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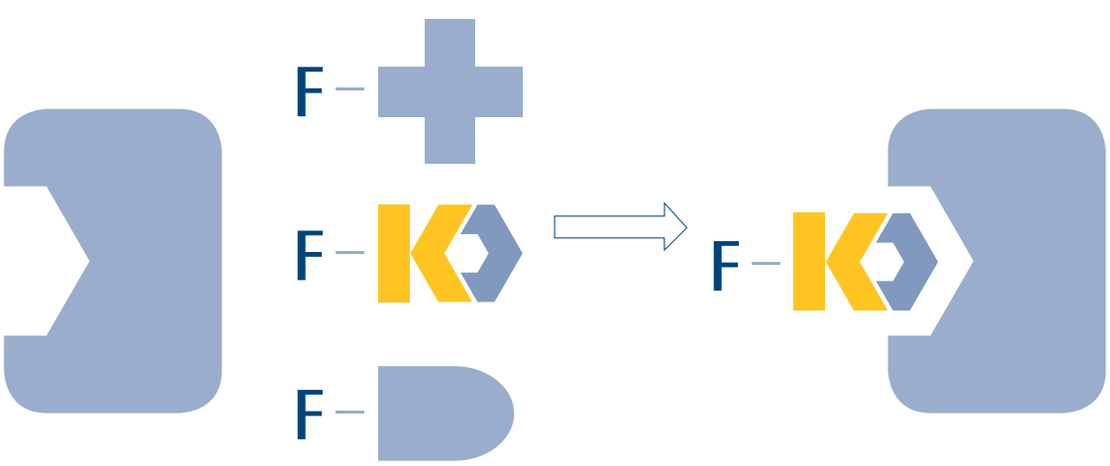
BIONET Fluorine Fragment Library



BIONET

Fragment Libraries

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Key Organics have expanded the BIONET Fluorine Fragment Library which now includes 533 fluorinated fragments.

Key features and benefits:

- Measured solubility in PBS buffer ≥ 100μM by ^{1}H NMR
- Fragments soluble in DMSO at 100mM
- Purity ≥ 95%
- Filtered for PAINS substructures
- Excludes fragments likely to form aggregates

Customers are supplied with the following data package for each fragment purchased:

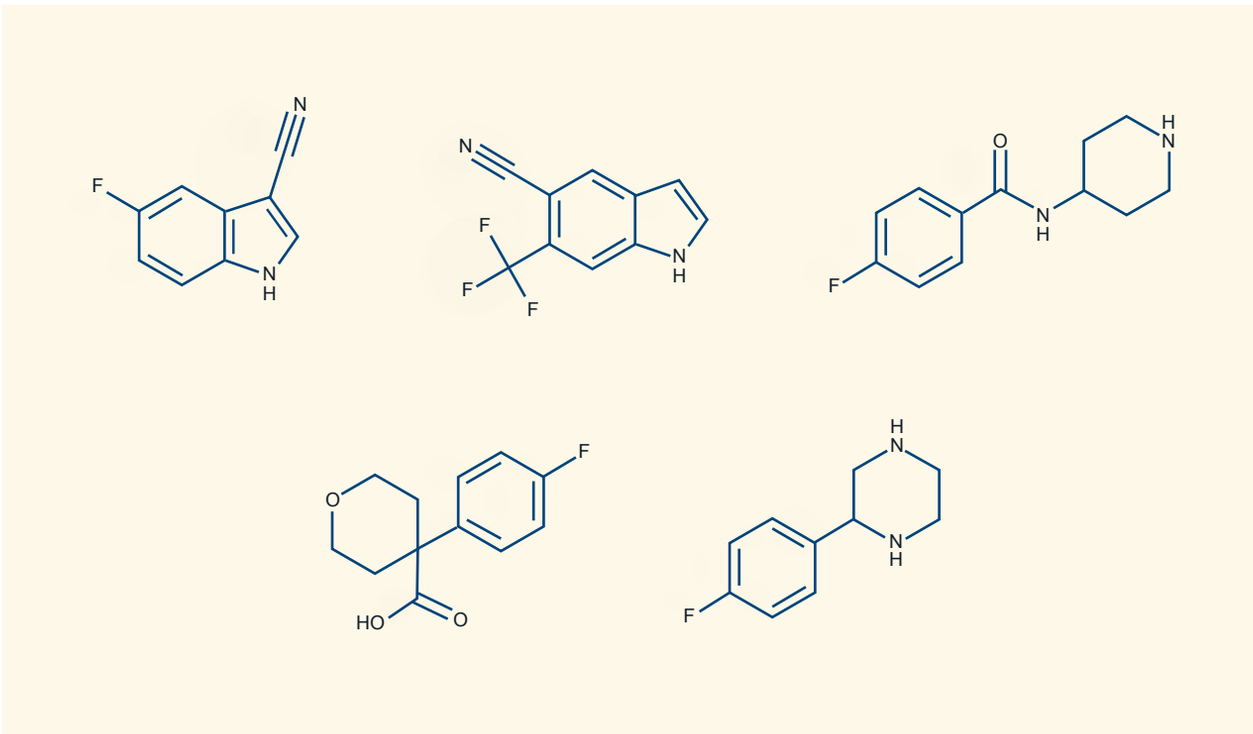
- Aqueous buffer ^{19}F NMR raw data file
- Aqueous buffer ^{1}H NMR raw data file
- ^{19}F NMR chemical shifts
- Structures and Physiochemical properties in an sd file

