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Assessment of the Commercially Available Chemical Space for Using in the ^{19}F NMR FAXS Method: a Enamine Ltd. Case

Abstract

Aim. To analyze commercially available fluorine containing compounds for the possibility of their use in the ^{19}F NMR FAXS method.

Materials and methods. The selection of fluorine-containing fragments for the study was performed using 3.9 million in-stock screening compounds and 248,000 in-stock building-blocks from Enamine Ltd library. The selection and classification of the compounds was carried out using the DataWarrior and KNIME software. The Fluorinated Fragments library of Enamine Ltd. containing 6377 compounds, was also analyzed. To analyze the abovementioned sets of substances, the multistep workflows specially designed were used.

Results and discussion. As a result of applying the workflow developed to the compound sets (both screening compounds and building blocks), 13 800 compounds were selected and further classified according to the presence of one out of 12 fluorine-containing groups. The Fluorinated Fragments library was also subjected to a similar workflow. For the latter, 8 out of 12 fluorine-containing groups were identified. Additionally, experimental ^{19}F NMR chemical shift values for Fluorinated Fragments library compounds spectra were analyzed. It has been found that some structural classes have areas of chemical shifts intersection. On the other hand, the ranges from −40 to −60 ppm and beyond −160 ppm are free from any group of compounds from the library analyzed.

Conclusions. The analysis has shown that commercially available fluorine-containing fragments do not satisfy the needs of the ^{19}F NMR FAXS method, and further expansion of the chemical space of fluorine-containing compounds by increasing their diversity is required.

***Keywords*:** fluorinated fragments; fragment-based drug design; ^{19}F NMR; FAXS method; chemoinformatics; chemical space analysis of compounds

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Аналіз застосовності комерційно доступного хімічного простору для використання у [19]F ЯМР FAXS методі на прикладі НВП «Єнамін»

Анотація

Мета. Проаналізувати комерційно доступні флуоровмісні сполуки на можливість їх застосування в конкурентному скринінгу за допомогою [19]F ЯМР FAXS методу.

Матеріали та методи. Відбір флуоровмісних фрагментів для дослідження проводили з використанням наявних на складі компанії ТОВ «НВП «Єнамін» 3,9 млн скринінгових сполук та 248000 будівельних блоків. Відбір та розподіл сполук по групах виконували за допомогою програм DataWarrior та KNIME. Проаналізували бібліотеку флуорованих фрагментів ТОВ «НВП «Єнамін», що містить 6377 сполук. Для аналізу вищезазначених наборів речовин використовували спеціально розроблені багатоступеневі алгоритми.

Результати та їх обговорення. У результаті застосування розробленого алгоритму до скринінгових сполук та будівельних блоків відібрано 13800 представників, які додатково класифіковано за наявністю однієї з 12 флуоровмісних груп.

Бібліотеку флуорованих фрагментів також піддано подібній процедурі. Для останньої групи досліджуваних сполук ідентифіковано наявність 8 з 12 флуоровмісних фрагментів. Крім того, проаналізовано експериментальні значення хімічного зсуву, отримані із ^{19}F ЯМР спектрів бібліотеки флуорованих фрагментів. З'ясовано, що деякі структурні класи мають зони перетину хімічних зсувів. З іншого боку, у діапазонах від −40 до −60 м.д. і більше −160 м.д. не представлено жодної сполуки з аналізованої бібліотеки.

Висновки. Аналіз засвідчив, що наявні комерційно доступні флуоровмісні фрагменти не задовольняють потреби ^{19}F NMR FAXS методу, а тому необхідно розширювати хімічний простір флуоровмісних сполук шляхом збільшення їх різноманіття.

Ключові слова: флуоровмісні фрагменти; дизайн лікарських препаратів на основі фрагментів; ^{19}F ЯМР; метод FAXS; хемоінформатика; аналіз хімічного простору сполук

■ Introduction

Fluorine-containing substances have recently gained considerable attention and relevance from a scientific and practical point of view [1−5]. This increased attention can be explained by the unique properties of the fluorine atom. It can form strong bonds with the carbon atom, but that is not what makes it special. Due to the small radius of the atom, fluorine (like deuterium) is the bioisosteric substitute for the hydrogen atom, and due to its high electronegativity, it can participate in the formation of hydrogen bonds. This combination of properties makes it possible to replace hydrogen atoms in molecules with fluorine, and it can lead to changes in the physicochemical and pharmacokinetic properties of biologically active compounds and the metabolic stability as well [6−9]. In addition, the presence of a fluorine atom in a molecule makes it possible to determine the presence or absence of ligand-protein interactions for the compound studied with further hit-to-lead optimization. Herewith, the modified molecules do not inevitably contain fluorine atoms [10].

