February 2019

Key Organics
Chemistry | Innovation | Quality

Newsletter

Key Organics Covalent Fragment Libraries

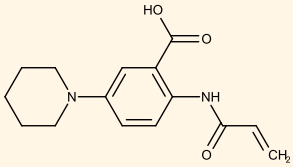
Drugs that covalently bond to their biological targets have a long history in drug discovery. There is an increased interest in covalent therapeutics in the literature and recent years have witnessed a significant increase in the number of drug candidates with covalent mechanism of action progressing 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.

Acrylamide and Chloroacetamide Fragments available from Key Organics

Key Organics is assembling a library of covalent fragments containing cysteine-reactive electrophiles such as chloroacetamides and acrylamides which will be available to purchase in February 2019.

Examples of Key Organics Acrylamide and Chloroacetamide fragments: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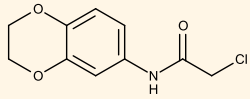
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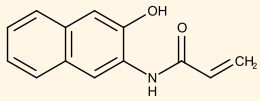
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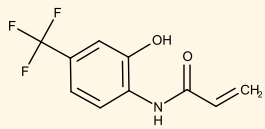
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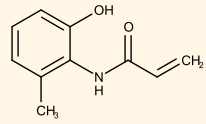
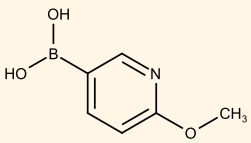

GP-0682

Boronic Acid Fragments available from Key Organics

Multiple researchers have assembled libraries of fragments containing reversible covalent "warheads". An example by Marion Lanier, Mark Hixon, and collaborators at Takeda, featuring boronic acids appears in *J. Med. Chem.* 2017, 60, 5209-5215.
Key Organics has over 500 in-stock boronic acids available in small milligram quantities for Fragment screening.

Examples of Key Organics Boronic acid fragments: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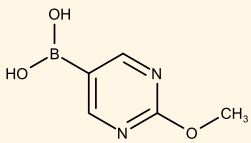
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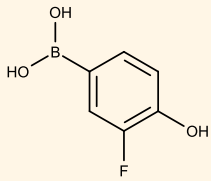
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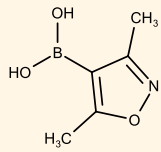
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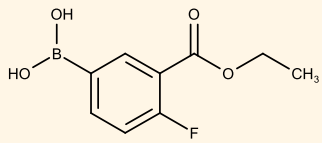
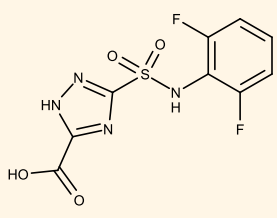

DS-0916

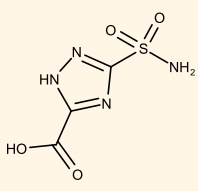
For more information please contact **Andrew Lowerson at andrewl@keyorganics.net**

Metabolite / Impurity identification and synthesis

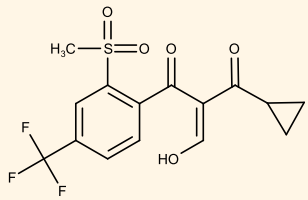
Key Organics has a wealth of experience in identifying and synthesising impurities and metabolites, whether it's profiling an active compound from a Medicinal Chemistry project or part of a 5 batch analysis in the Agrochemical area. We have also provided synthesis support for many Agrochemical companies putting together registration packages.

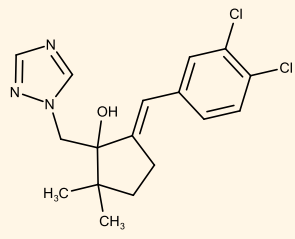
Examples of Agrochemical metabolites synthesised at Key:


DFP-ASTCA


ASTCA

Difficult to access Florasulam metabolites


Isoxaflutole metabolite


Triticonazole metabolite prepared using novel synthetic route developed at Key Organics

Key Organics Compound Management Service

Key Organics can support some or all your key compound management activities including compound procurement, receipt, storage, formatting and distribution needs. We provide both standalone activities on a fee-for-service basis, as well as fully integrated compound management services.

