Issue 8 | October 2014

Key Organics

Chemistry | Innovation | Quality

Newsletter

New USA Facility now open for business!

We are delighted to announce that our new USA Sales Office and Compound Handling Unit opened for business on 2nd September 2014.

Based in Bedford, MA our North American customers can now enjoy our premium next-day delivery service and reduced shipment costs together with the assured quality and service associated with BIONET. To celebrate this milestone, we are offering all current and new customers* a 15% discount on all BIONET list prices until 31st December 2014.

For more information please visit our website at: www.keyorganics.net or our BIONET shop and apply the discount code: **USA2014**

*(*this offer is not available to resellers, agents or intermediaries)*

BIONET Fragment Libraries

Fragments from Nature

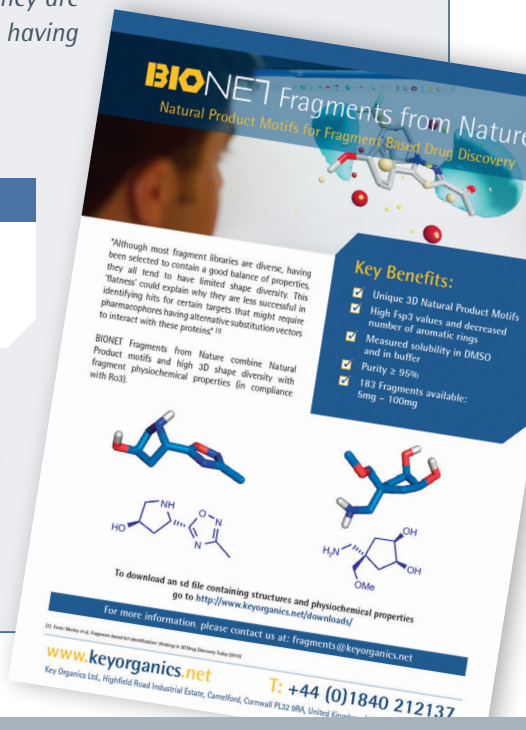
New Natural Product Motifs for Fragment Based Drug Discovery

"Although most fragment libraries are diverse, having been selected to contain a good balance of properties, they all tend to have limited shape diversity. This 'flatness' could explain why they are less successful in identifying hits for certain targets that might require pharmacophores having alternative substitution vectors to interact with these proteins[1]."

Our new BIONET "Fragments from Nature" combine natural product motifs and high 3D shape diversity with fragment physiochemical properties (in compliance with Ro3).

Key Benefits:

- Unique 3D Natural Product Motifs
- High Fsp3 values and decreased number of aromatic rings
- Measured solubility in DMSO and in buffer
- Purity ≥ 95%
- 183 Fragments available: 5mg – 100mg



Don't take our word for it...

In a recent on-line publication, Cambridge MedChem Consulting (CMC) compared the frequency with which published fragments are contained within the commercial fragment collections[2], Key Organics Premium BIONET fragment collection was cited as second out of a list of 21 that CMC reviewed. We are currently in the process of finalizing a 2nd generation premium fragment library in collaboration with The Broad Institute, and NMX Research and Solutions, more information is provided within.

References:
1. Morley et al. Fragment-based hit identification: thinking in 3D Drug Discovery Today (2013)
2. http://www.cambridgemedchemconsulting.com/resources/hit_identification/fragment_based_screening_reported_hits.html

BIONET Fragment Libraries

New 2nd Generation Premium Fragment Library

Key Organics is pleased to announce that it has entered into a collaboration with The Broad Institute, (Cambridge, MA) and NMX Research and Solutions, (Montreal, Canada) to produce our new **2nd generation BIONET Premium Fragment Library**.