One of the available and highly effective biophysical tools for detecting ligand-protein interactions is ^{19}F NMR screening [11−17]. The FAXS method (Fluorine Chemical Shift Anisotropy and Exchange for Screening) is used in both direct and competitive modes and allows identification of an interaction between a fluorine-containing fragment and the target under study. As a rule, well-characterized libraries of fluorine-containing compounds are required for using in the FAXS method [11]. This method also allows the analysis of large mixtures (or "cocktails") of the fluorinated molecules-candidates simultaneously, which makes it one of the most relevant for the fragment screening against highly scarce and/or expensive protein targets.

However, for such a procedure, it is necessary to have pre-validated cocktails of fluorine-containing substances. An increased number of compounds in a cocktail, which contains insufficiently diverse structural groups, leads to an uneven distribution of chemical shifts of fluorine atoms and a decrease in the distance between shift signals, curbing the potential of the FAXS method.

Thus, to assess the possibility of a widespread use of the FAXS method, we decided to analyze all fluorine-containing in-stock screening compounds (SCs) and building blocks (BBs) offered by Enamine Ltd. [18, 19], one of the largest suppliers of small molecules, in terms of applicability in a competitive fragment screening.

■ Materials and methods

The mining of fluorine-containing fragments for further analysis was carried out from 3.9M in-stock SCs [20] and 248K in-stock BBs [21] deposited on the Enamine website since compounds suitable for fragment-based methods occupy an intermediate region between the given classes. The selection and classification of compounds were implemented using the DataWarrior [22] and KNIME [23−25] software. For the analysis of the abovementioned sets of substances, the workflow shown in Figure 1 was used.
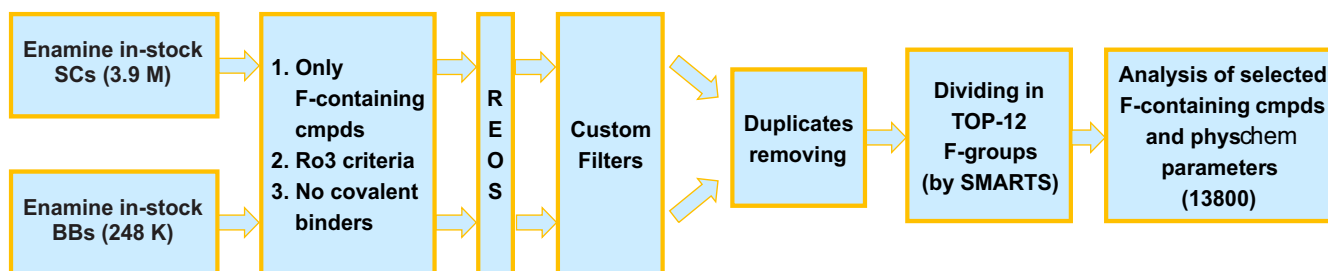
Figure 1. The workflow 1 for in-stock compound sets (Set A)

According to the presented step-by-step procedure, we performed the following operations:

Step 1 – Initial filtering:

1.1 Only fluorine-containing compounds were filtered out;

1.2 The "Rule of 3" criteria from Astex were applied ($100 < MW < 300$, $logP \leq 3$, $HBA \leq 3$, $HBD \leq 3$, MW was calculated for unsalted forms) [26–28];

1.3 Possible covalent binders (various Michael acceptors, terminal alkynes methylene-active compounds, etc.) were removed.

Step 2 – Substances that might exhibit high reactivity according to REOS (Rapid Elimination of Swill) were removed in order to eliminate possible competing processes in the screening process (for list of SMARTS see *Supporting Information* file) [29].

Step 3 – Due to peculiarities of the experiment (water solution and single signal in ^{19}F NMR per substance), the following compounds were removed:

3.1 Those unstable in water due to the hydrolysis or other processes;

3.2 Those displaying two or more signals (containing several different fluorine-containing groups, diastereomers mixture, tautomers);

3.3 Those containing highly reactive fluorine-containing groups that were not included in the filter of Step 2 (arylators, sulfonyl fluorides, etc.) (see "Custom Filters" in *Supporting Information* file).

Step 4 – The comparison of the filtered compounds was performed, and all duplicates were removed.

Step 5 – Classification of the remaining fluorine-containing compounds. For this, an analysis of articles covering the Fluorine fragments libraries topic and the use of fluorine-containing substances in medicinal chemistry was carried out [1–5, 30–36]. For further classification, we used the substructural search with SMARTS of fluorine-containing groups [37] since such an approach has long been practiced in analyzing large sets of compounds [38–40]. As a result, we created a library of different SMARTS, consisting of the 12 frequently encountered and used fluorine-containing fragments (Table 1).