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Our services include:

- Compound Procurement, via preferred suppliers
- Compound Weighing
- Compound Dissolution
- Automated Reformatting & Plating
- Compound Shipping & Logistics to in-house & partner testing laboratories
- Quality Control
- Reaction ready precursors and reagents

Reaction ready precursors and reagents

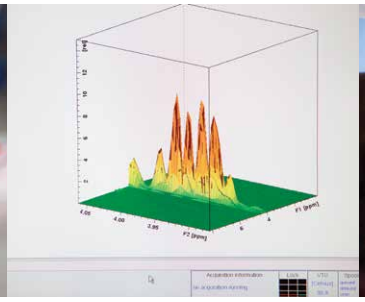
Key Organics can provide reaction ready pre-weighed reagents and precursors for your in-house chemistry programs, either from customers own reagent and precursor collection or from Key Organics stock of BIONET reagents, building blocks, screening compounds and fragments.

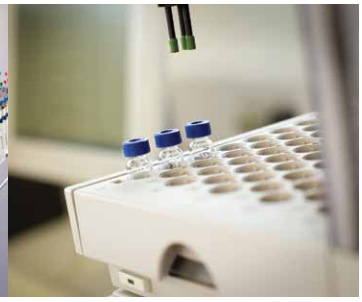
Quality Control

Key Organics provides access to high-end analytical services and support for the pharmaceutical, agrochemical, petrochemical and allied industries, including;

- Compound identification and structure elucidation.
- Compound purity screening.
- Compound purification.
- HPLC and GC method development and/or optimisation.

Our dedicated team of experienced and qualified staff can deliver these services and, working with the Chemistry team, can also support PRI synthesis -for robust process control and known impurity quantification purposes.



Our analytical department is equipped with the following instrumentation:

NMR	Bruker 400MHz AVIII NMR with a 1H/13C multinuclear probe. Utilising Topspin and ICONNMR software, the instrument can perform routine 1D experiments and 2D experiments such as COSY, HSQC, HMBC, and NOESY –plus variable temperature and solvent suppression experiments.
LCMS	Agilent LCMS, comprising an Agilent 1260 LC with a binary gradient pump and multiple wavelength UV/Vis detector. Coupled to an Agilent 6130 Single Quadrupole Mass Spectrometer. Waters LCMS, coupled to a Micromass ZQ 2000 mass spectrometer, with ESCi probe.
Preparative LC	Waters LCMS equipped with a preparative-scale pump, sample manager and fraction collectors –to perform mass-directed fraction collection.
HPLC	Agilent 1100/1200 HPLC systems, equipped with binary gradient pumps and diode array detectors.
Gas Chromatography	Agilent 6890 GC, equipped with autosampler, split/split-less inlet and flame ionisation detector.

Whatever your requirement; from single analyses to more complex projects, we will be happy to review your request and provide a quotation.

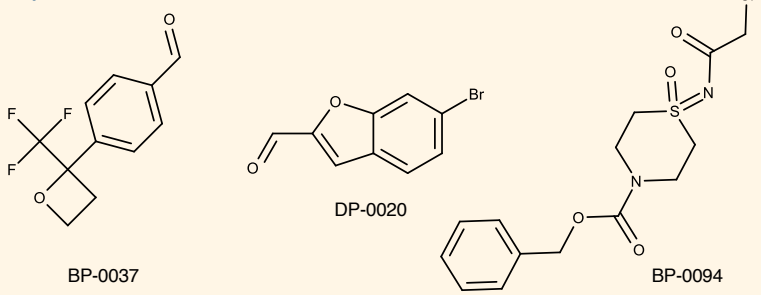
Enhancing Building Block Collections

The rational design of novel, high quality building blocks has been shown to accelerate discovery projects and lead to an increase in compound quality and Enhanced IP position; many companies have had these initiatives "in-house" in the past.

Key Organics have many years of experience in generating novel building blocks and are always seeking to synthesise such compounds to enhance our catalogue. The design of these can be driven by observation of trends in Medicinal and Agrochemical Research, populating an under represented area of chemical space or by exploiting new published synthetic chemistry.

