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Produktinformation

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- Diagnostik & molekulare Diagnostik
- Laborgeräte & Service

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See the following pages for more information!

Lieferung & Zahlungsart

siehe unsere Liefer- und Versandbedingungen

Zuschläge

- Mindermengenzuschlag
- Trockeneiszuschlag
- Gefahrgutzuschlag
- Expressversand

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Key Organics
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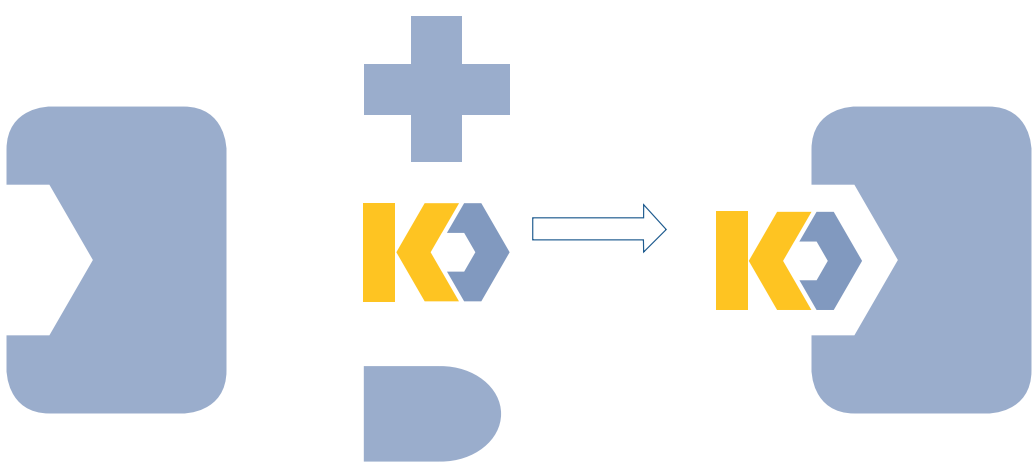
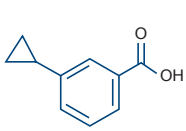
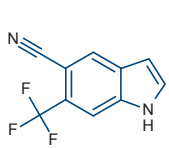
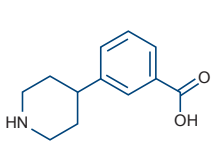
BIONET Premium Fragment Library

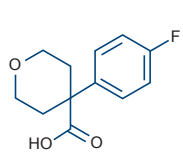


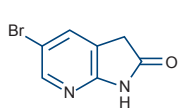
Building a Diverse and Experimentally-Curated Fragment Library











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BIONET
Fragment Libraries

BIONET
Fragment Libraries

Key features and benefits:

- Measured solubility in PBS buffer by ^{1}H NMR
- Fragments soluble in DMSO at 100mM
- SPR Clean Screen performed at 1mM in PBS-P+ Buffer
- Purity ≥ 95%
- Excludes fragments likely to form aggregates

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

- Aqueous buffer ^{1}H NMR raw data file
- Structures and Physiochemical properties in an sd file
- SPR Clean Screen results

The parameters used in the design of the library are:

- Heavy atoms ≤ 16
- clogP ≤3
- Hydrogen bond donors ≤3
- Hydrogen bond acceptors ≤3
- tPSA ≤ 60
- Rotatable bonds ≤ 3

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

- Lilly MedChem Rules[1]
- PAINS[2]
- BMS[3]

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

^{1}H NMR was employed to select compounds with appropriate solution behavior 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 ^{1}H NMR spectra were acquired along with a series of 1D ^{1}H 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.)[4]. 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.).

The Fragment Library excludes fragments likely to form aggregates

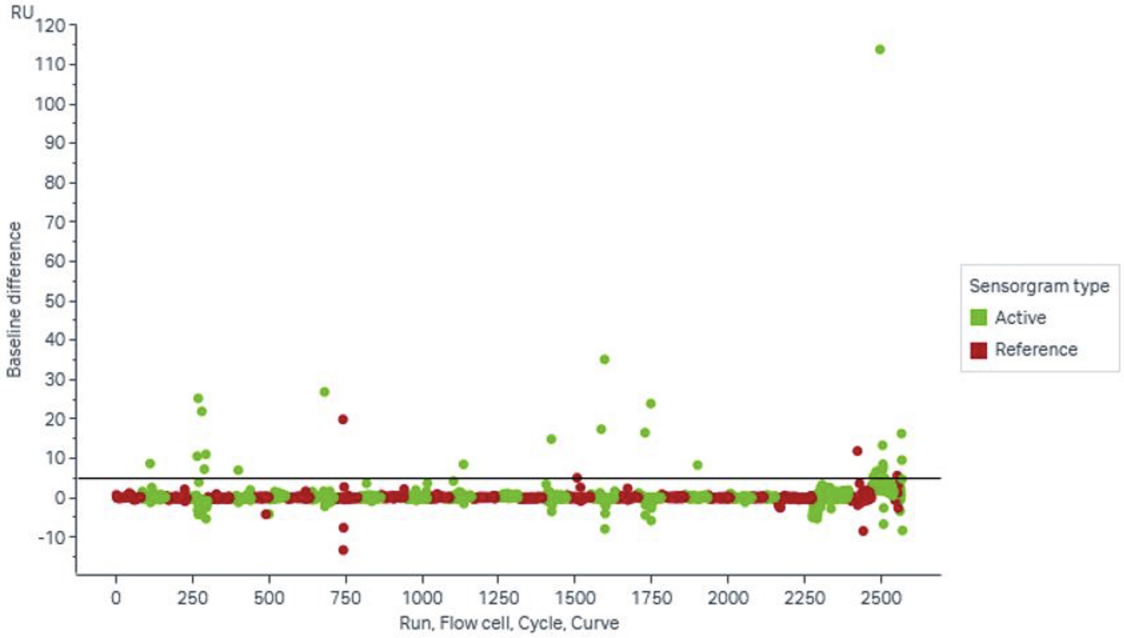
The spin–spin relaxation Carr–Purcell–Meiboom–Gill NMR experiment has been employed to detect and remove aggregate species from Key Organics BIONET Premium Fragment library.[5]

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.

