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Troelsen, Nikolaj Sten; Shanina, Elena; Gonzalez-Romero, Diego; Dankova, Daniela; Jensen, Ida S. A.; Sniady, Katarzyna J.; Nami, Faranak; Zhang, Hengxi; Rademacher, Christoph; Cuenda, Ana

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The 3F Library: Fluorinated Fsp³-rich Fragments for Expeditious ¹⁹F-NMR-based Screening

Nikolaj S. Troelsen,^[a] Elena Shanina,^{[b],[c]} Diego Gonzalez-Romero,^[d] Daniela Danková,^[a] Ida S. A. Jensen,^[a] Katarzyna J. Śniady,^[a] Faranak Nami,^[a] Hengxi Zhang,^{[b],[c]} Christoph Rademacher,^{[b],[c]} Ana Cuenda,^[d] Charlotte H. Gotfredsen,^[e] Mads H. Clausen^{*[a]}

Abstract: Fragment-based drug discovery is a popular method in academia and the pharmaceutical industry for the discovery of early lead candidates. Despite its wide-spread use, the approach still suffers from laborious screening workflows and a limited diversity in the fragments applied. Here we present the design, synthesis, and biological evaluation of the first fragment library specifically tailored to tackle both these challenges. The 3F library of 115 fluorinated, Fsp³-rich fragments is shape diverse and natural product-like with desirable physicochemical properties. The library is perfectly suited for rapid and efficient screening by NMR spectroscopy in a two-stage workflow of ¹⁹F- followed by ¹H-NMR methods. Hits against four diverse protein targets are widely distributed among the fragment scaffolds in the 3F library and a 67% validation rate was achieved using secondary assays. This is the first synthetic fragment library tailor-made for ¹⁹F-NMR screening and our results underline that the approach should find broad application in the FBDD community.

Fragment-based drug discovery (FBDD) is a powerful tool for the discovery of new drug leads.^[1] Screening of low-molecular 'fragments' (typically MW < 300 Da) affords key advantages over traditional high-throughput screening (HTS) including higher hit rates and better sampling of chemical space.^[1,2] FBDD relies on biophysical screening techniques such as NMR spectroscopy, surface plasmon resonance, and X-ray crystallography to detect the inherently weaker binding of fragments.^[1] NMR is considered one of the most robust and sensitive screening methods for the identification of weak binders and has become one of the most widely applied techniques.^[3,4] In particular, ligand-based ¹H-NMR

experiments are popular and are typically performed by simultaneous screening of multiple fragments in cocktails. Unfortunately, because these methods are proton based, overlap of signals from compounds, buffers, and additives is a major hurdle and effectively limits the cocktail composition to only a handful of fragments.^[4]

In contrast, ¹⁹F-NMR-based screening provides increased sensitivity and simplicity primarily owing to a broad chemical shift range spanning over 350 ppm for organofluorine compounds.^[5] Furthermore, fluorinated fragments typically only contain a single fluorinated moiety while most solvents and additives can be completely ignored due to the absence of fluorine. These advantages reduce the risk of signal overlap and enable the screening of cocktails of up to 40 fragments, significantly decreasing the amounts of fragment and protein required.^[5]

Currently, ¹⁹F-NMR-based screening in FBDD is limited by the low availability and poor diversity of available fluorinated fragments.^[4,5] Thus, to increase the efficacy of ¹⁹F-NMR-based screening, we herein report the first synthesis of a fluorinated fragment library for this purpose. Using a variety of cycloadditions and Michael-addition initiated cyclization reactions, the library was constructed with a high degree of shape diversity and a low average ALogP. To demonstrate the usefulness of the fluorinated library, we present NMR screening results against four protein targets – two oncology-related kinases p70S6K1^[6] and p38γ,^[7] the Alzheimer's disease target BACE1,^[8] and the C-type lectin receptor DC-SIGN^[9] involved in autoimmunity and viral infection.

While most drug-like small molecules tend to be flat in shape (exemplified by a high fraction of sp²-hybridized carbon atoms, Fsp²),^[10,11] natural products (NPs) generally have greater saturation (higher Fsp³) and more chiral centers, resulting in more 'three-dimensional' (3D) structures.^[12–14] Interestingly, compounds with higher Fsp³ also tend to be superior leads for drug discovery due to improved solubility and less off-target binding.^[11,12,15] Thus, there has been a push towards synthesizing and screening more 3D structures.^[16,17] For these reasons, we designed our library of fluorinated fragments to be more natural product-like with a higher degree of shape diversity. For optimal ¹⁹F-NMR sensitivity, we targeted trifluoromethylated fragments with a molecular weight (MW) limit of 354 Da. The 'rule of three' (Ro3) guidelines for fragments suggest MW<300,^[18] but it is generally accepted that the increased mass of fluorine over hydrogen can be ignored for efficiency metric calculations and ¹⁹F-NMR-based screening.^[5,19] We decided to exploit the synthetic versatility of a trifluoromethylated α,β-unsaturated system to construct this fluorinated Fsp³-rich fragment (3F) library (Figure 1). Finally, all chiral fragments were synthesized as racemates to not bias screening towards a single enantiomer.^[20]