This unique library builds upon our previous CNS and Premium Fragment libraries and has been developed with the following design criteria:

- **Rule of 3 compliant: MW ≤300, cLogP ≤ 3, number of HBA/HBD ≤ 3, PSA ≤ 60 and Number rotatable bonds ≤3**
- **Heavy atom count (HAC) ≤ 16**
- **Does not include substructures identified as promiscuous or reactive by empirically determined rules (BMS[1], PAINS[2], Kazius and Bursi toxicophores[3], Lilly Med Chem Rules[4]).**
- **Inclusion of diverse scaffolds that are present in bioactive compounds and that have 3-dimensionality**
- **Clustering and Diversity analysis**
- **Passes chemist visual inspection**
- **Solubility at 1mM in PBS buffer and signs of aggregation determined by 1H NMR spectra**

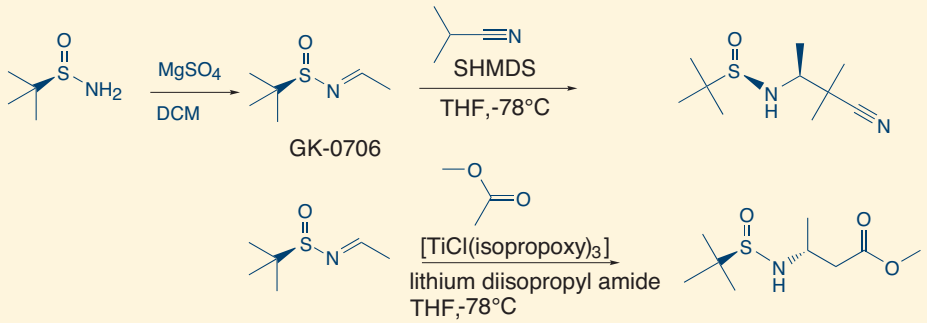
"**Selection by scaffolds**" is a powerful way of selecting molecules to yield synthesizable and recognizable structures. The goal of selection will be to find fragment-like molecules with diverse scaffolds that are present in bioactive compounds and that have 3-dimensionality. The final library will also maintain a good diversity in functional groups.

NMX Research and Solutions will produce 1H NMR spectra (1 mM PBS at pH 7.4) for each fragment and analyze the spectra with regard to quality, solubility and signs of aggregation. Customers will be able to Chemical Shift Encode (CSE) their fragment collection without the need for additional resources. CSE increases the number of fragments per pool that may be screened thereby reducing the total number of experiments to be performed. The reduced machine time and greater screening efficiency will deliver significant cost savings.

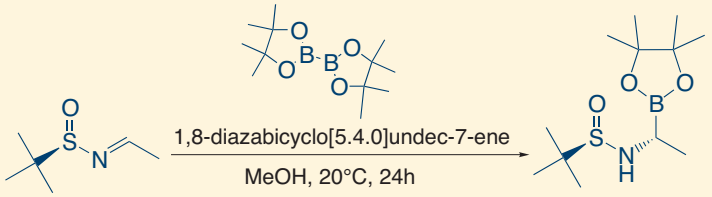
The Eli and Edythe L. Broad Institute of MIT and Harvard was launched in 2004 to empower this generation of creative scientists to transform medicine. The Broad Institute seeks to describe all the molecular components of life and their connections; discover the molecular basis of major human diseases; develop effective new approaches to diagnostics and therapeutics; and disseminate discoveries, tools, methods, and data openly to the entire scientific community.

New BIONET Reagents

Tert-Butylsulfonylimines are extremely versatile materials for the introduction of a chiral centre to a range of chemical substrates and functional groups (e.g. methyl groups, boronates, methylenes, grignards, silanes, acetylenes, dialkyl phosphites etc.), some examples are presented opposite. We are able to offer GK-0706 and its enantiomer together with other analogies, please contact us for more information.



JOC, 2002, vol. 67, 22, p7819-7832.



Organic and Biomolecular Chemistry, 2013 , vol. 11, 37 p6350 – 6356

References:

1. Bradley C. Pearce, Michael J. Sofia, Andrew C. Good, Dieter M. Drexler, and David A. Stock. An Empirical Process for the Design of High-Throughput Screening Deck Filters. *Journal of Chemical Information and Modeling* **2006**, 46, 1060-1068.
2. 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.
3. Jeroen Kazius, Ross McGuire, and Roberta Bursi. Derivation and Validation of Toxicophores for Mutagenicity Prediction. *Journal of Medicinal Chemistry* **2005**, 48, 312-320.
4. Robert F. Bruns and Ian A. Watson. Rules for identifying potentially reactive or promiscuous compounds. *Journal of Medicinal Chemistry* **2012**, 55, 9763-9772.

