Journal of Cheminformatics

DATABASE

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FluoBase: a fluorinated agents database

Rafal Mulka[1†], Dan Su[2†], Wen-Shuo Huang[2†], Li Zhang[2†], Huaihai Huang[2], Xiaoyu Lai[1], Yao Li[1*] and Xiao-Song Xue[1,2*]

Abstract Organofluorine compounds, owing to their unique physicochemical properties, play an increasingly crucial role in fields such as medicine, pesticides, and advanced materials. Fluorinated reagents are indispensable for developing efficient synthetic methods for organofluorine compounds and serve as the cornerstone of organofluorine chemistry. Equally important are fluorinated functional molecules, which contribute specific properties necessary for applications in pharmaceuticals, agrochemicals, and materials science. However, information about these agents' structure, properties, and functions is scattered throughout vast literature, making it inconvenient for synthetic chemists to access and utilize them effectively. Recognizing the need for a dedicated and organized resource, we present FluoBase—a comprehensive fluorinated agents database designed to streamline access to key information about fluorinated agents. FluoBase aims to become the premier resource for information related to fluorine chemistry, serving the scientific community and anyone interested in the applications of fluorine chemistry and machine learning for property predictions. FluoBase is freely available at https://fluobase.siochemdb.com.

Scientific contribution

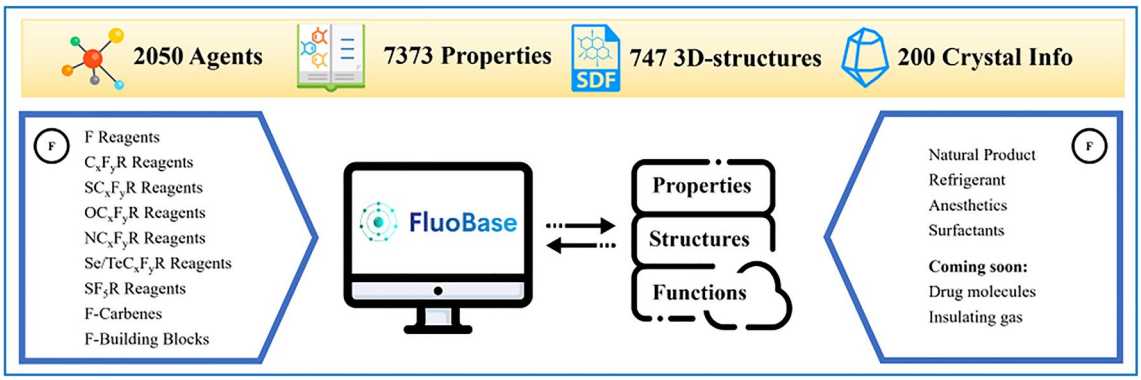
FluoBase is a database designed to provide comprehensive information on the structures, properties, and functions of fluorinated agents and functional molecules. FluoBase aims to become the premier resource for fluorine chemistry, serving the scientific community and anyone interested in the applications of fluorine chemistry and machine learning for property predictions.

Keywords Organofluorine chemistry, Database, Reagent, Agent

†Rafal Mulka, Dan Su, Wen-Shuo Huang and Li Zhang have contributed equally to this work.

*Correspondence:
Yao Li
liyao@sioc.ac.cn
Xiao-Song Xue
xuexs@sioc.ac.cn
Full list of author information is available at the end of the article

Graphical Abstract



Introduction

Due to their unique biological, physical, and chemical properties, organofluorine compounds are becoming increasingly important in various fields of chemistry and everyday life [1–3]. For instance, fluorine has emerged as a "magic element" in pharmaceuticals and agrochemicals, with approximately 30% of all agrochemicals and 20% of pharmaceuticals on the market containing fluorine [4–11]. This is due to the fact that the incorporation of fluorine or fluoroalkyl groups into drug molecules often enhances pharmacokinetic properties, binding selectivity, and metabolic stability, thereby contributing to their overall efficacy and stability. Additionally, fluorinated compounds are extensively utilized in many advanced functional materials [12–17]. This growing utilization has led to an increased demand for safe and efficient reagents and selective synthetic methodologies for introducing fluorine or fluorine-containing groups into organic compounds [18–33].

Over the past few decades, diverse fluorinating and fluoroalkylating reagents have been developed [34–50], significantly advancing synthetic fluorine chemistry. However, the details regarding the structure, properties, and functions of these reagents, as well as fluorinated functional molecules, are scattered across numerous sources, presenting a challenge for synthetic chemists seeking to efficiently integrate this information into their work.

In light of the growing significance of databases in the pharmaceutical and chemical sciences-particularly with the advent of artificial intelligence [51–56], establishing a dedicated open-source database for fluorinated agents presents a valuable opportunity. Existing resources, such as PubChem [57, 58], ChEMBL database [59], ZINC database [60], Protein Data Bank [61], DrugBank [62], Open Reaction Database [63], *i*Bond [64], database for natural products [65–67] and so on, underscore the benefits of centralized information.

In this contribution, we wish to report a comprehensive and publicly accessible database, FluoBase, dedicated to fluorinated agents. FluoBase will provide detailed information on the physical and chemical characteristics and synthetic methods of various fluorinating reagents. By offering this valuable and easily accessible resource, FluoBase aims to foster the development and application of fluorinated reagents. In addition to fluorinating reagents, FluoBase will also encompass a wide range of fluorinated functional molecules, including natural products, refrigerants, anesthetics, surfactants, and drug molecules. Launched in 2024, FluoBase aspires to become the premier resource for information related to fluorine chemistry, serving the scientific community and anyone interested in the applications of fluorine chemistry and machine learning for property predictions.

Construction and content

The main objective of this work is to accelerate research and stimulate new discoveries in fluorine chemistry. To achieve this, a robust and efficient database was developed using MongoDB, a document database designed for modern application development and cloud environments, storing data in BSON (Binary JSON) format, which allows for a flexible schema. This means documents with different structures can be stored within the same collection. Despite MongoDB's non-relational nature and lack of foreign keys, an ID system was implemented in the *reference* collection. This ID was then used within the *reagent* collection as a pseudo foreign key, enabling each dataset to be linked back to its source in the literature. This design facilitates easy verification of

data origins by allowing users to access the corresponding journal page directly through provided links.