[a] N. S. Troelsen, D. Danková, I. S. A. Jensen, K. J. Śniady, F. Nami, M. H. Clausen

Center for Nanomedicine and Theranostics
Department of Chemistry
Technical University of Denmark
Kemitorvet 207, 2800 Kongens Lyngby, Denmark
E-mail: mhc@kemi.dtu.dk

[b] E. Shanina, Hengxi Zhang, C. Rademacher
Max Planck Institute of Colloids and Interfaces
Am Mühlenberg 1, 14424 Potsdam, Germany

[c] E. Shanina, Hengxi Zhang, C. Rademacher
Department of Biology, Chemistry and Pharmacy
Freie Universität Berlin
Takustrasse 3, 14195 Berlin, Germany

[d] D. Gonzalez-Romero, A. Cuenda
Department of Immunology and Oncology
Centro Nacional de Biotecnología/CSIC
Campus UAM, 28049 Madrid, Spain

[e] C. H. Gotfredsen
NMR Center • DTU, Department of Chemistry
Technical University of Denmark
Kemitorvet 207, 2800 Kongens Lyngby, Denmark

Figure 1. A selection of diverse ring systems accessed from a (trifluoromethylated) α,β -unsaturated system.

While fluorine in this context was installed to facilitate screening, it is worth noting its significant role in modern medicinal chemistry. Fluorine is routinely used as a bioisostere in drug development to improve properties like metabolic stability or permeability and is found in about 20% of all marketed drugs.^[19]

Starting from six similar and readily available trifluoromethylated compounds (**1–6**), nine core and natural product-like scaffolds were initially synthesized (see SI for resemblance to natural products and drugs). Each core scaffold contained 3–5 synthetic handles that were further functionalized or modified to afford a novel library of structurally diverse fluorinated fragments in a maximum of five steps from **1–6** (Figure 2). A highlight of the chemistry follows.

Reacting **1** or **2** with various hydrazines afforded pyrazolidinone fragments **7–9**. The non-decorated **7** could be further derivatized to afford **10**, or condensed with benzaldehyde to form an iminium ion that subsequently underwent a [3+3] cycloaddition with an azomethine ylide to generate **11** and **12**. A [3+2] cycloaddition between **1** and ethyl diazoacetate formed the dihydropyrazole **13**, from which fragments **14** and **15** were obtained. Similarly, amidation of **3** followed by a [3+2] cycloaddition afforded dihydropyrazole fragments **16** and **17**.

A series of 6–8 membered rings (**18–22**) were prepared using a domino Michael addition and intramolecular amidation between **3** and various dinucleophiles. Fragments **18** and **21** were further functionalized (two examples, **23** and **24**, are shown in Figure 2).

Carboxylic acid **3** readily reacted with 2-methylfuran in a Diels-Alder reaction to form oxabicyclo[2.2.1] scaffold **25** in a highly regio- and diastereoselective manner, installing four consecutive stereocenters. Coupling of **25** with a primary amine

followed by alkene epoxidation set up a base-mediated intramolecular cyclization affording tricyclic lactams **33** and **34**. A series of *cis*-fused [5,7], [5,8], and [5,9] bicyclic scaffolds (**35–38**) were formed from olefin-containing amides in a ring opening/ring closing metathesis (ROM/RCM) cascade reaction. Additional fragments (**39** and **40**) were created *via* olefin dihydroxylation followed by acetal formation (**41**) or oxidative cleavage/reduction (**42**).

In an intramolecular Diels-Alder approach, amidation of **3** with different furfurylamines followed by heating led to tricyclic fragments **45–48** with excellent diastereoselectivity. Alkene dihydroxylation, oxidative bond scissoring and reductive cyclization with various amines afforded ring-expanded fragments **52–58**. In the absence of amines this sequence afforded ring-opened diol products **59** and **60**. Acetal formation from diol **49** gave tetracyclic fragment **61**. Analogously, starting material **5** could be converted into tricyclic fragment **62** containing a CF_3 -substituted quaternary carbon center. From **62**, fragments **63** and **64** were synthesized.