Copyright © Key Organics 2014

Key Organics
Chemistry Services

An Extension of your R&D Capabilities

Key Organics' Chemistry Services team offers bespoke synthesis solutions on an FTE/Research (fee-for-service) or one-off custom synthesis (fee-for-compound) basis. We offer a customer-driven synthetic organic chemistry service on mg to kg scale.

Our core chemistry competencies includes:

- **Heterocyclic compounds**
- **Asymmetric Synthesis**
- **High pressure reactions**
- **Focused arrays for hit explosion or hit-to-lead optimisation**

We routinely undertake research projects in the areas of medicinal chemistry, agrochemistry, petrochemistry, aromachemicals and provide direct access to project and experimental data through our ilabber e-notebook platform. This is backed up by a state-of-the-art analytical chemistry team facilities, with over 26 years expertise we are accustomed at managing large FTE programmes from discovery and medicinal chemistry through to the provision of the first toxity batch/GMP supply.

Over the last decade we have accumulated vast experience in the custom synthesis of various types of certified agrochemical reference standards in mg (initial identification purposes) to 100's grams (toxicity, process validation and environmental fate studies). This work encompasses the synthesis of both manufacturing impurities and metabolites, whether through repeat synthesis of known (literature) compounds, or application of standard methods to novel route development.

Process Related Impurity Case Study

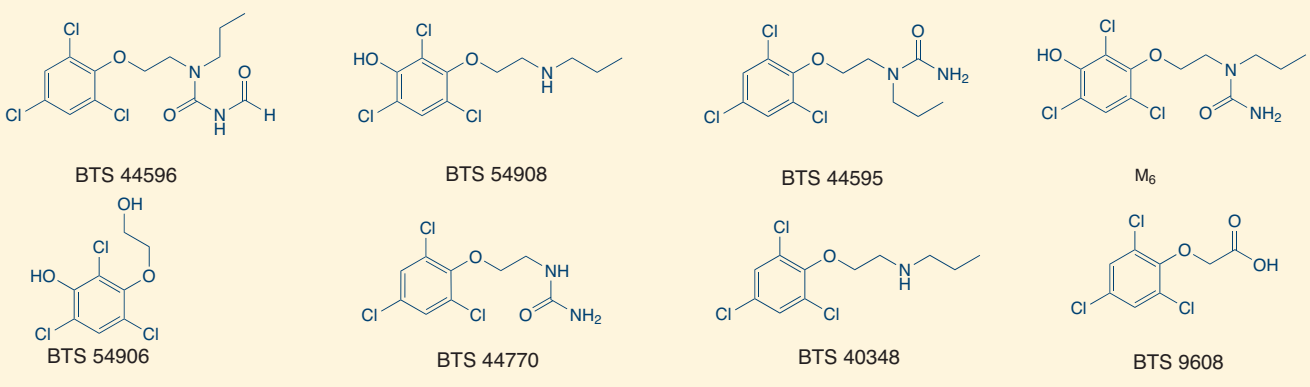
We have substantial experience in the identification, quantification and independent synthesis of process related impurities in both drug substance and agorchemical active ingredients. While these impurties are required to be quantified and qualified at quantities >0.1% for new products as part of the GMP process, the registration of generic agrochemicals now also requires the same.

Key Organics supports global agrochemical companies in complying with their pesticide registration efforts related to the synthesis of impurities for 5-Batch Analysis and compliance with harmonized OCSPP 830.1700 guidelines. Typically we produce process related impurities to support their independent verification and quantification.

In addition, metabolites (derived from the parent pesticide via *in vivo* biochemical modification) are often also required to be identified and quantified. One such project, undertaken at Key Organics over the period of several years, is the synthesis of a number of prochloraz metabolites in high (>98%) purity, initially as analytical standards (0.5g scale) and subsequently in 100g quantities for environmental fate studies.