In addition to the curated collections, the database integrates a wide range of comprehensive data sourced from scientific literature. This includes detailed information on 2050 molecules (comprising 1810 fluorinated reagents and 240 fluorinated functional molecules), 7373 properties, 747 3D structures, 200 CCDC crystal data and 1208 references spanning all these datasets. This wealth of information provides researchers with an invaluable resource to explore, analyze, and advance the field of fluorine chemistry.

To facilitate efficient interaction with the database, both GraphQL and REST APIs were implemented. The REST API is primarily used for retrieving images from SMILES representations, while GraphQL handles all other data operations, enabling more flexible and efficient queries. These powerful developer tools not only simplify the process of evolving APIs over time but also offer a complete and unified view of the data within the database (Fig. 1). Furthermore, the APIs allow for seamless integration with artificial intelligence systems, making the database a valuable resource for predicting the properties of fluorinated compounds.

Furthermore, the database offers carefully curated information on a wide range of fluorinated compounds. Key data, such as molecular structures and properties, are easily accessible through well-organized features, with regular updates ensuring that the database remains a reliable and up-to-date resource for the scientific community.

Utility and discussion

We have developed a dedicated web page for the Fluorinated Agent Database, enabling users to search for information directly from its homepage (refer to Fig. 2). Users can find desired data by entering criteria such as name in Chinese or English, chemical formula, CAS Registry Number (CASRN), abbreviation (Abbr), DOI, or SMILES into the search bar. This user-friendly interface ensures efficient access to comprehensive information on fluorinated reagents (with support for additional agents in the future), enhancing usability for researchers and practitioners alike. This database is also available in two languages. By default, the language is set according to the browser settings: Chinese remains in Chinese, while all other languages default to English. Additionally, in the navigation bar you can choose between English and Chinese. Given that these are the most widely spoken languages globally, this option enhances the database's accessibility for a larger audience.

Fluorinated reagents

The database contains extensive information on a wide variety of fluorinated reagents, encompassing more than twenty distinct groups. Figure 3 highlights the largest group, each containing over 50 reagents. In addition, there are many other fluorinated reagents in the database, but as there are not so many, it was decided not to include them in the Fig. 3, but to write them down. Below all possible reagents, which are not in the Fig. 3, have been listed: *fluorinated reagents*,