Enamine Ltd. also offers a Fluorinated Fragments library, which contains 6377 compounds and is available for download on the website [41]. Among the initial data for compounds presented in this library, there are chemical shifts of ^{19}F NMR (in DMSO-d_6 and/or D_2O), which are of significant value for further analysis of their applicability in cocktails for competitive screening.

Several filters from the workflow earlier mentioned were applied to this set of compounds (Figure 2):

Step 1 – Pre-filtering:

1.1 The "Rule of 3" criteria were applied to this set [26–28];

1.2 Custom Filters (listed in the *Supporting Information* file) were used to eliminate compounds that might exhibit multiple signals (such as a mixture of diastereomers or tautomers), as well as undesirable reactive groups (e.g., arylators, sulfonyl fluorides, etc.).

Step 2 – Classification of the fluorine-containing compounds with SMARTS mentioned in Table 1.
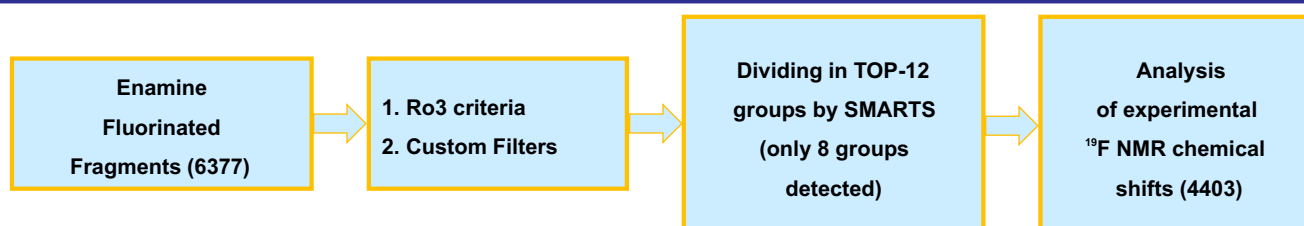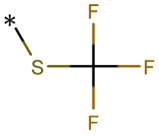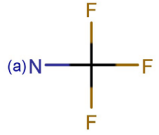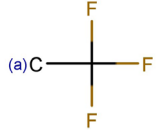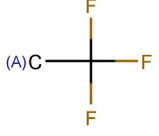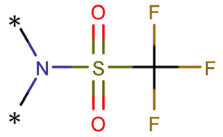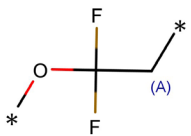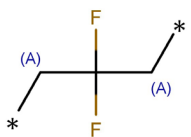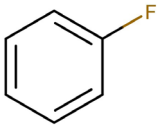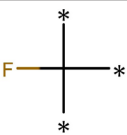

Figure 2. The workflow 2 for Fluorinated Fragments library (Set B)

Table 1. TOP-12 fluorine-containing groups and their SMARTS notations

#	Group	SMARTS	Structure
1	CF_3S	FC(F)(F)[#16]	
2	CF_3n	[#7;a]C(F)(F)F	
3	CF_3O	[#8]C(F)(F)F	
4	CF_3c	[#6;a]C(F)(F)F	
5	CF_3C	[#6;A]C(F)(F)F	
6	CF_3SO_2N	[#7]S(=O)(=O)C(F)(F)F	
7	OCF_2C	[#6;A]C([#8])(F)F	
8	CCF_2C	[#6;A]C([#6;A])(F)F	
9	CCF_2c	[#6;A]C([#6;a])(F)F	
10	c(Aryl)F	([#6;a;$([#6]-1=[#6]-[#6]=[#6]-[#6]=[#6]-1)])F	(with only phenyl ring)
11	c(Hetaryl)F	([#6;a;!$([#6]-1=[#6]-[#6]=[#6]-[#6]=[#6]-1)])F	F—C(a) (all aromatic systems, except phenyl)
12	tert-CF	[#6]C([#6])([#6])F	

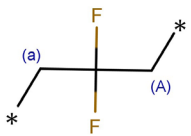Note: 'n' or N(a) – endocyclic nitrogen included into the aromatic system; 'c' or C(a) – carbon included into the aromatic system; 'N' or N(A) – aliphatic nitrogen atom; 'C' or C(A) – aliphatic carbon atom.