Prochloraz {*N*-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]-imidazole-1-carboxamide; CAS 67747-09-5} is a broad-spectrum imidazole fungicide which acts through the inhibition of ergosterol biosynthesis. Active against a range of diseases caused by ascomycetes and fungi imperfecti in field crops, fruit and vegetables, it is also used on mushrooms, and as a seed treatment for cereals. The following scheme indicates the diversity of structures known to arise through prochloraz metabolism in rats, where the highlighted compounds were those required for the study. These *in vivo* pathways are often difficult or impractical to reproduce in a synthetic environment. The successful synthesis of this series of compounds was achieved through novel route design, and allowed our client to progress their registration process.

Figure 1: Key Prochloraz Metabolites



Events that we will attend during Q4 2014

7th – 9th October
CPhI Worldwide 2014
Paris Nord, Villepinte, France
http://www.cphi.com

23rd October
2nd Annual CRO CMO 'East-West' Summit
Marriott La Jolla, San Diego, USA
http://www.bvsweb.com/CRSD.2014-10-23.Flyer.pdf

9th December
Genesis 2014
London
http://www.genesisconference.com

Staff Interview

James Dolan, Deputy Head of Chemistry Services

Q: Please tell us a bit about yourself?

A: I grew up in Plymouth and graduated in 2000 from the University of Wales, Swansea with a Bsc Hons in Chemistry. Shortly after I joined Key Organics as a synthetic organic chemist; initially preparing heterocyclic compounds for our Bionet screening database. My role has greatly varied over the years, I have experienced all sectors of our business allowing me to service a broad spectrum of the chemical industry; I have worked on research and development projects for pharmaceutical, biotech, agrochemical and the petrochemical industry and contributed to all of our Bionet product lines.

Working in Cornwall was a conscious decision for me as I love the benefits the county can offer permitting me to devote my free time to surfing, sailing, fishing and simply walking along coastal paths. I like cycling and have recently competed in a 24hr enduro mountain bike race. These activities are necessary as it allows for the indulgence of my other passion; food.

Q: What is your role within Key Organics?

A: I am a senior chemist and deputy head of the services sector. I lead FTE projects and when I am not exclusively working for a customer I provide quotations for custom synthesis or proposals for small libraries, whilst maintaining a strong laboratory presence.

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

A: The Key Organics team. It is a privilege to be part of a talented group of likeminded professionals who are always willing to discuss chemical synthesis. This is vital in a fast paced problem solving environment where the constraints of time and money are pressing.

I also love the variety of chemistry we deal with; I never know what challenges are around the corner! I can be running a small team for pharma one month then I can then be quoting on custom synthesis projects the next whilst working on agrochemical metabolites and then have to synthesize a small library or a peptide; all of these examples could be on milligram to kilogram quantities. This variation allows me to appreciate and develop a broad feel and understanding of organic synthesis producing an environment of continuous learning which I find both stimulating and rewarding.

Additionally, I enjoy the identification and synthesis of interesting tractable targets for our Bionet Intermediates catalogue. This area of the business is great as it allows synthetic creativity in building block development, aiming to efficiently hone compound selection and synthesis optimized for commercialization. Observing growing sales from building blocks I have invented is a buzz and indeed the challenge of chemistry is made all the more exciting.

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

A: Customer service. We are a company which put the customer first; our aim is to provide an all encompassing quality chemistry service and of course this can only be possible with our first class team.

Key Organics

Chemistry | Innovation | Quality

For more information, please contact us at:

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

T: +44 (0)1840 212137
F: +44 (0)1840 213712
E: enquiries@keyorganics.net

Key Organics Inc.,
Suite 100,
55 North Road,
Bedford,
MA 01730

Toll Free No: 855 808-2700
Or: 781 280-5000
E: enquiries@keyorganics.net

www.keyorganics.net

Acknowledgements: *Design by* David Anthony, AK Design (Scotland) Ltd.