We also gain insights into researcher's needs from our customer interactions, this may be along more general lines eg. more sp3 character, novel phenyl isosteres, physical property modifying groups, metabolic site blocking, or something more exclusive to the Company/Organisation. In these cases, we can assist with enhancing the building block collection through an exclusive arrangement, where the building blocks are the property of the company for an agreed period of time.

Examples of recent novel additions:



Compound Quality

One way to improve compound quality, while enhancing and accelerating drug discovery projects, is to access a high quality, novel, diverse building block collection. Goldberg et al (*Designing novel building blocks is an overlooked strategy to improve compound quality, Drug Discovery Today Volume 20, Number 1 January 2015*) has outlined general principles that should be applied to ensure that a building block collection has the greatest impact on drug discovery projects, by discussing design principles for novel reagents and types of reagents popular with medicinal chemists in general. They initiated a program in 2009 to address this and subsequently has already delivered three candidate drugs. The success of that program provides evidence that focussing on building block design is a useful strategy for drug discovery.

An analysis was performed on reagents that had been used for library synthesis. This analysis showed that molecular weight and clogP were important factors in the frequency of use of reagents. PSA, hydrogen bond acceptor count, hydrogen bond donor count, and rotatable bond count, were less important. From this analysis, they defined a simple guideline that popular reagents could be defined as those that typically do not add more than 200 Da in MW or 2 units of clogP. They aimed for an HBD count ≤ 2 and HBA count ≤ 4, which in combination with the MW and clogP guidelines gave a 'Rule of 2' mnemonic.

Key Organics can implement fast substructure and compound similarity filtering, calculation of physico-chemical properties like MW, logP, logS, tPSA, calculation of druglikeness, flexibility, complexity and atom/ring counts. We also have the expertise to detect toxicity risk factors for four toxicity categories, scaffold analysis (ring systems on Murcko scaffolds), diverse subset selection and compound clustering.

In Figure 2 the H-Acceptor, H-Donor and MW sliders have been used to construct a 7598-compound subset of the BIONET building block collection. The subset has H-Acceptor ≤ 3, H-Donor ≤ 1 and MW ≤ 160. Individual compounds can be picked out from the 3D space (in RED) and their properties shown on the right-hand side of the graphic.

Selecting Diverse subsets from a compound collection

Once a collection of compounds has been selected, Key Organics can cluster compound collections into smaller groups of similar compounds, or locate a most diverse subset within a given set of molecules.

