Key Organics

Chemistry | Innovation | Quality

October 2024

Newsletter

Welcome to our 2024 Newsletter

It is with great pleasure that we can now announce the completion of a major $1 M investment project within Key Organics; our new process R&D and scale-up facility is now complete and fully operational. This will enable us to better support our customers and deliver more diverse, scale-up projects up to a 30 L capacity, with scope for further scale as needed. We have also completed our Ecovadis accreditation and are on course to be ISO9001 compliant later this year.

Key Organics' New Scale-Up Facility Now Open!

Key Organics' experienced Chemists have supported many Process R&D and scale up programs, from route scouting, synthesis of preclinical tox batches, scale up of key intermediates and synthesis of intermediates for GMP manufacture.

We have successfully worked with clients in Pharma, Biotech, Academia, Agrochemicals, Oil and Gas, Materials and Consumer Health industries and therefore have a very broad range of Synthetic Chemistry experience.

As many of our customers work to tight deadlines, we seek to optimise the efficiency of a scale up route by getting to the heart of the issues quickly.

A video tour of our new facility can be found here: **https://www.keyorganics.net/services/process-development-scale-up**

New Scale Up Lab Profile

- Six bespoke walk in Fume Hoods, fully flexible from benchtop to scale up chemistry
- Two bespoke walk in scrubbed and wash down Fume Hoods to enable chemistry that needs an extra level of safety and containment
- Two vented hoods fully accessible from all sides for general small-scale chemistry
- 100m^2 lab space
- 40m^2 office and storage space
- Designed to be fully flexible to allow our chemists to carry out chemistry from benchtop to 30 litre scale (in future, potential to house up to 100 litre vessels)
- Fully serviced high spec design

A BIONET Fluorine Fragment Library has been constructed employing Rule of Three and industry standard substructure filtering including PAINS analysis. All fragments in the Fluorine Fragment Library have been analyzed by ^{1}H NMR for structure verification, purity, solubility, and lack of aggregation. Spectra are available to customers for Chemical Shift Encoding (CSE), thus allowing custom pools to be built with significant time and cost savings.

Build Strategy

RULE OF 3 COMPLIANT
- MW ≤ 300
- clogP ≤ 3
- HBA ≤ 4
- HBD ≤ 2
- Rot Bonds ≤ 3

REMOVE THE UNDERSIRABLES
- PAINS
- FAFDrugs4
- Lilly Med Chem Rules
- Med Chem Curation

QC BY NMR
- Structure Verification
- Purity
- Solubility
- Aggregation Status

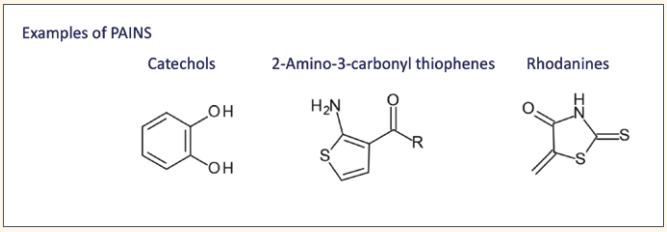
SUITABILITY FOR FRAGMENT SCREENING
- Pooling
- Fragment Screening
- Hit Identification
- Singleton Confirmation

Remove the Undesirables

As part of our Fragment selection process, industry-standard substructure filtering - including PAINS filtering - was implemented and as a result the BIONET 2nd Generation Fluorine Fragment Library does not include substructures identified as promiscuous or reactive by empirically determined rejection rules. A fragment was rejected if it failed any one of 3 rejection rules: PAINS,[1] FAFDrugs4[2] and Lilly MedChem Rules.[3]

Focus on Pan Assay Interference Compounds (PAINS) substructure filtering – a deciding factor in the quality of a fragment library.

PAINS are compounds that frequently show up as screening hits, but that act through non-specific mechanisms such as covalent attachment to proteins or generation of hydrogen peroxide. The problem with PAINS is that they may show convincing biochemical and even cell based activity, but mechanistically be useless for further advancement to drugs or even chemical probes. PAINS remain common in many vendors' Fragment Libraries. PAINS compounds have been identified and substructure filters constructed that recognise these compounds.[1]

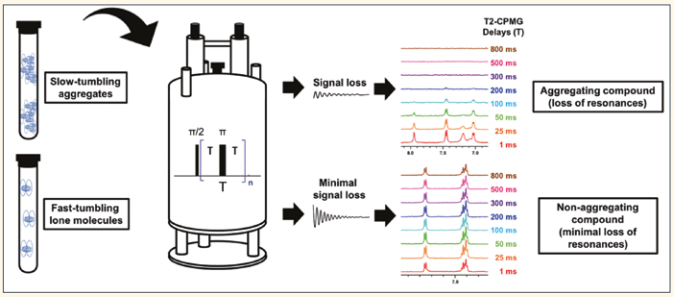


Aggregation Filtering

Key Organics Fluorine Fragment Library excludes fragments likely to form aggregates.

