May 2023

Key Organics

Chemistry | Innovation | Quality

Newsletter

Welcome to our 2023 Newsletter

During the last few years we have continued to invest and expand our BIONET fragment collections and can now offer a range of Covalent Fragments and an expanded Fluorine set that complements our primary offerings in FBDD. Our collaboration with the University of Nottingham's chemistry department has generated a new best-in-class range of "Himbert diene" ligands for application in asymmetric catalysis. Profs. Hon Lam, Simon Woodward and colleagues have demonstrated their effectiveness in the enantioselective Rh(I)-catalyzed 1,4-addition or 1,2-addition reactions with considerable success. Our BIONET product group now has over 280,000 Intermediates, Building Blocks, Biochemicals and Fragments; many available for same day dispatch.

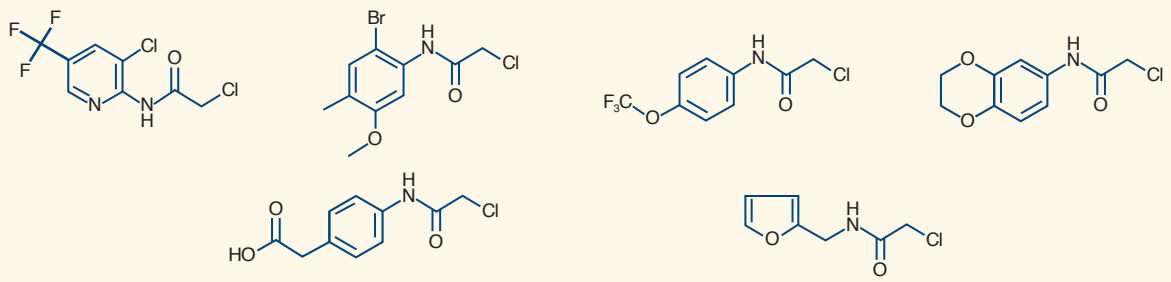
Colleagues from our analytical department; Dan Griffiths and Lorna Bankole provide an insight into their backgrounds and expertise. We hope to meet you at one of our forthcoming events where we will be exhibiting or attending.

Dr Joe Carey, *Managing Director.*

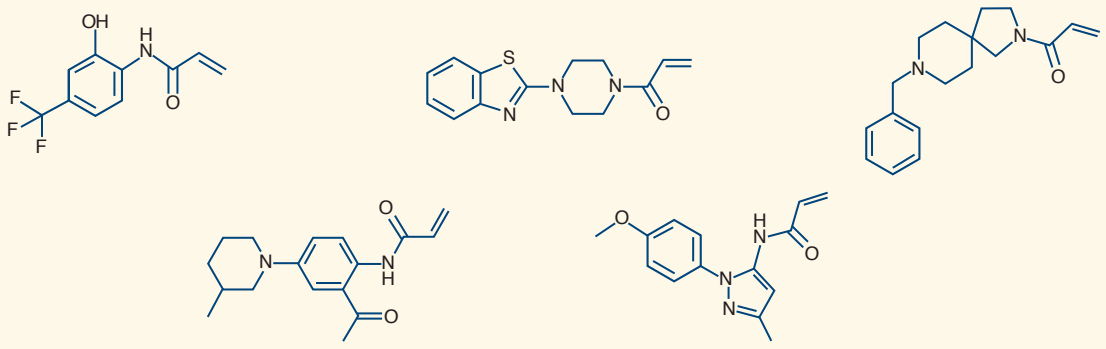
BIONET Covalent Fragments

Drugs that covalently bond to their biological targets have a long history in drug discovery. There is an increased interest in covalent therapeutics in the literature and recent years have witnessed a significant increase in the number of drug candidates with covalent mechanism of action progressing through clinical trials or being approved; moreover, about 30% of marketed drugs are covalent binders. Screening fragments has its challenges, principally, the requirement for sensitive biophysical assays due to the low affinity of typical fragment hits. Fragments that can form a covalent bond with their target protein can overcome this challenge due to the increased affinity between the fragment and the target.

Examples of Key Organics Chloroacetamide fragments



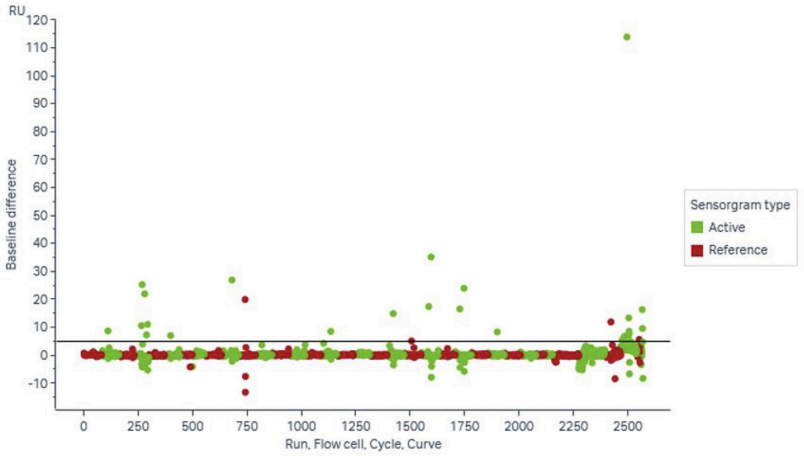
Examples of Key Organics Acrylamide fragments