The parameters used in the design of the library are:

- Heavy atoms ≤21
- clogP ≤3
- Hydrogen bond donors ≤2
- Hydrogen bond acceptors ≤4
- tPSA ≤ 72
- Rotatable bonds ≤ 3

The library excludes substructures identified as promiscuous or reactive by the following empirically determined rejection rules:

- Lilly MedChem Rules[3]
- PAINS[4]
- FAFDrugs4[2]



^{19}F and ^{1}H NMR curation for fragment prioritisation and library characterization

^{19}F and ^{1}H NMR were employed to select compounds with appropriate solution behavior to be amenable to biophysical analysis in physiologically relevant aqueous solution. Each singleton sample consisted of nominal 300 µM compound in buffer (50 mM sodium phosphate pH 7.4, 100 mM NaCl). ^{1}H NMR spectra were acquired on a 600 MHz spectrometer equipped with a helium cryoprobe that significantly increased signal-to-noise. Simple 1D ^{19}F and ^{1}H NMR spectra were acquired along with a series of 1D 1H CPMG spectra, which were used to detect compounds showing potential aggregation in aqueous solution. The CMC Assist automation software allowed for automatic readout of the fragment concentration that was experimentally derived from integrating the NMR resonances of each singleton sample and referencing to standardized samples using the ERETIC module (Bruker Spectrospin Inc.)10. The CMC Assist module also allowed for verification of each singleton spectrum to determine if the spectral attributes were consistent with the proposed primary structure of the corresponding fragment. This exercise was also complemented by an automated analysis using Spectral DB software (ACD Inc.).

Key Organics Fluorine Fragment Libraries exclude fragments likely to form aggregates.