The spin–spin relaxation Carr–Purcell–Meiboom–Gill NMR (CPMG) experiment has been employed to detect and remove aggregate species from Key Organics BIONET Premium and Fluorine Fragment libraries.[4]

Small molecules can self-assemble in aqueous solution into a wide range of nanoentity types and sizes (dimers, n-mers, micelles, colloids, etc.), 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 T2-CPMG NMR experiment is sensitive to molecular tumbling rates and can expose larger aggregate species that have slower rotational correlations in solution. The strategy easily distinguishes lone-tumbling molecules versus nanoentities of various sizes. The technique is also 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.



J. Med. Chem. 2019,62, 7885-7896

References

1. Jonathan B. Baell and Georgina A. Holloway. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. Journal of Medicinal Chemistry 2010, 53, 2719-2740.

2. David Lagorce, Lina Bouslama, Jerome Becot, Maria A Miteva, and Bruno O Villoutreix. FAF-Drugs4: free ADME-tox filtering computations for chemical biology and early stages drug discovery. Bioinformatics 2017 Nov 15;33(22):3658-3660. BMC Bioinformatics 2008, 9:396.

3. Robert F. Bruns and Ian A. Watson. Rules for identifying potentially reactive or promiscuous compounds. Journal of Medicinal Chemistry 2012, 55, 9763-9772.

4. Yann Ayotte, Victoria M. Marando, Louis Vaillancourt, Patricia Bouchard, Gregory Heffron, Paul W. Coote, Sacha T. Larda, and Steven R. LaPlante. Exposing Small-Molecule Nanoentities by a Nuclear Magnetic Resonance Relaxation Assay. Journal of Medicinal Chemistry 2019, 62, 7885-7896.

QC by NMR

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

^{19}F and ^{1}H NMR were employed to select compounds with appropriate solution behavior to be amenable for rigorous biophysical analysis in physiologically relevant aqueous solution conditions. 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 ^{1}H T2-CPMG spectra, which were used to detect compounds showing potential aggregation in aqueous solution. Compounds with solubility at 100µM and higher were prioritised given that most fragment screens and assays require high concentrations.

Data analyses involved combination of manual and automation tools. The CMC Assist automation software (Bruker Spectrospin Inc.) had multiple practical uses. It allowed for an automatic readout of the fragment concentration that was experimentally derived from integrating the NMR resonances of each singleton sample and referencing to standardised samples using the ERETIC module. The CMA 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 (Advanced Chemistry Development, Inc.).

The compounds and respective spectra were then re-subjected to visual inspection by medicinal chemists experienced in the art of fragment-based drug discovery. Compounds that were inconsistent with the NMR spectra were removed, along with those that showed signs of insolubility, instability or aggregation. Moreover, the NMR curation also allowed us to evaluate and characterise the final library. This experimental data served to verify structural integrity, purity, solubility, stability, aggregation status, and chemical shift positions. The final library consisted of 719 fragments that were soluble to at least 100µM in PBS aqueous buffer.

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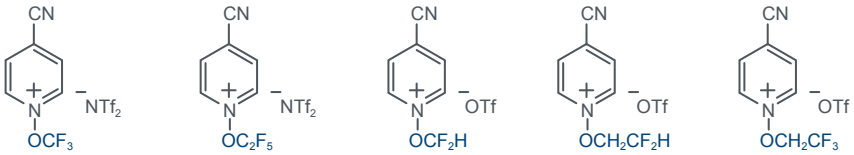
C-H fluoroalkoxylation reagents

- Shelf stable solids, radical OCF_3, OC_2F_5 and OR_F transfer reagents
- Direct C-H fluoroalkoxylation of aromatics and heteroaromatics
- Generation of OR_F containing candidates for patent example extension purposes

Available products:



Commercial products

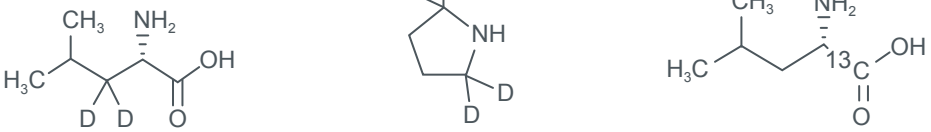
https://doi.org/10.1002/anie.201806296
https://www.cfplus.cz/trifluoromethoxylation-reagent
https://doi.org/10.1021/acs.orglett.2c02408

CF PLUS CHEMICALS
Fluoroalkylation and bioconjugation

Stable label collection

Now over 1,000 stable label compounds in our collection, we can also provide custom stable labels and have many years' experience in incorporating D2 and C13 into compounds for screening and DMPK studies.