Other chemical classes are available including Epoxides; Terminal alkynes; Nitro alkyls; Isothiocyanates; 2-Chloropyridines; Michael acceptors; Aldehydes; Boronic acids; Alkyl Halides and Activated nitriles.

SPR Clean Screen

Key Organics in collaboration with Cayman Chemical have implemented an SPR Clean screen on the BIONET Premium 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.



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.

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+.

Your Partner for Fragment-Based Drug Discovery (FBDD)

Use of a fragment-based lead generation strategy in a discovery program is now a well-established option for modern biotech and pharmaceutical companies. Multiple drugs have received regulatory approval which had their origins from a fragment-based approach, and there are many more compounds in industry drug pipelines at various stages of preclinical and clinical development. Key Organics has a long history of providing support to teams working on Fragment-Based Drug Design (FBDD) programs, ranging from provision of the original fragment libraries used in screening, through the fragment growth and lead optimisation process, all the way to scale-up and beyond.

THE FBDD PROCESS

The operational workflow for a fragment-based discovery program (*Figure 3*) is broadly similar to that used with a conventional small molecule screening approach such as HTS.

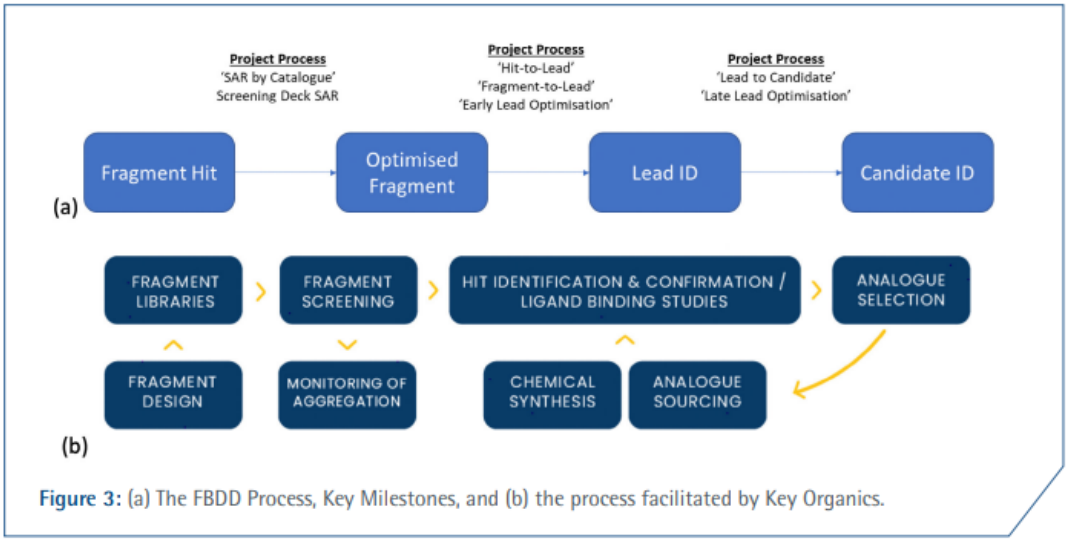


Figure 3: (a) The FBDD Process, Key Milestones, and (b) the process facilitated by Key Organics.

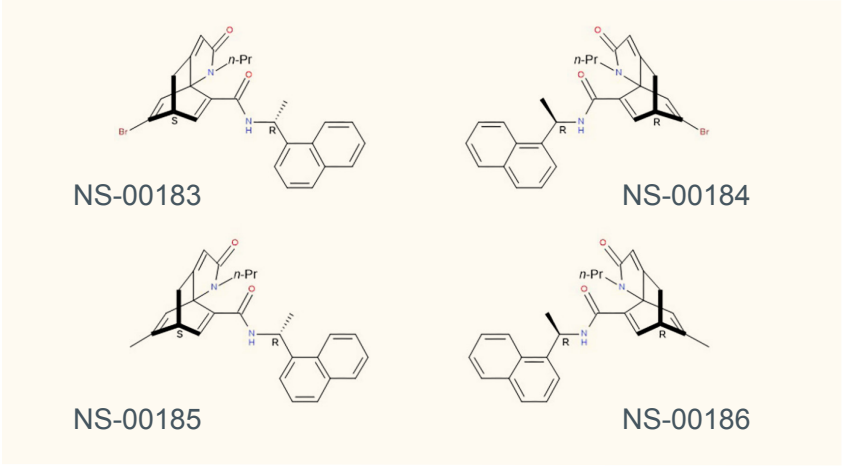
Key Organics has a long history and well-deserved reputation of applying their collective years of chemistry knowledge to projects from early stage discovery through to pre-clinical candidate stage. They occupy a unique position by being able to offer fragment and screening libraries for very early-stage projects. Key can follow this up by performing SAR by catalogue and custom synthesis of further analogues. Additionally, they offer FTE support for accelerating project progress – process development and scale up when the project approaches candidate selection phase. And finally, key Organics offers a deep well of experience in chemical procurement, which adds maximum value to all projects.