Table 2. Fluorine-containing groups, the number of compounds in each (for Set A and Set B), and the range of chemical shift values (only for Set B)

#	Group	Set A, cmpds	Set B, cmpds	Experimental ^{19}F NMR for the Set B	
				δ_{min}, ppm	δ_{max}, ppm
1	CF_3S	21	0	–	–
2	CF_3n	2	0	–	–
3	CF_3O	161	15	−57	−60
4	CF_3c	1413	451	−57	−71
5	CF_3C	2267	323	−61	−84
6	CF_3SO_2N	5	0	–	–
7	OCF_2C	18	1	–	–
8	CCF_2C	1113	2	−92	−92
9	CCF_2c	113	2	−100	−103
10	c(Aryl)F	8078	3247	−104	−150
11	c(Hetaryl)F	297	342	−109	−159
12	tert-CF	312	20	−137	−144
Total		13800	4403		

The chemical shift values from the ^{19}F NMR spectra for each subgroup from the Fluorinated Fragments library were analyzed, compiled into a joint table, and displayed on a common chemical shift scale. These data are discussed in the next section.

■ Results and discussion

As a result of the implementation of Workflow 1 (Figure 1) to 3.9M in-stock SCs [20] and 248K in-stock BBs [21], 13 800 compounds (Set A) comprising one of the 12 fluorine-containing groups listed in Table 2 were classified. Next, we applied Workflow 2 (Figure 2) for the Fluorinated Fragments library. Finally, only 8 out of 12 fluorine-containing groups were identified. The experimental data of ^{19}F NMR spectra (in DMSO-d_6 and D_2O) for a part of the substances (Set B, 4403 compounds) from the Fluorinated Fragments library presented on the Enamine Ltd. website were analyzed [41]. The chemical shift values for each group fall within a definite range, the minimum and maximum values of which, as well as the number of compounds sharing certain structural groups, are given in Table 2.

Based on the data obtained, it is obvious that some structural classes have certain areas of chemical shift intersection, which makes it difficult to create cocktails without considering the initial experimental data. To solve this problem, we decided to combine some of them into more general groups. The main criterion for combining was the absence of the chemical shift overlap regions in a potential cocktail of fluorine-containing molecules.

Thus, we observe several groups with practically no intersection between themselves in the range of location on the chemical shift axis. Figure 3 shows eight fluorine-containing groups divided into three ranges. The first range (weak field) contains F-aryl and F-heteroaryl derivatives and tertiary F-compounds. There are two types of difluoro compounds in the middle of the shift axis. In the strong field, three types of trifluoromethyl derivatives are located. Correspondingly, the range from −40 to −60 ppm is not occupied by any group of compounds from the library analyzed, and the span with values beyond −160 ppm is also abandoned.

Thus, it has been found that combining several groups, including a variety of fluorinated fragments, allows improving and simplifying the preparation of cocktails for further screening. However, to realize all the possibilities of the FAXS method, the use of the most common fluorine-containing groups is insufficient since they do not cover the entire range of the chemical shifts. This point requires further study, considering the deeper structural features of the compounds.

Based on the values of the range for some structural groups obtained, it can be assumed that to realize the maximum possible number of compounds in a cocktail, it is necessary to collect more experimental spectral data for different fluorine-containing compounds or, in an alternative way – develop a powerful mathematical algorithm for predicting the chemical shift for ^{19}F NMR.