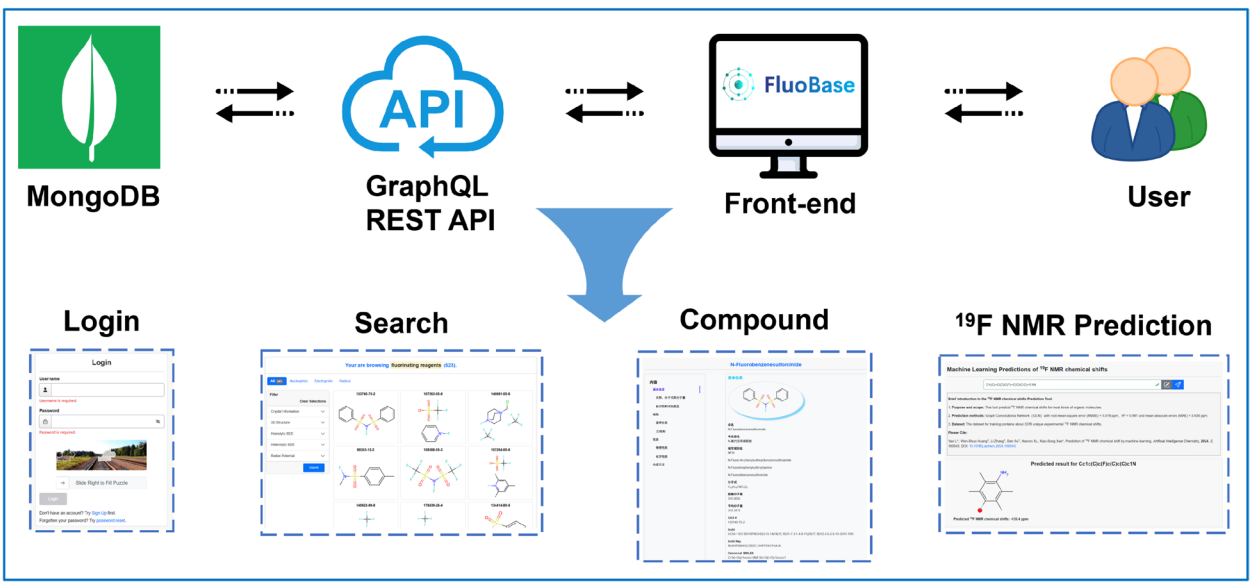


Fig. 1 Workflow of FluoBase

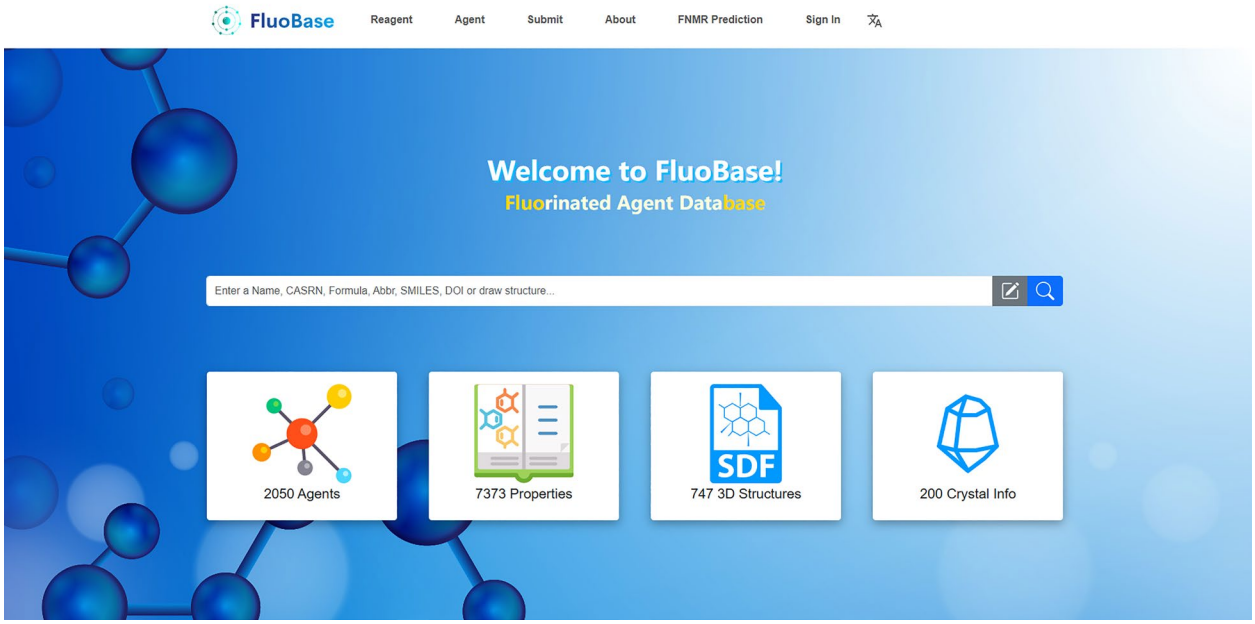


Fig. 2 Main page of FluoBase

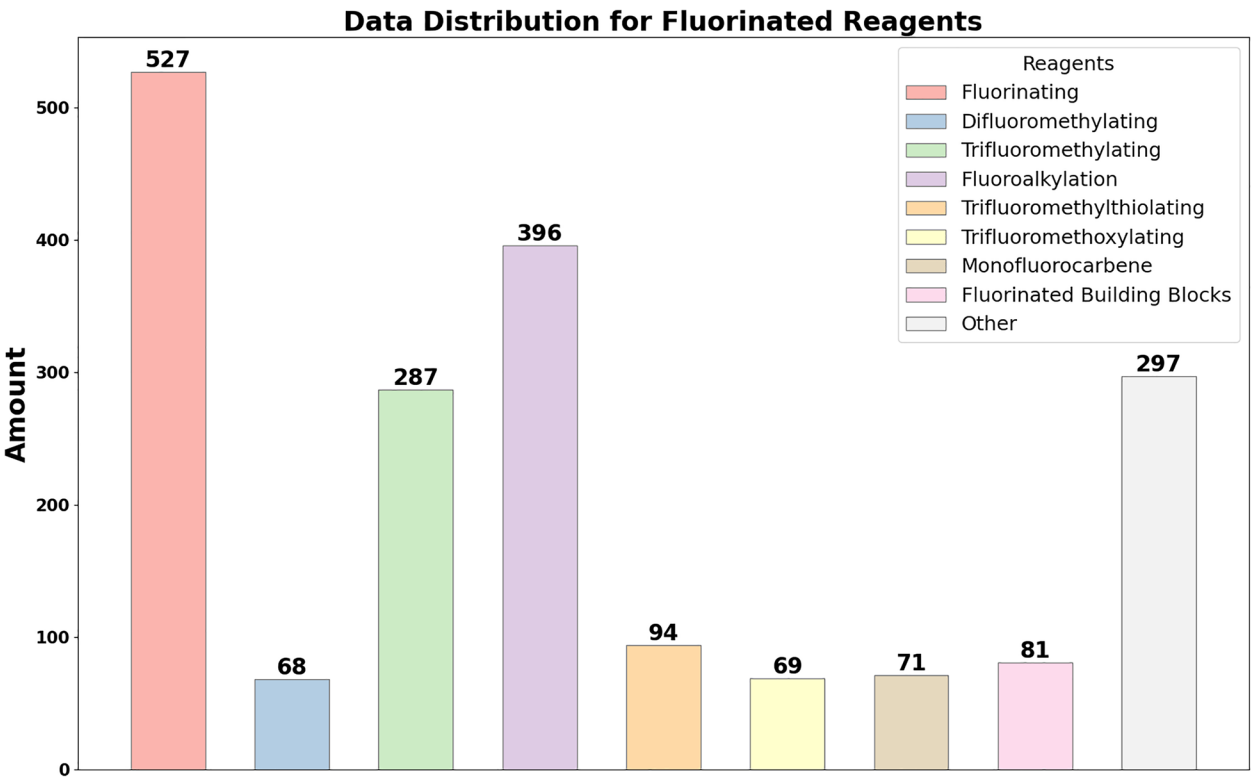


Fig. 3 Data distribution for fluorinated reagents in FluoBase

monofluoromethylating, monofluoromethylthiolating, difluoromethylthiolating, trifluoromethylsulfinylation, trifluoromethylsulfonylation, fluorosulfonylation, fluoroalkylthiolation, monofluoromethoxylating, monofluoromethoxylating, fluoroalkoxylation, trifluoromethylaminating, fluoroalkylamination, fluoroalkylselenylation,

