Extended SMILES and SMARTS - CXSMILES and CXSMARTS Available online: <https://docs.chemaxon.com/display/docs/chemaxon-extended-smiles-and-smarts-cxsmiles-and-cxsmarts.md> (accessed on 22 June 2023).

39. Krenn, M.; Häse, F.; Nigam, A.; Friederich, P.; Aspuru-Guzik, A. Self-Referencing Embedded Strings (SELFIES): A 100% Robust Molecular String Representation. *Mach. Learn.: Sci. Technol.* **2020**, *1*, 045024, doi:10.1088/2632-2153/aba947.
40. Krenn, M.; Ai, Q.; Barthel, S.; Carson, N.; Frei, A.; Frey, N.C.; Friederich, P.; Gaudin, T.; Gayle, A.A.; Jablonka, K.M.; et al. SELFIES and the Future of Molecular String Representations. *Patterns Prejudice* **2022**, *3*, 100588, doi:10.1016/j.patter.2022.100588.
41. Rajan, K.; Zielesny, A.; Steinbeck, C. STOUT: SMILES to IUPAC Names Using Neural Machine Translation. *J. Cheminform.* **2021**, *13*, 34, doi:10.1186/s13321-021-00512-4.
42. Cahn, R.S.; Ingold, C.; Prelog, V. Specification of Molecular Chirality. *Angew. Chem. Int. Ed Engl.* **1966**, *5*, 385–415, doi:10.1002/anie.196603851.
43. Rego, N.; Koes, D. 3Dmol.js: Molecular Visualization with WebGL. *Bioinformatics* **2015**, *31*, 1322–1324, doi:10.1093/bioinformatics/btu829.
44. Rajan, K.; Brinkhaus, H.O.; Sorokina, M.; Zielesny, A.; Steinbeck, C. DECIMER-Segmentation: Automated Extraction of Chemical Structure Depictions from Scientific Literature. *J. Cheminform.* **2021**, *13*, 20, doi:10.1186/s13321-021-00496-1.
45. Rajan, K.; Brinkhaus, H.O.; Isabel Agea, M.; Zielesny, A.; Steinbeck, C. DECIMER.ai - An Open Platform for Automated Optical Chemical Structure Identification, Segmentation and Recognition in Scientific Publications. *ChemRxiv* **2023**, doi:10.26434/chemrxiv-2023-xhcx9.
46. McKay, B.D.; Yirik, M.A.; Steinbeck, C. Surge: A Fast Open-Source Chemical Graph Generator. *J. Cheminform.* **2022**, *14*, 24, doi:10.1186/s13321-022-00604-9.
47. Schaub, J.; Zielesny, A.; Steinbeck, C.; Sorokina, M. Too Sweet: Cheminformatics for Deglycosylation in Natural Products. *J. Cheminform.* **2020**, *12*, 67, doi:10.1186/s13321-020-00467-y.
48. Wilkinson, M.D.; Dumontier, M.; Aalbersberg, I.J.J.; Appleton, G.; Axton, M.; Baak, A.; Blomberg, N.; Boiten, J.-W.; da Silva Santos, L.B.; Bourne, P.E.; et al. The FAIR Guiding Principles for Scientific Data Management and Stewardship. *Sci Data* **2016**, *3*, 160018, doi:10.1038/sdata.2016.18.
49. Hoyt, C.T.; Zdrazil, B.; Guha, R.; Jeliaskova, N.; Martinez-Mayorga, K.; Nittinger, E. Improving Reproducibility and Reusability in the Journal of Cheminformatics. *J. Cheminform.* **2023**, *15*, 62, doi:10.1186/s13321-023-00730-y.
50. Prometheus Overview Available online: <https://prometheus.io/docs/introduction/overview/> (accessed on 23 June 2023).
51. Chakraborty, M.; Kundan, A.P. Grafana. In *Monitoring Cloud-Native Applications: Lead Agile Operations Confidently Using Open Source Software*; Chakraborty, M., Kundan, A.P., Eds.; Apress: Berkeley, CA, 2021; pp. 187–240 ISBN 9781484268889.
52. Chandrasekara, C.; Herath, P. Introduction to GitHub Actions. In *Hands-on GitHub Actions: Implement CI/CD with GitHub Action Workflows for Your Applications*; Chandrasekara, C.,

Herath, P., Eds.; Apress: Berkeley, CA, 2021; pp. 1–8 ISBN 9781484264645.

53. Gaulton, A.; Hersey, A.; Nowotka, M.; Bento, A.P.; Chambers, J.; Mendez, D.; Mutowo, P.; Atkinson, F.; Bellis, L.J.; Cibrián-Uhalte, E.; et al. The ChEMBL Database in 2017. *Nucleic Acids Res.* **2017**, *45*, D945–D954, doi:10.1093/nar/gkw1074.
54. Taneja, S.; Gupta, P.R. Python as a Tool for Web Server Application Development. *JIMS8/-International Journal of Information* **2014**.
55. Hanson, R.M.; Musacchio, S.; Mayfield, J.W.; Vainio, M.J.; Yerin, A.; Redkin, D. Algorithmic Analysis of Cahn-Ingold-Prelog Rules of Stereochemistry: Proposals for Revised Rules and a Guide for Machine Implementation. *J. Chem. Inf. Model.* **2018**, *58*, 1755–1765, doi:10.1021/acs.jcim.8b00324.
56. John, M. (2018). Centres: Perception and Labelling of Stereogenic Centres in Chemical Structures (*Version 1.0*) [*Computer software*]; Github.
57. Herráez, A. Biomolecules in the Computer: Jmol to the Rescue. *Biochem. Mol. Biol. Educ.* **2006**, *34*, 255–261, doi:10.1002/bmb.2006.494034042644.
58. Hanson, R.M.; Prilusky, J.; Renjian, Z.; Nakane, T.; Sussman, J.L. JSmol and the next-Generation Web-Based Representation of 3D Molecular Structure as Applied toProteopedia. *Isr. J. Chem.* **2013**, *53*, 207–216, doi:10.1002/ijch.201300024.
59. PubChem Testosterone Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/6013> (accessed on 23 June 2023).
60. Dai, G.; Sun, J.; Peng, X.; Shen, Q.; Wu, C.; Sun, Z.; Sui, H.; Ren, X.; Zhang, Y.; Bian, X. Astellolides R-W, Drimane-Type Sesquiterpenoids from an *Aspergillus Parasiticus* Strain Associated with an Isopod. *J. Nat. Prod.* **2023**, doi:10.1021/acs.jnatprod.3c00215.
61. Senart, T. *Vegeta: HTTP Load Testing Tool and Library. It's over 9000!*; Github.