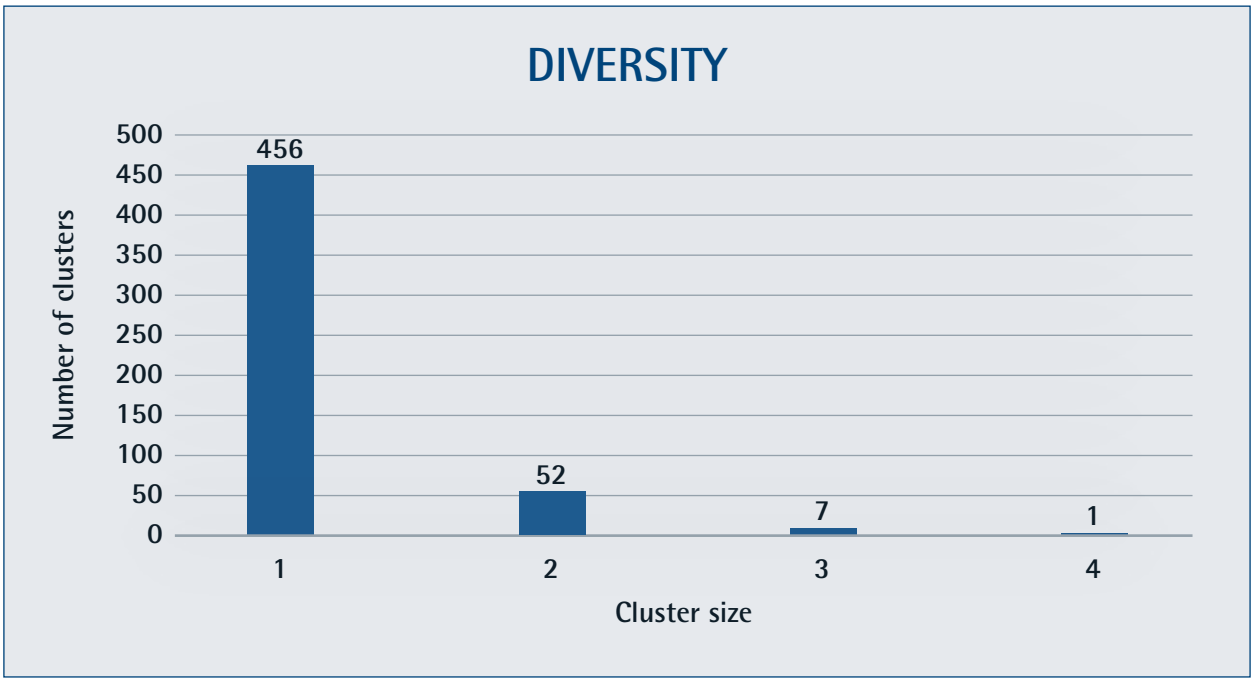
The spin–spin relaxation Carr–Purcell–Meiboom–Gill NMR experiment has been employed to detect and remove aggregate species from Key Organics BIONET Bromine Fragment library.[5]

Small molecules can self-assemble in aqueous solution into a wide range of nanoentity types and sizes each having their own unique properties. This has important consequences in the context of drug discovery including issues related to nonspecific binding, off-target effects, and false positives and negatives. The spin–spin relaxation Carr–Purcell–Meiboom–Gill NMR experiment is sensitive to molecular tumbling rates and can expose larger aggregate species that have slower rotational correlations. The strategy easily distinguishes lone-tumbling molecules versus nanoentities of various sizes. The technique is highly sensitive to chemical exchange between single molecule and aggregate states and can therefore be used as a reporter when direct measurement of aggregates is not possible by NMR.

Overview of calculated properties of the final library

Property	Average	Min	Max
Molecular Weight	198	122	300
Heavy Atom Count	13.5	9	21
tPSA	38	3	72
cLogP	1.5	-0.9	3
H-bond acceptors	2.5	1	4
H-bond donors	0.7	0	2
Rotatable bonds	1.6	0	3

Diversity Statistics:
 # clusters at 0.85 similarity = 456 singletons. 490 clusters / 533 fragments = 91.9%



Fragment hits and SAR by catalogue

Key Organics can certainly help regarding following up on any hits, whether that is via SAR by catalogue, where we can search BIONET and commercial space for analogues of compounds of interest or via custom or contract synthesis. For those analogues available through other vendors, we can offer a compound management service to provide the following services:

- Compound Procurement
- Compound Weighing
- Compound Dissolution
- Automated Reformatting & Plating
- Compound Shipping & Logistics to in-house & partner testing laboratories
- Quality Control

The BIONET Fluorine Fragment Library is available custom-weighed in milligram or micromolar quantities. Customers can purchase the entire library or select any number of compounds as required.

References

1. DataWarrior: An Open-Source Program for Chemistry Aware Data Visualization and Analysis. *J Chem Inf Model* **2015**.
2. FAFDrugs4: M.; Miteva, S.; Violas, M.; Montes, D.; Gomez, P.; Tuffery, B.; Villoutreix. *Nucleic Acids Research*. **2006**, 34 (2), W738–W744.
3. Rules for identifying potentially reactive or promiscuous compounds. Bruns et al, J. Med. Chem, **2012** (53).
4. Baell, J. B.; Holloway, G. A. *J. Med. Chem.* **2010**, 53 (7), 2719–2740.

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For more information please contact us at:

T: +44 (0)1840 212137 E: enquiries@keyorganics.net www.keyorganics.net

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Key Organics Ltd.,
Highfield Road Industrial Estate,
Camelford,
Cornwall PL32 9RA,
UK

T: +44 (0)1840 212137

E: enquiries@keyorganics.net

www.keyorganics.net