Figure 3

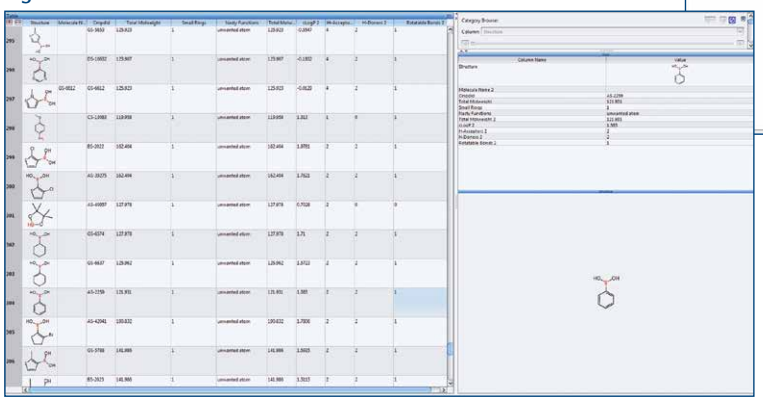


Figure 1

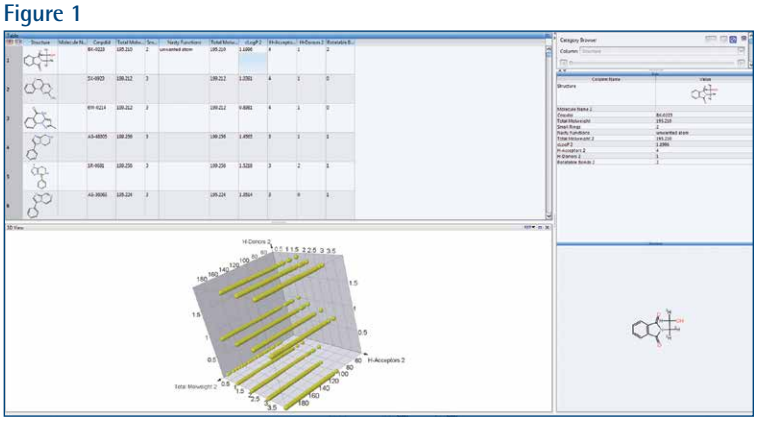
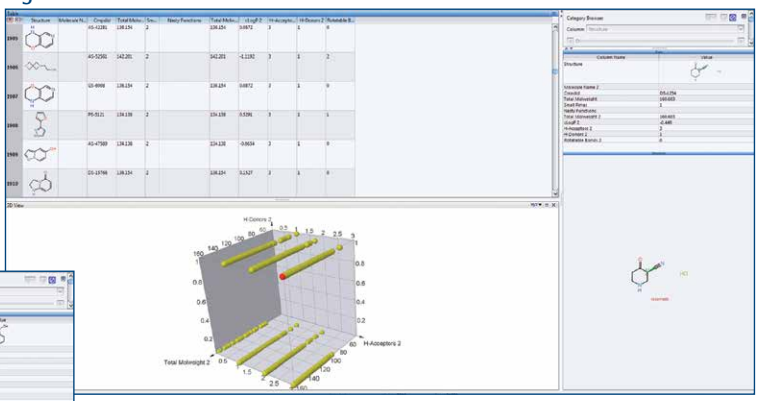


Figure 1 illustrates the Key Organics BIONET Building Block collection filtered by Goldberg's Rule of 2. A 3D graphic has been created illustrating three axes (H-Acceptor, H-Donor and MW) that define the numerical/category space in which each data is shown.

Figure 2



Functional Group Subsets

Goldberg et al also investigated what constituted a commonly used or popular reactive group. Amines, acids, and boronic acids/boronate esters were ranked most highly on desirability, followed by aryl halides, alkyl/benzyl halides, aldehydes, alcohols, and anilines, and finally, sulfonyl halides, ketones and isocyanates.

Key Organics can supply subsets by Functional Group and Rule of 2. Figure 3 illustrates such a set for the Boronic functionality.

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

February 6th	BVS-AbbVie Chemistry Dept. (Biotech Vendor Services)	Worcester, MA US
March 8th	Women in Chemistry	Nottingham, UK
March 24th-26th	Fragments 2019	Cambridge, UK
April 8th-12th	Drug Discovery Chemistry	San Diego, CA US
May 2nd	30th Symposium on Medicinal Chemistry in Eastern England	Hatfield, UK

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

Staff Interview Glen Chapman, Synthetic Organic Chemist

Q: Please tell us a bit about yourself?

A: I grew up in Stamford, Lincolnshire, UK, a small country town. A town with over 1000 years of rich history ranging from Danelaw times, the black death and highway rogues on to winning the honour of The Sunday Times "Best Place to Live in the UK 2013". Forward to my university years - I studied my degree in Chemistry at Reading and then moved on to do a Ph.D at the University of Northumbria. Since then, I have been employed as an organic chemist within various research laboratories and companies around the world, some as far as Beijing. When I am not performing my duties at Key Organics, I enjoy watching movies, home cooking, and playing chess.

Q: What is your role within Key Organics?

A: As a synthetic organic chemist my main role includes the creation of pure chemical products for the massive range of items we have in our catalogue. These include compounds from the fragment, screening, biochemicals and intermediate BIONET collections. I also carry out custom synthesis of novel and literature compounds for our customers. Also, I am currently learning the ropes in the analytical department to help them from time to time.

Q: What do you enjoy about working at Key Organics?

A: I enjoy the friendly atmosphere that has been created from being an excellent company to work for. Due to the large number of products, the chemistry does not become too repetitive. In the year that I have been here I have worked on several projects that have involved new synthetic approaches, something always of interest to a chemist.

Q: What do you think is Key Organics' greatest strength?

A: Key Organics strength is derived from having a team environment with a varied skillset and infrastructure. Having a dedicated compound handling team to synthetic and analytical chemists to office-based staff that work as a team supplying timely and orderly service. From a chemical production point of view, we have a wide range of experienced chemists from small scale library synthesis to large scale custom synthesis.

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