From alkyne **6**, a series of cycloaddition reactions constructed additional four core scaffolds. Two consecutive azomethine ylide [3+2] cycloadditions afforded the bicyclic compound **65**. Modification of the ester and amine functionalities gave five fragments from this ring system (**66–70**). Starting material **6** also underwent an intermolecular Diels-Alder reaction with *N*-Boc-pyrrole to give azabicyclo[2.2.1] scaffold **71**. Michael addition with methylamine gave *endo*-product **72** after amine functionalization while hydrogenation and ester hydrolysis of **71** afforded *exo*-product **74**, which was further decorated to provide fragments based on the azabicyclic scaffold (**75–80**). Finally, subjecting **71** to an azomethine ylide afforded the tricyclic fragment **73** after removal of the amine protecting groups.

A *cis*-fused [5,4] ring system was realized in **81** through a [2+2] cycloaddition between alkyne **6** and trimethylsiloxy cyclopentene. Hydrogenation afforded **82** while reductive conditions gave fragmented diol **86**. Interestingly, scaffold **81** also underwent a base-mediated rearrangement to generate an α,β -unsaturated ketone which was trapped with an azomethine ylide to give tricyclic **83** and spirocyclic fragments (**83–84**).

Employing a [5+2] cycloaddition with an oxidopyrylium ylide, alkyne **6** and alkene **4** were converted into oxabicyclo[3.2.1] scaffolds **87** and **94**, respectively. Hydrogenation and subsequent reduction of **87** afforded fragments **88** and **89**, while Michael addition with methylamine yielded fragments **92** and **93**. Lewis acid mediated ether bridge cleavage gave tropones **90** and **91**. Scaffold **94** was used to create lactone **95** *via* NaBH_4 reduction and the tricyclic fragment **96** through a cycloaddition reaction.

In total, 115 fluorinated fragments were synthesized based on 67 distinct frameworks (Figure 2). An overview of calculated physicochemical properties of the 3F library and two commercial fluorinated fragment collections is given in Table 1. Notably, the 3F library exhibited a significantly lower average ALogP of 0.8 compared to 1.9 and 3.2 for the two commercial libraries. Furthermore, the 3F library stands out due to significantly higher Fsp^3 and natural product-likeness.

Figure 2. Synthesis of the 3F library containing 115 fluorinated fragments based on 67 distinct frameworks (not all shown). Starting from six similar and readily available fluorinated compounds 1–6, nine central scaffolds were synthesized (color-coding indicates starting material used). The main reaction types used to form each of the central scaffolds are listed in the top left hand corner of each box. Yields refer to isolated, pure compounds. For reaction conditions and structures of all synthesized fragments along with similarity to natural products and drugs, see SI.

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Table 1. Physicochemical properties of the 3F, Key Organics, and Maybridge fluorinated fragment libraries.

	Ideal range ^[a]	3F Library	Key Organics ¹⁹ F library	Maybridge ¹⁹ F library
MW	<300	284 ± 41	187 ± 29	285 ± 55
ALogP	≤3	0.8 ± 0.9	1.9 ± 0.6	3.2 ± 1.2
HBA	≤3	2.7 ± 1.2	1.4 ± 0.9	2.2 ± 1.3
HBD	≤3	0.8 ± 0.8	0.6 ± 0.6	0.8 ± 0.8
Chiral centers	-	3.3 ± 1.8	0.1 ± 0.3	0.2 ± 0.5
Fsp ³	≥0.47 ^[11]	0.7 ± 0.2	0.2 ± 0.2	0.2 ± 0.2
NP-likeness ^[b]	≥0	0.0 ± 0.5	-1.0 ± 0.5	-1.1 ± 0.4

[a] based on the Ro3.^[18] [b] compared to a score of 1.4 ± 0.6 for a collection of 2712 NPs (logarithmic scale, see SI). MW = molecular weight; ALogP = atomic partition coefficient; HBA = hydrogen bond acceptors, HBD = hydrogen bond donors; Fsp³ = fraction sp³-hybridized carbon; NP = natural product; green: inside ideal range; yellow: extreme of ideal range; red: outside ideal range. See SI for plots.

To evaluate the shape diversity of the 3F library, a principal moment of inertia (PMI) analysis^[23] was carried out (Figure 3). Satisfyingly, the fragments showed a close-to uniform distribution in the plot indicating a high level of shape diversity. The high degree of saturation (average Fsp³ = 0.7) and complexity of the 3F library led to significantly higher degree of 3D character compared to a representative commercial (fluorinated) fragment library (Key Organics, Fsp³ = 0.2). While the vast majority of the commercial fragments were more two-dimensional and situated in the so-called “flatland” of the plot,^[12] only 5% of the 3F fragments were found here. Compared to a collection of natural products (Fsp³ = 0.5) the shape diversity was similar, further indicating a high natural product-likeness of the 3F library (Figure 3). The diversity of the fragments was also evident from a large ¹⁹F chemical shift (δ) distribution of more than 23 ppm.