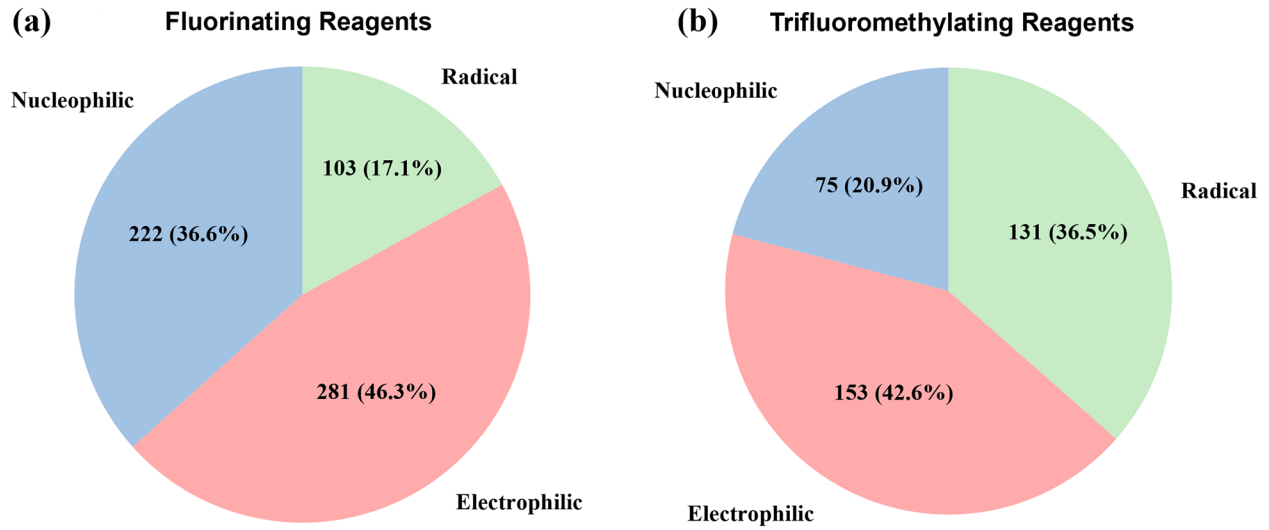


Fig. 4 **a** The proportion of types for fluorinating reagents. **b** The proportion of types for trifluoromethylating reagents

fluoroalkyltellurylation, pentafluorosul, fanylation, difluorocarbene and *fluoroalkyl carbenes reagents*.

Furthermore, the fluorinated reagents have been categorized into three main classes: nucleophilic, electrophilic and radical. Examples of these categories are illustrated in Fig. 4a, b. It is noteworthy that in cases where the electrophilic class is not absent, the amount of this electrophilic class is the most numerous one or almost equal to another group. Such situation occurs for almost all other fluorinated reagents except for *trifluoromethoxylating* reagents and fluoroalkylation reagents.

These data can be got by using search bar, as previously mentioned, or by utilizing the Ketcher tool [68] (by clicking picture of pen next to magnifying glass icon). The Ketcher tool within the interface allows user to draw molecules and then convert them into SMILES format. This SMILES format is then used to search for data within the Fluorinated Agent Database. In addition, the Ketcher tool made it possible to obtain a molecule image of the base of the SMILES representation. Apart from Ketcher, they are few more tools which can be used. For example, it is possible to mark favourite reagents to be remembered. Navigation is facilitated through the top navigation bar, where users can select desired reagents. After pressing the button inside the navigation bar, the desired reagents will be displayed in the next open page. Then on the left side it is possible to use filter. Filter contains possible options to choose like "Crystal Information", "3D Structure", "Homolytic BDE", "Heterolytic BDE" or "Redox Potential" (Fig. 5). After selected options, "Submit" button can be pressed and desired reagents will appear. In addition to the internal options of the filter, it is possible to select the range, like for example "Enable HBDE range" or "Enable Redox range" (Fig. 5b). Then on the top can be selected "All", "Nucleophilic", "Electrophilic" or "Radical" (Fig. 5c). In addition, by clicking on the pencil icon next to the magnifying glass icon in the search bar, it is possible to draw a chemical structure and use it to search for the desired results. If result was not found then there is small tool called "structure similar search". This tool also evaluates similarity and show it under the figure (for instance: "Similarity: 0.74").

Result page contains basic information like for example: name, formula, InChI, InChI Key, canonical SMILES and link to reference (Please visit our website for more details). It is then possible to check properties such as: appearance, density, boiling point, melting point, refractive index**,** solubility, stability, Mayr's electrophilicity/nucleophilicity parameter [69, 70] and homolytic or heterolytic BDE (Please visit our website for more details). Besides result page contains synthetic method and 3D structure (Fig. 6), which is particularly helpful for young scientists seeking guidance. 3D structures are sourced from crystallographic data when available; if not, PubChem data is used [71], and in the absence of both, no 3D structure is provided. Users can also copy data and save images in svg format.

Other fluorinated agents

In addition to comprehensive information on a wide range of fluorinated reagents, FluoBase also aims to provide detailed data on a broad array of fluorinated functional molecules such as natural products, refrigerants, anesthetics and surfactants (Fig. 7). This database is constantly being improved and some new agents like drug