SPR Clean Screen

Key Organics in collaboration with Cayman Chemical have implemented an SPR Clean screen on the Fragment Library and the results are available to customers. An SPR Clean Screen aids identification of residual binding of fragments to the target molecule and/or the sensor surface. Fragment screening cycles do not normally include regeneration, and residual binding can affect subsequent cycles and mask weak binding of other fragments. An SPR Clean Screen is performed by injecting single concentrations of each fragment over reference and target surfaces.

All the fragments in the clean screen, with exception to those that showed irregular sensorgrams, were run at 1mM and showed the typical square-shaped sensorgram expected. Therefore, in the given experimental conditions, the fragments are soluble ≥ 1mM in PBS-P+.



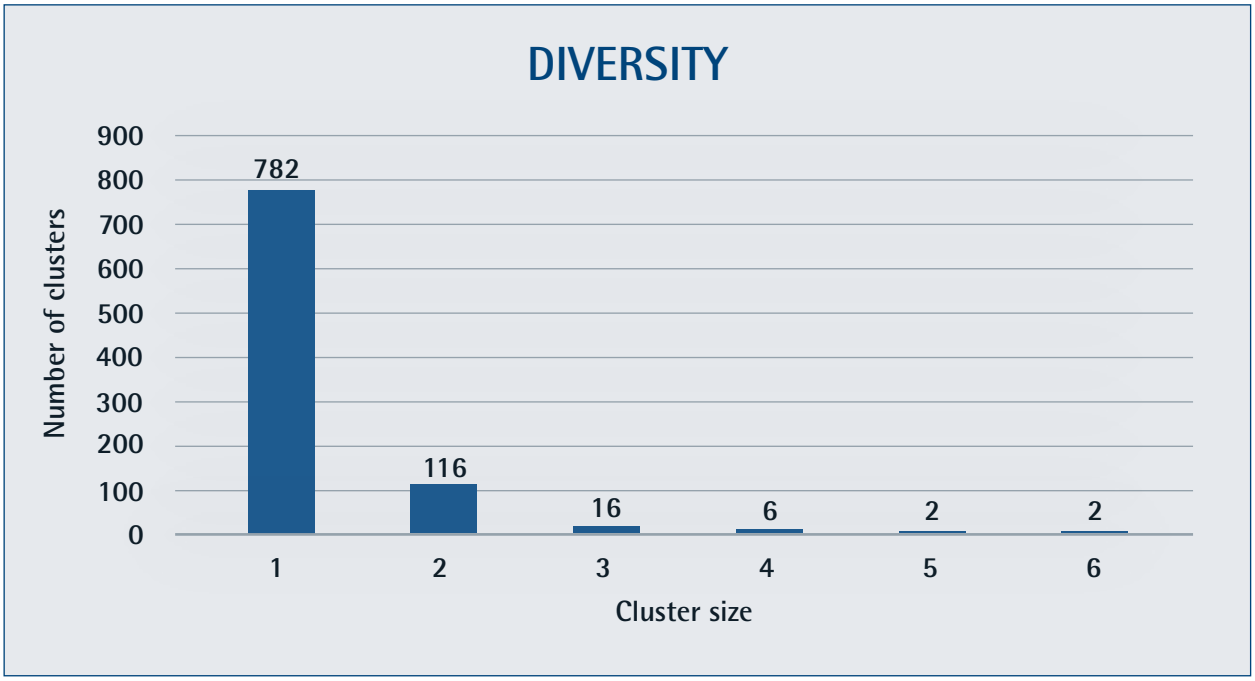
Clean Screen Plot. Total of 1149 fragments were screened against dextran surface (reference) and TNF-α immobilized target surface (active) on CM7 sensor chip. Clean screen identified 26 fragments (2.3%) as sticky.

Fragment Pooling

The NMR files include analyses data derived from the CMC Assist module which automatically picked resonance peaks and tabulated the data within the spectral files. These can then be used for chemical shift encoding purposes. Access to this distribution of resonance shifts then allows for "smart pooling" of fragments that to minimize the overlap of resonances. Fragment pooling is a common strategy employed for NMR-based fragment screening to minimize the use of expensive NMR time and amount of target protein. Minimizing the overlap of resonance via smart pooling helps with the subsequent deconvolution steps when a hit is identified from screening pools of fragments.

Diversity Statistics:

 # clusters at 0.85 Tanimoto similarity (MACCS 166-bit MOE) = 924



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

References

1. Rules for identifying potentially reactive or promiscuous compounds. Bruns et al, *J. Med. Chem,* **2012** (53).
2. Baell, J. B.; Holloway, G. A. *J. Med. Chem.* **2010**, 53 (7), 2719–2740.
3. Pearce, B. C.; Sofia, M. J.; Good, A. C.; Drexler, D. M.; Stock, D. A. J. Chem. Inf. Model. 2006, 46 (3), 1060–1068.
4. Akoka, S.; Barantin, L.; Trierweiler, M. Anal. Chem. 1999, 71, 2554-2557.
5. Yann Ayotte, Victoria M. Marando, Louis Vaillancourt, Patricia Bouchard, Gregory Heffron, Paul W. Coote, Sacha T. Larda, and Steven R. LaPlante, J. Med. Chem. 2019, 62, 7885–7896.

BIONET Fragment Libraries

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