To demonstrate the usefulness of the 3F library, fragments were screened against four diverse protein targets – p70S6K1, p38 γ , BACE1, and DC-SIGN – using a primary ¹⁹F-NMR assay. The assay was based on a transverse (T₂) relaxation-based experiment that exploits the large difference in tumbling rates between large biomolecules and fragments and the chemical exchange contribution arising from the difference in chemical shifts between free and bound states. This effect can be easily visualized using a T₂-filter such as the Carr–Purcell–Meibom–Gill (CPMG) pulse scheme and binding was determined as significant decrease (>50%) of ¹⁹F signal intensities.

After quality control,^[24] 102 of the 115 fragments were selected for screening and pooled into cocktails of 17–24 fragments (based on chemical shift dispersion, see SI for cocktail compositions). Gratifyingly, this also ensured excellent chemical diversity with each cocktail containing members from at least six of the nine major scaffold groups. Relying on the ease and elegance of ¹⁹F-NMR screening, the 3F library was screened against one target per day. Figure 4 shows an example of screening results from one cocktail against BACE1.

Based on the primary ¹⁹F-NMR screen, 30 hits were identified against the four targets resulting in hit rates ranging from 3–11% (Table 2). In the screens against p70S6K1 and DC-SIGN, a competitive inhibitor was subsequently added to determine whether binding was associated with a known binding site or not. Initial hits against three of the targets were validated using the orthogonal ¹H-NMR methods saturation transfer difference (STD) and WaterLOGSY. An R₂-filtered ¹⁹F-NMR assay was employed to validate and measure K_i-values of hits against DC-SIGN. Hits against p38 γ were further tested for *in vitro* activity in an enzymatic assay and four of the 11 hits were able to inhibit the kinase at 0.1 or 10 mM (see SI). An excellent average validation rate of 67% was achieved using these secondary assays.

Figure 3. Principal moment of inertia (PMI) analysis of the 3F library (blue), a commercial fluorinated fragment library (Key Organics, red), and a collection of 1356 natural products (green). “Flatland” is situated below the dashed line (NPR1 + NPR2 < 1.1).^[12] The three corners of the plot represent three geometrical extremes - rod-like, disc-like, and spherical shapes, respectively. NPR: normalized PMI ratios.^[25]

Figure 4. Example of ^{19}F -NMR screening results, here against BACE1 (both spectra with CPMG filter). Hits are identified from a significant reduction of signal intensity upon addition of protein. The spectra shown were recorded at 800 MHz with 1024 scans using a T_2 -relaxation delay of 200 ms.

Table 2. ^{19}F -NMR screening results against four protein targets. Fragments hits highlighted with grey were validated by a secondary screening assay. For p70S6K1, p38 γ , and BACE1, the ^1H -NMR methods STD and/or WaterLOGSY were used. For DC-SIGN, validation and measurements of K_d -values were achieved using a R_2 -filtered ^{19}F -NMR assay (K_d -value and binding site for **90** was determined using ^1H - ^{15}N HSQC NMR). Hits against p38 γ were tested for *in vitro* activity using an enzymatic assay – inhibitors are marked with a star (*). K_d -values for p38 γ hits were determined using ^{19}F -based differential chemical shift perturbation. A black frame indicates that binding was associated with a known binding site as determined by a competition experiment. Hit rates are given for the primary ^{19}F -NMR screen.

Target	Hits	Hit rate
p70S6K1 ^[a]		3%
p38 γ ^[b]		11%
BACE1		7%
DC-SIGN ^{[c],[d]}		9%

[a] Inhibitor PF-4708671 used as competitor. [b] Inhibition of p38 γ was achieved at 100 μM (**90**, **97**, and **99**) and 10 mM (**98**), see SI. [c] Ca^{2+} used as competitor. [d] Site III identified as pocket for **90**.

As demonstrated, ^{19}F -NMR screening provides a fast, sensitive, and simple primary screening assay ideally suited for detection of weakly binding fragments. Since many modern NMR probes include a coil tunable to fluorine, the approach is easy to adopt for most labs. The highly diverse 3F library is the first synthetic fragment library tailor-made for ^{19}F -NMR screening and our results underline that the approach should find broad application in the FBDD community. With hit rates of 3–11% for these fluorinated fragments, libraries do not necessarily need to be particularly large to obtain useful hits. Our hits came from eight of the nine central scaffold groups and shows the importance of library diversity when screening targets from different protein classes. To further improve the usefulness of ^{19}F -NMR screening, we are calling for the continued synthesis of diverse fluorinated fragments. In the meantime, we hope that the 3F library will find use for other researchers and we encourage anyone interested in screening the fragments to contact us.

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Layout 1:

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A large library of diverse and three-dimensional fluorinated fragments was designed and synthesized to address the need for better sampling of chemical space and easier screening workflows. The incorporation of fluorine enabled efficient screening by ^{19}F -NMR and was demonstrated against four disease-relevant targets, providing a series of starting points for lead discovery.

Layout 2:

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