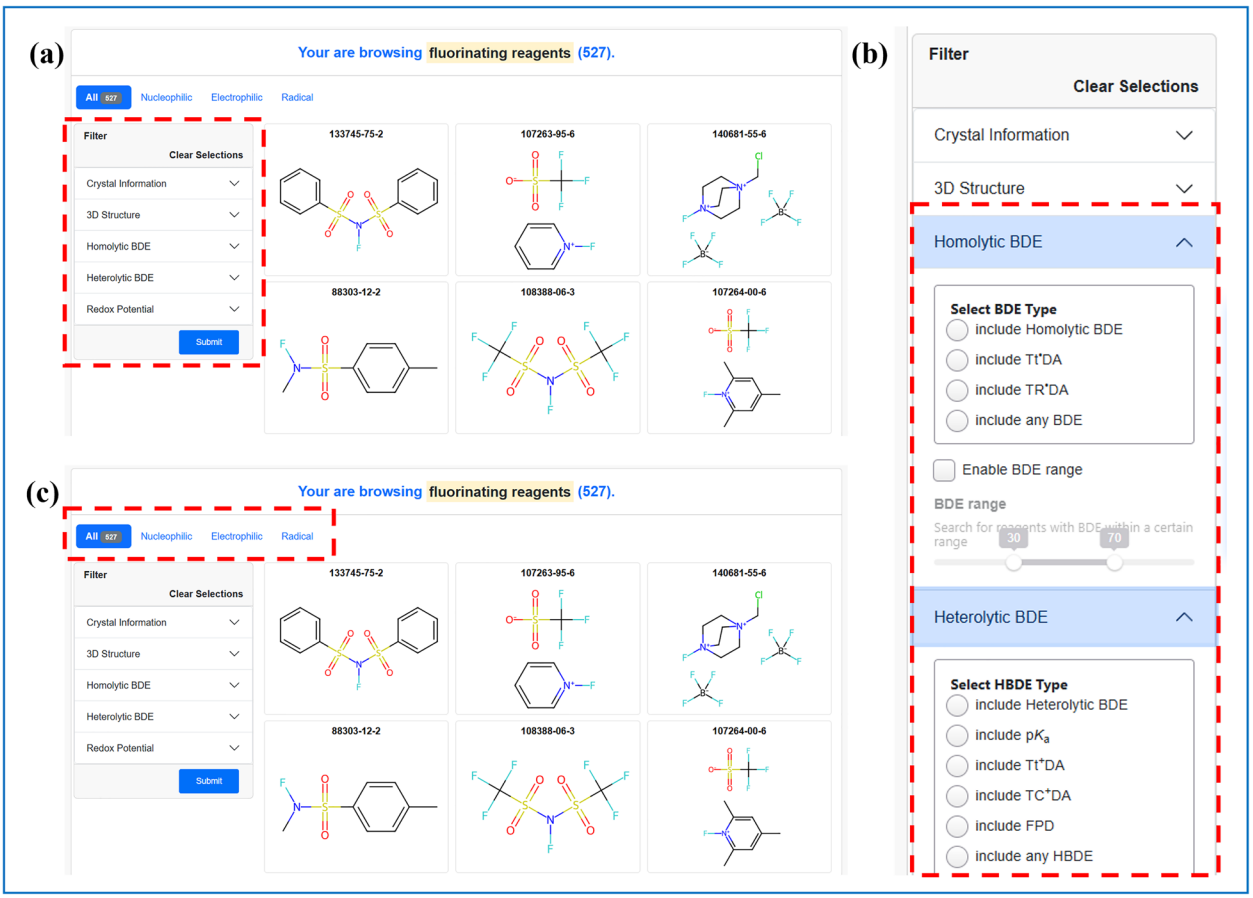


Fig. 5 Three classes possible to choose from top menu: **a** View from the filter. **b** Filter for Homolytic BDE range and Heterolytic BDE. **c** Filter for reagent type

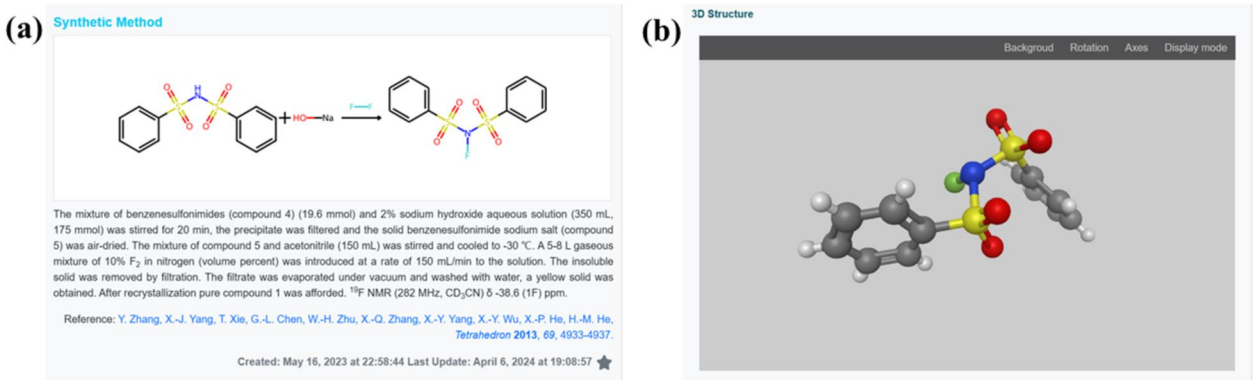


Fig. 6 **a** View of the synthetic method. **b** View of the 3D structure

molecules, insulating gas are under construction and will be available soon.

The search for substances can also be facilitated by the top navigation bar, where the user can select the substances of interest. The second option to choose desired fluorinated agent is to press image on the main page in section "Agent" which will send user directly to the page containing agents. The possible agents that can be reviewed are: natural product, refrigerant, anesthetic and surfactant. All of the above can be selected from the

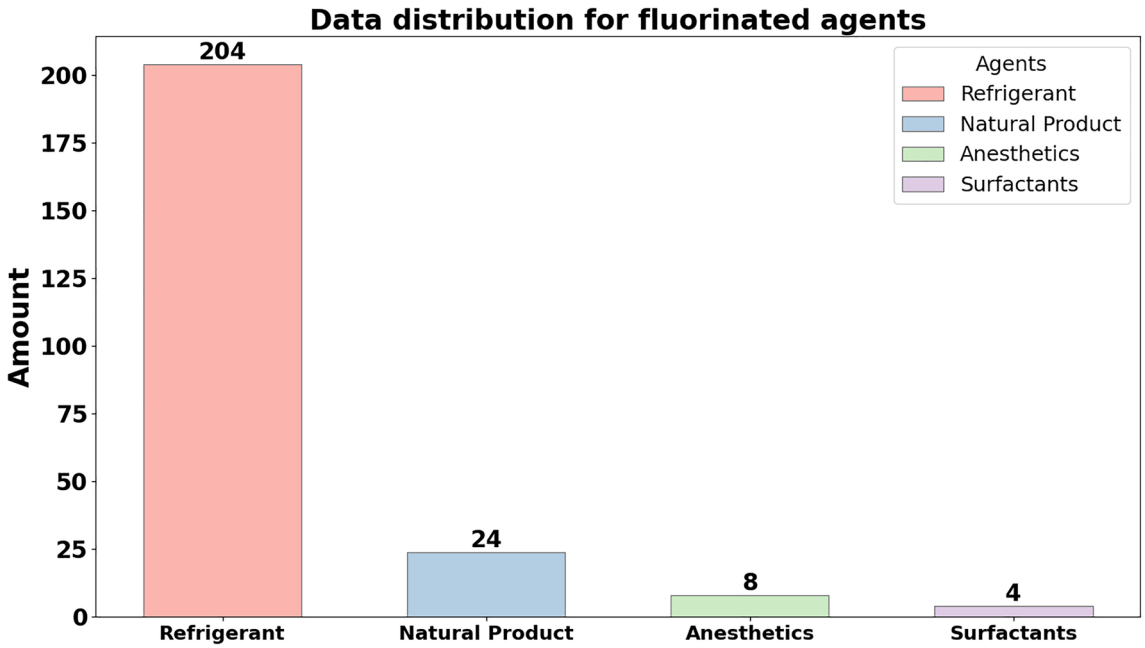


Fig. 7 Data distribution for fluorinated agents in FluoBase

navigation bar. Below is an example of the results page for Agent—Natural Product. In Fig. 8a there are fluorinated natural products. Clicking on the first image (24751-69-7) opens the details page (Fig. 8b). The subpage is divided into three sections. The first section called Basic Information contains details such as formula, abbreviation, Chinese name, exact mol weight, InChI, other name or CAS register number. The second section called property contains details such as density, boiling point, bioactivity. The last section called biological source contains data such as reference. Clicking on this reference will take you to an external page with the paper used to obtain the data. On the left is a vertical navigation bar that runs along the side of a page and shows all the links that will take the user to different parts of a page.