The disadvantage of both sets – Set A (Figure 4) and Set B, is the apparent overpopulation of some groups, which leads to a pronounced limitation of the chemical diversity of compounds in probable
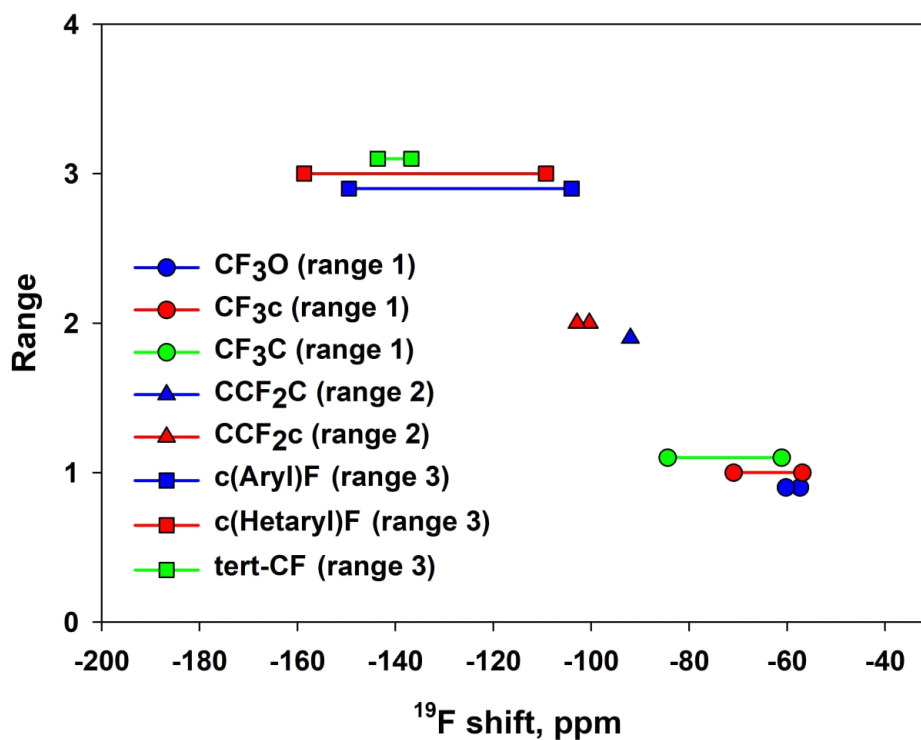
Figure 3. Distribution of chemical shift ranges of eight fluoridated groups for Set B
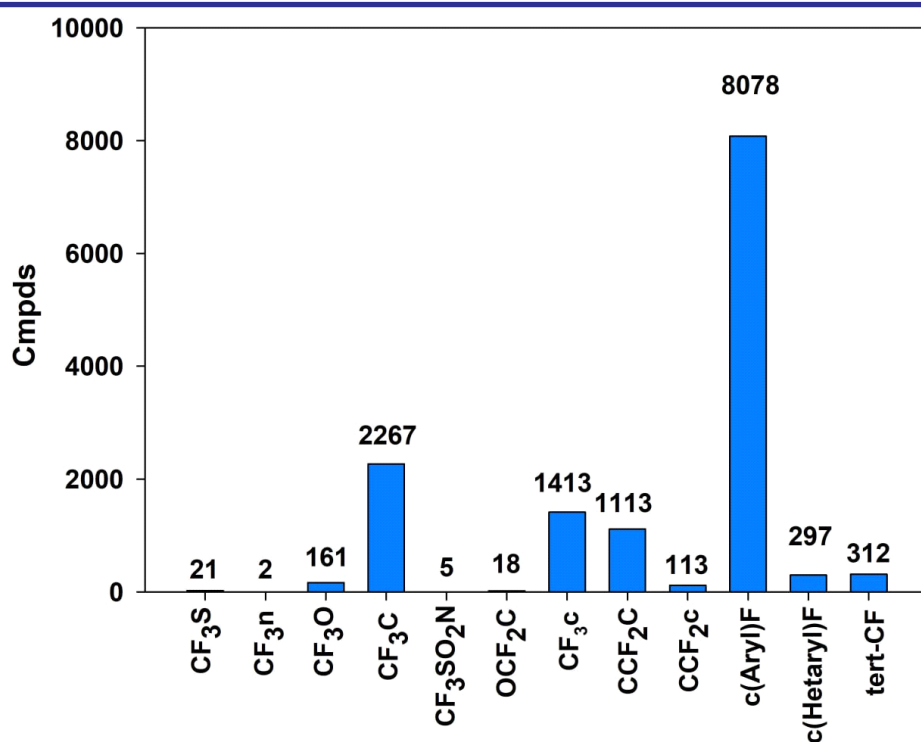
Figure 4. Distribution of compounds among 12 fluorine-containing groups for Set A (13800 cmpds)

cocktails. Therefore, it is necessary either to reduce the total number of possible cocktails of the fluorine-containing compounds included in the cocktails or to populate already existing groups with compounds to obtain a uniform distribution both in chemical diversity and in the signal shift for the fluorine atom.

■ **Conclusions**

The analysis has revealed that relying solely on the most commonly used fluorine-containing fragment groups is inadequate for achieving the desired cocktail outcomes. It necessitates more precise fragment modifications based on the structural

characteristics of the compounds. Two possible ways of enhancing compound collections suitable for the FAXS method have been suggested. The first one is collecting experimental spectral data for various promising fluorine-containing compounds. The second one is to develop a high-performance mathematical tool for predicting the chemical shift for fluorinated compounds with a desirable diversity. The analysis has also shown the presence of a pronounced overpopulation and underpopulation of several structural groups of fluorine-containing substances. As a result, to effectively use commercially available collections of fluorine-containing compounds and realize the full power of fragment screening methods, it is necessary to increase the representation in underpopulated areas to create ideal and full-fledged cocktails.

■ Acknowledgments

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