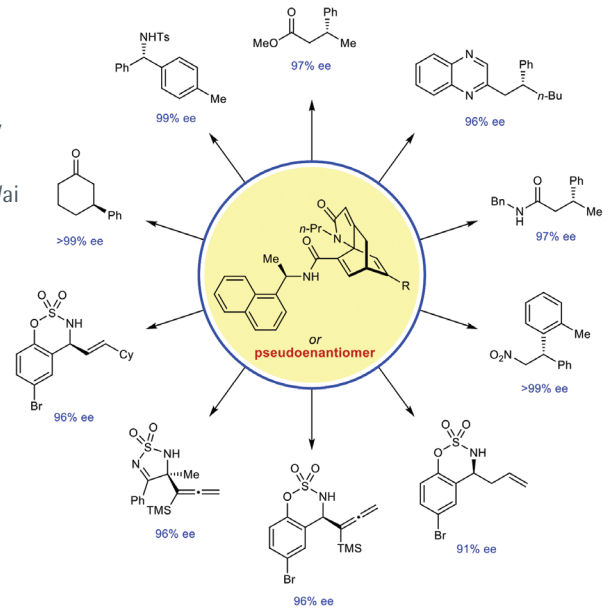
Chiral diene ligands

Chiral dienes are important ligands in asymmetric catalysis but they are less accessible than other commonly used ligands such as chiral bisphosphines and few are commercially available. Key Organics is pleased to offer new chiral "Himbert diene" ligands for sale.

University of Nottingham
UK | CHINA | MALAYSIA

Developed by the groups of Simon Woodward and Hon Wai Lam at the University of Nottingham, these new ligands match, or exceed, the performance of existing "best-in-class" chiral dienes over nine types of enantioselective Rh(I)-catalyzed 1,4-addition or 1,2-addition reactions.



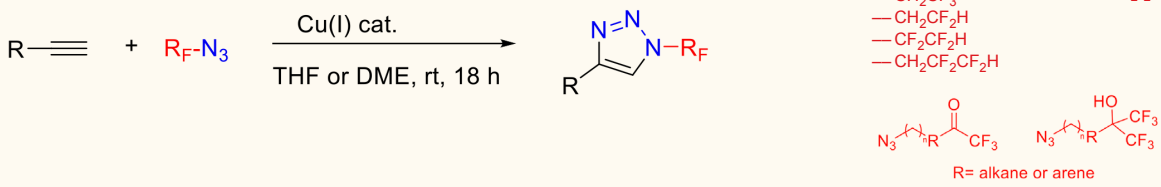


Further details can be found in the Research Article: *"A Scalable Synthesis of Chiral Himbert Diene Ligands for Asymmetric Catalysis"* Adv. Synth. Catal. 2023, DOI: 10.1002/adsc.202300039.

Fluorinated chemical space simply clicked

CF PLUS CHEMICALS
Fluoroalkylation and bioconjugation

Small-molecule fluorinated azides as easy-to-handle dilute solutions are now available for drug discovery programs. The fluoroalkyl azides undergo copper-catalyzed alkyne-azide cycloaddition, forming 1,4-regioisomers in high selectivity or they can generate disubstituted triazoles by reaction with acidic ketones.



—CF_3
—C_2F_5
—CF_2H
—CH_2CF_3
—CH_2CF_2H
—CF_2CF_2H
—$CH_2CF_2CF_2H$

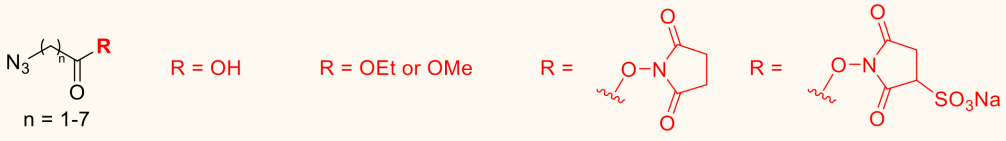
—CF_2CO_2Et
—CF_2CONH_2
—CF_2CH_2OH
—PH-3,5-$(CF_2)_2$

R= alkane or arene

1,4-disubstituted N-perfluoroalkyl triazoles can be transformed using Rh-catalysis to various, difficult to access heterocycles, such as N-perfluoroalkyl imidazoles, pyrroles, imidazolones and pyrrolones.