Submit your own data

Additionally, users have the capability to submit their own data to the Fluorinated Agent Database, including references, reagents, and files in "SDF" and "CIF" formats for 3D structures. The whole procedure for adding new data has been divided into five steps. All steps have to be prepared to finish the procedure, but user in every moment can return to the previous step. In the first four steps the user can add his own data such as: smiles, name, CSD Doi, CCDC No (Fig. 9a); density, electrophilicity, stability, solubility (Fig. 9b); reaction references, reaction method, reaction smiles (Fig. 9c); type reference, redox (redox potential) reference, bde (bond dissociation energy) reference, hbde (heterolytic bond dissociation energy) reference (Fig. 9d). Furthermore, there is an option to check if the input for the drawing is correct, if it exists in the database and then there is a possibility to obtain canonical smiles. Once all four steps have been well prepared, the fifth and final step allows the user to update the reference and send their data. Once the data has been sent, there is no way of going back, so the user should prepare his data very carefully. The data provided must first undergo a verification process. In the event of a problem, the user will be informed of any errors, ambiguities or missing data. If there is no problems then obviously new data will be approved.

However, to access this feature, users must first log in to the system. If user does not have account, it is possible to create one by providing data like username, institution, email and password. After provide captcha from received email it is possible to sign in and submit own data. Later user can update his details in the: User Info page. Registering for an account is free of charge and takes only a short amount of time to complete (Fig. 10). Then using FluoBase is free of charge and is intended for non-profit academic purposes only. Users of the database are kindly requested to register and cite the website: https://fluobase.siochemdb.com, as well as the original literature in their work.

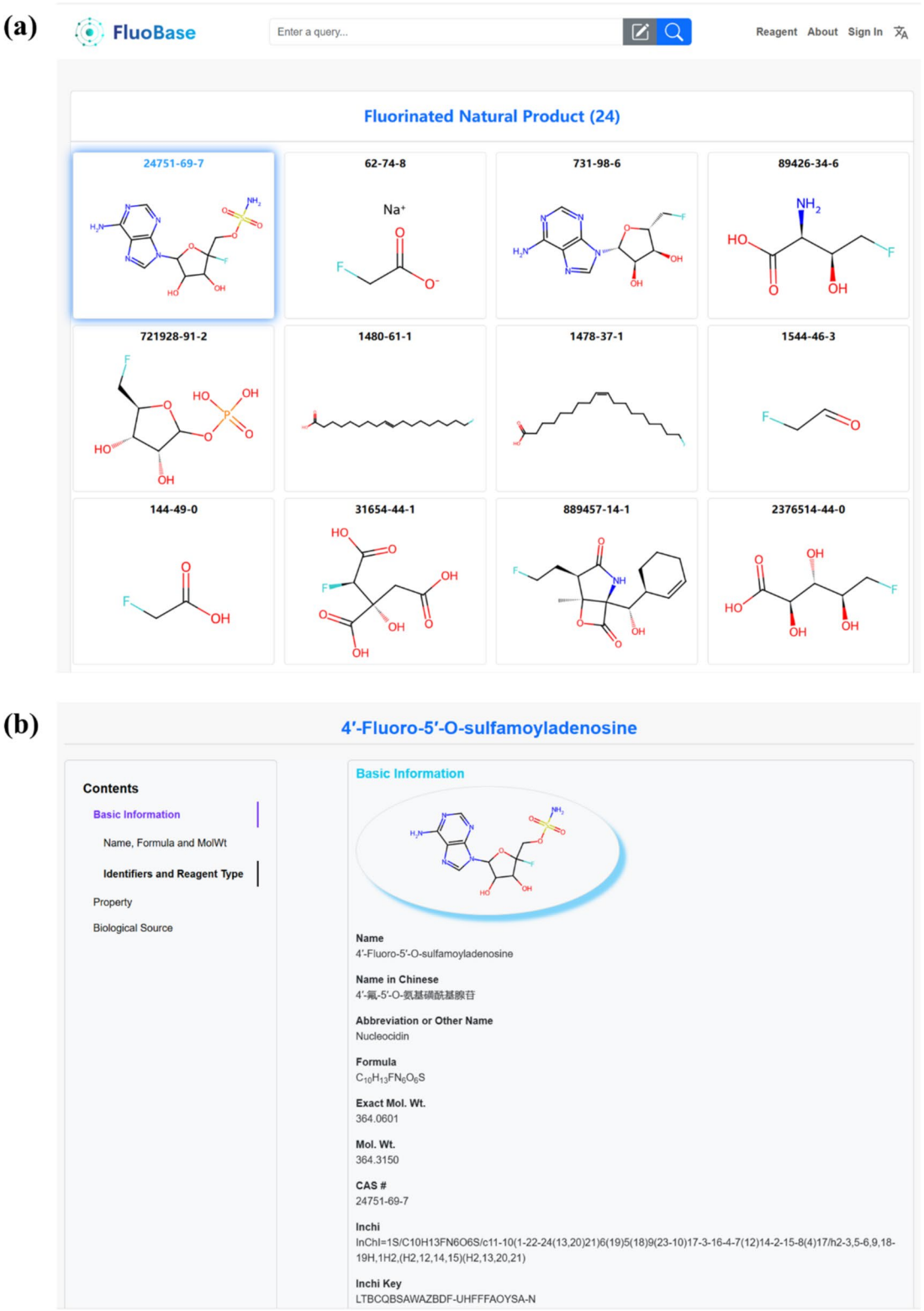


Fig. 8 **a** View of the fluorinated natural products. **b** View of the details for 4′-Fluoro-5′-Osulfamoyaladenosine