Example structures



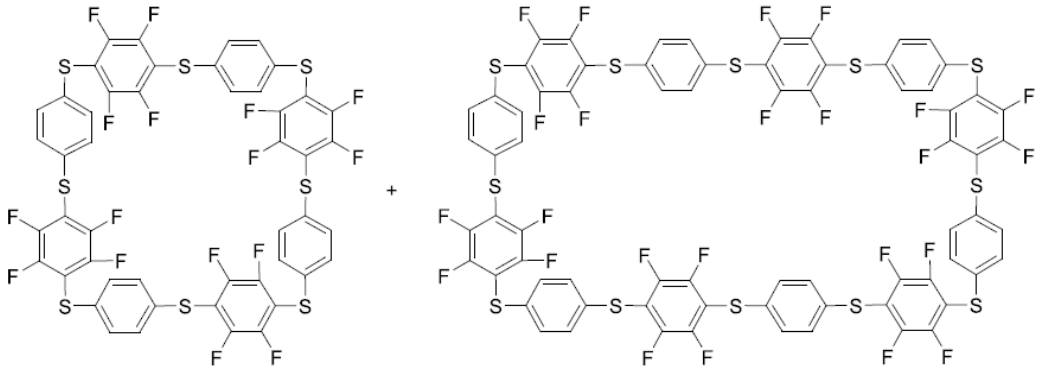
Showcasing research from Professor Woodward's laboratory, GSK Carbon Neutral Laboratories for Sustainable Chemistry and School of Chemistry, University of Nottingham.

Previously inaccessible large S8-corona[n]arene macrocycles (n = 8–12) with alternating aryl and 1,4-C6F4 subunits are easily prepared on up to gram scales, without the need for chromatography (up to 45% yield, 10 different examples) through new high acceleration SNAr substitution protocols (catalytic NR4F in pyridine, R = H, Me, Bu). Macrocycle size and functionality are tunable by precursor and catalyst selection. Equivalent simple NR4F catalysis allows facile late-stage SNAr difunctionalisation of the ring C6F4 units with thiols (8 derivatives, typically 95+% yields) providing two-step access to highly functionalised fluoromacrocycle libraries.

Chem. Sci., 2023, 14, 70

S_n-[*4F,4H*]-corona[n]arene mixture (n = 8, 12), technical grade

The mixture is composed of two components, the major of which is the corona[8]arene (**I**) (≥85%), other [n]arenes may be present of which the corona[12]arene (**II**) is major.



I (>85 mol-%) **II** (ca. 12 mol-%)

Upcoming Exhibitions

We regularly attend and exhibit at the leading Chemistry, Drug Discovery and Biotech Conferences around the world.

11th & 12th November	Automated Synthesis Forum 2024	Oxford Belfry Hotel & Spa, Oxford, UK
15th November	The International Isotope Society UK Group 30th Annual Symposium	The Møller Institute, Cambridge, UK
9th - 11th December	10th Winter Process Chemistry Conference	Birmingham, UK

For more information, please visit: https://www.keyorganics.net/about/exhibition-conference-attendance

Key visit to the University of Sussex

"We were thrilled to welcome Key Organics to our campus for an inspiring day of connection and collaboration!

Our discussions spanned the chemical industry, exploring exciting possibilities for future collaborations between Innovation and Business Partnerships and the School of Life Sciences. Thank you to our brilliant academics, Barny Greenland, Mark Bagley, and StormHassel-Hart, for their warm welcome and insightful conversations. Your enthusiasm and curiosity truly made this visit a resounding success!

In particular, we delve into the possibility of selling more of our molecules patented by Sussex and developed by Barnaby Greenland's research group, a promising venture that could further strengthen our industry ties.

We were incredibly proud to see Dr Joe Carey, Managing Director and Sussex alumni, leading the charge for Key Organics. His presence reaffirmed the strong ties between our university and the industry. We eagerly anticipate the opportunities arising from this dialogue and look forward to continuing these critical conversations."

UNIVERSITY OF SUSSEX

Courtesy of the University of Sussex.

Key Organics' Staff Profile:

Jon Ponting

"I completed my undergraduate degree from Swansea University in 1991, joining Maybbridge Chemicals in April 1992 working as a scale up chemist. I joined Key Organics in 1994, undertaking a range of chemical and managerial roles.

I have been involved with the design, construction and management of 2 kilo laboratories and have been responsible for all scale up chemistry within Key for nearly 30 years. I have successfully undertaken many FTE and custom projects for many customers covering a wide range of chemistry and often to a very high client specification"

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