ω-Azidocarboxylic acids and their derivatives in bulk

We offer an extensive, competitively priced portfolio of ω-azido-alkanecarboxylic acids differing in chain length, spanning from ω-azidoacetic up to ω-azidooctanoic acid.

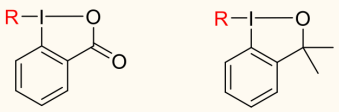


Upon enquiry

Moreover, the related methyl/ethyl esters, NHS esters and sulfo-NHS esters are also available for synthetic or large scale bioconjugation projects.

Hypervalent iodine-mediated functionalisation

We cover a whole range of cyclic hypervalent iodine reagents which are excellent electrophilic transfer agents, spanning from chlorination, fluorination, azidation, fluorinative functionalisation, cyclisation up to trifluoromethylation, penta-fluoroethylation or transfer of substituted fluoroalkyl groups.



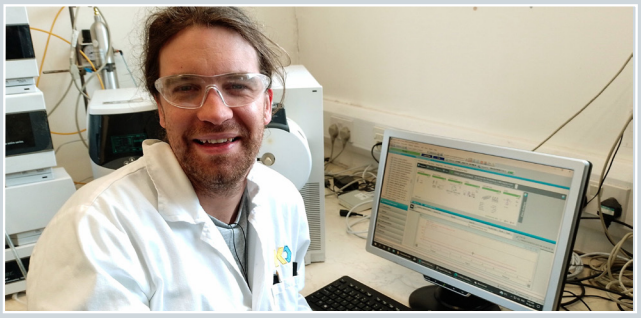
R = —Cl —F —N_3 —CF_3 —C_2F_5 —C_3F_7 —C_4F_9 —C_6F_{13} —C_8F_{17} —C_6F_5 —$CF_2CF_2R^2$ (R^2 = ArO, ArS, HetArN)

We will be exhibiting and/or attending the following exhibitions and conferences in the coming months:

25th - 27th April	CHPI North America	Philadelphia, USA
10th - 11th May	CHEMUK	Birmingham, UK
24th - 27th July	27th International Symposium: Synthesis in Organic Chemistry	Oxford, UK
6th - 8th September	Chem Outsourcing	Parsippany, NJ, USA
10th - 13th September	SCI / RSC 22nd Medicinal Chemistry Symposium	Cambridge, UK
25th - 26th September	A Celebration of Organic Chemistry	Alderley Park, UK
25th - 28th September	Discovery On Target	Boston, USA
24th - 26th October	CHPI Barcelona	Barcelona, Spain

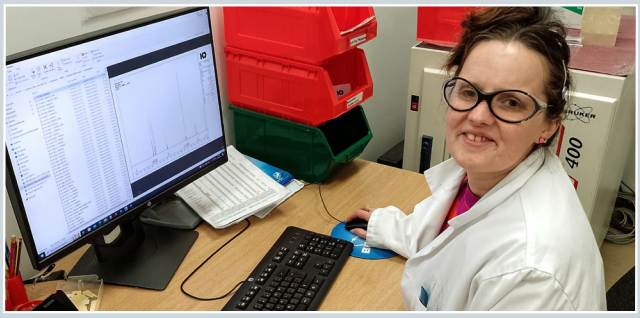
For more information, please visit: https://www.keyorganics.net/about/exhibition-conference-attendance/

An introduction to some of Key Organics' Analytical Staff:



Dan Griffiths graduated from Cardiff University with a degree in Chemistry with Industrial Experience.

He has a particular interest in Circus Arts having worked as a professional circus performer. He led the circus charity 'Performers Without Borders' in India. He is currently training to be a long distance swimmer. He recently swam 11 Km along the Thames and plans to complete two cross channel swims, one solo and one as part of relay team in June 2023 (just a week apart) to raise funds for a local charity 'Bude Sea Pool' in Cornwall and 'Performers Without Borders'. Dan says "It's not the distance that is difficult but the time spent in the cold water."



Lorna Bankole graduated from Paisley University (now the University of the West of Scotland) with an honours degree in Applied Biochemistry which was followed by an MSc in Pharmaceutical Analysis from Strathclyde University with an industrial placement.

Lorna's pastimes include exercise, gaming, music and watching TV gameshows. One item that is on her bucket list is to actually appear on one of those TV gameshows. Lorna had previously appeared on TV as part of the Commonwealth Games choir at the 1986 XIII Commonwealth Games opening ceremony which was in her home town of Edinburgh and thoroughly enjoyed the experience. Lorna also enjoys taking her Morris Minor to classic car shows.

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