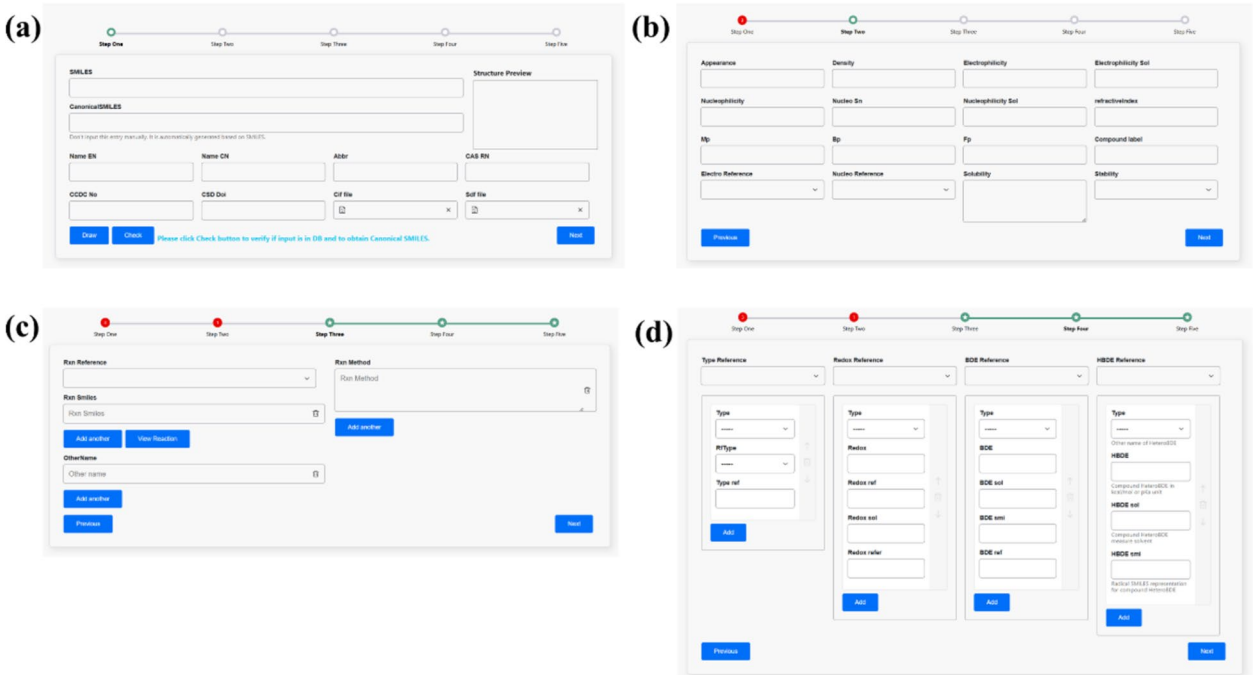


Fig. 9 Pages for data submission. **a** Step 1. **b** Step 2. **c** Step 3. **d** Step 4

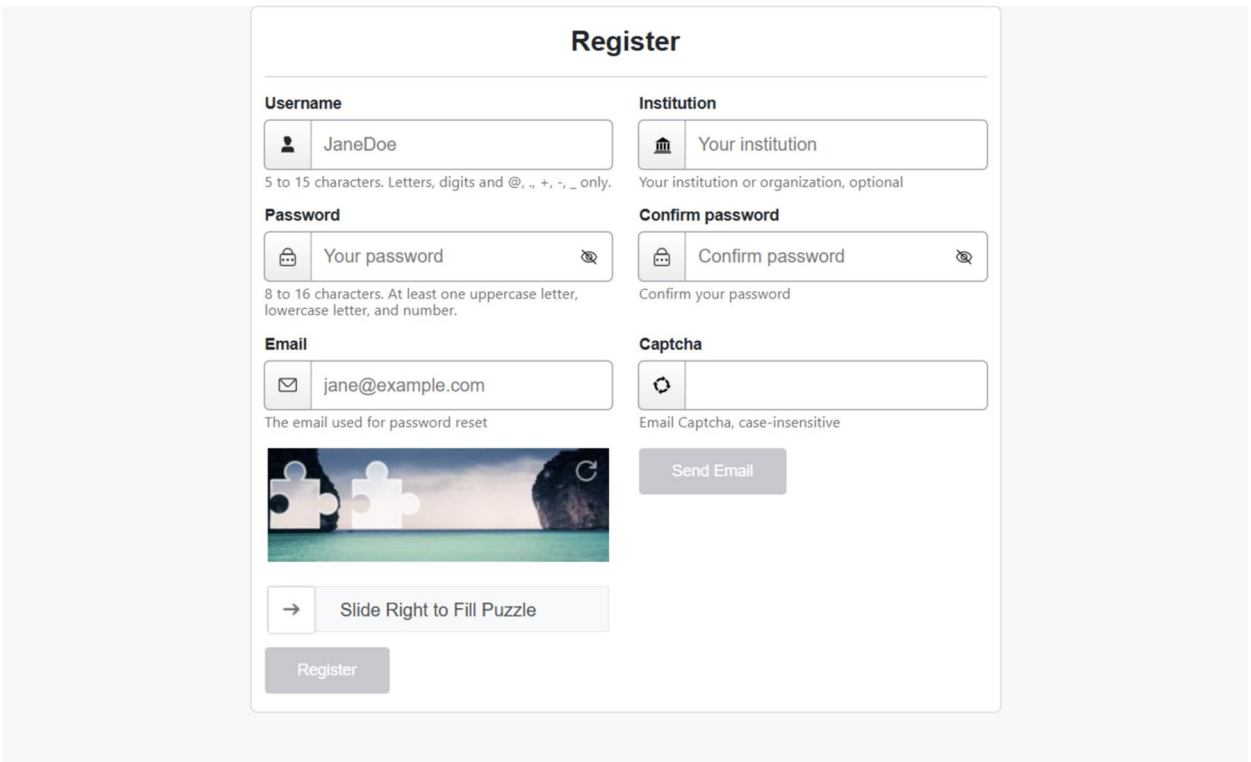


Fig. 10 Page for registration

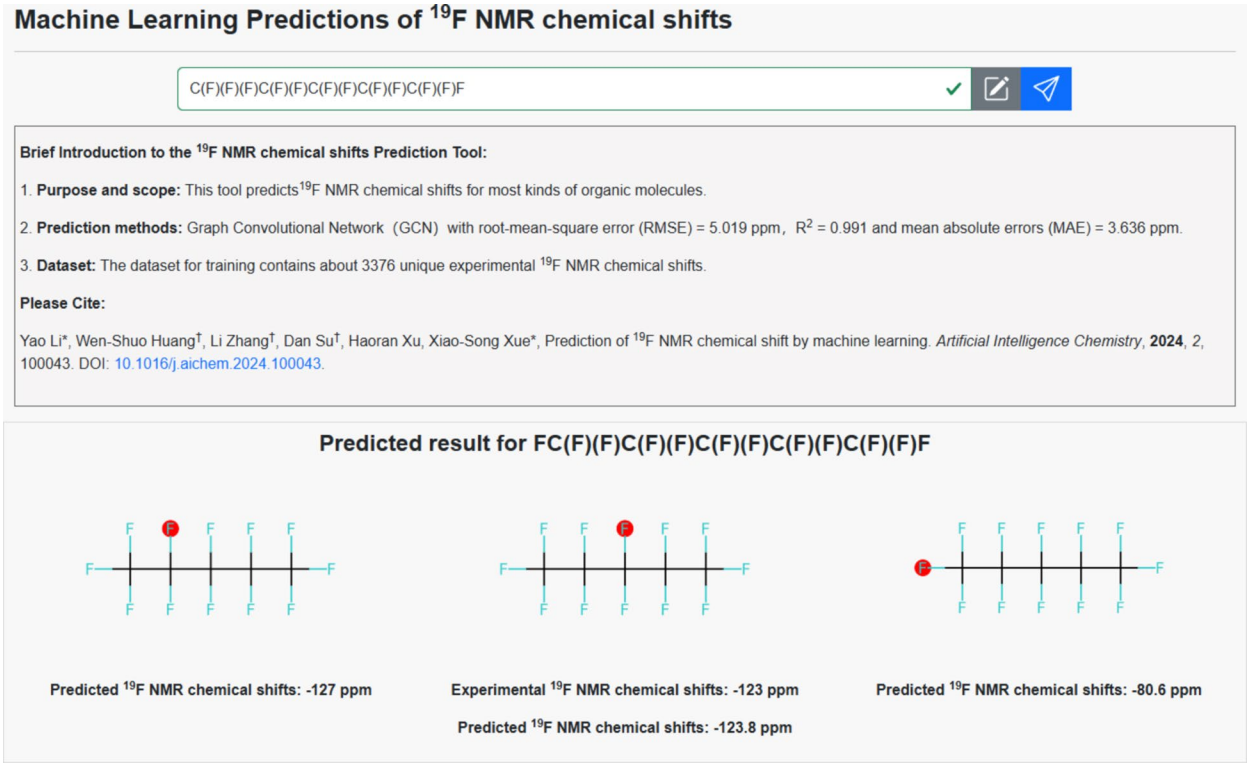


Fig. 11 Machine learning prediction of ^{19}F NMR chemical shifts

^{19}F NMR prediction tool

The last option in the navigation bar is not a link to the next set of data, but rather a tool called the "^{19}F NMR Prediction Tool." This tool enables users to predict the ^{19}F NMR chemical shifts for most types of organic molecules [72]. The training dataset consists of approximately 3,376 unique experimental ^{19}F NMR chemical shifts. After entering a SMILES string in the search bar or drawing a structure using Ketcher, the ^{19}F NMR Prediction Tool employs a Graph Convolutional Network (GCN) as its prediction method to generate the results. This model demonstrates high accuracy, with a root mean square error (RMSE) of 5.019, a coefficient of determination (R^2) of 0.991, and a mean absolute error (MAE) of 3.636 ppm (Fig. 11).

Future plans

In the near future, the database will be expanded to include fluorinated functional molecules, such as insulating gases, surfactants, drug molecules, and more. Furthermore, plans are underway to enrich the database with additional data, including key pharmacologically relevant properties such as logP/logD and water solubility. New tools will also be integrated to enable users to quickly locate desired information and analyze the data more efficiently.

Conclusions

In this study, we introduce FluoBase, a publicly accessible database dedicated to providing comprehensive information on the physical and chemical properties of various fluorinating agents. FluoBase will cover a wide range of fluorinated substances, including refrigerants, anesthetics, surfactants, and drug molecules. Committed to ongoing development, FluoBase will regularly introduce new services, tools, and enhancements to existing features. Systematic updates will ensure the incorporation of the latest advancements in fluorine chemistry. As a key platform for fluorine chemistry, FluoBase aims to serve the scientific community and anyone interested in the applications of fluorinating agents and machine learning for property prediction.

Abbreviations

REST	Representational state transfer
API	Application Programming Interface
CAS	Chemical Abstracts Service
InChI	International Chemical Identifier
SMILES	Simplified Molecular Input Line Entry System
CCDC	The Cambridge Crystallographic Data Centre
DOI	Digital Object Identifier
CIF	Crystallographic Information File
SDF	Structured Data File
BDE	Bond Dissociation Energy

Acknowledgements

Not applicable.

Author contributions
R.M., Y.L. and X.S.X. coordinated the writing of the paper. Y.L. designed and developed the FluoBase database. D.S., W.S.H., L.Z., H.H., X.L. contributed to data collection. Y.L. and X.S.X. conceived and supervised the project. All authors actively contributed to the FluoBase database and have read and approved the final manuscript.

Funding
This work was supported by the Ministry of Science and Technology of China (grant no. 2021YFF0701700), the National Natural Science Foundation of China (grant nos. 22122104, 22193012, and 21933004), the CAS Project for Young Scientists in Basic Research (grant nos. YSBR-052 and YSBR-095), and the Strategic Priority Research Program of the Chinese Academy of Sciences (grant no. XDB0590000).

Availiability of data materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Author details
[1] State Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. [2]School of Chemistry and Material Sciences, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, 1 Sub-Lane Xiangshan, Hangzhou 310024, China.

Received: 15 November 2024 Accepted: 6 January 2025
Published online: 11 February 2025

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