Issue 9 | January 2015

Key Organics Newsletter

Chemistry | Innovation | Quality

Key Organics wishes all its Newsletter readers a Happy New Year!

We begin 2015 with news of our new partnership with the University of Nottingham where we are supporting a new CASE studentship with Professor Simon Woodward that is focused on catalysis and new BIONET product development. We also announce further details of our new 'Second Generation Premium Fragment Library' which has been developed in close collaboration with the Broad Institute based in Boston, USA and NMX Research & Solutions based in Montreal, Canada. With this and other new fragment libraries planned in the coming months, we hope to further build upon our position as one of the world's leading providers of fragment libraries.

Our capabilities in parallel synthesis are also profiled and we interview Steven Brouillette, Manager of our US based facility in Bedford, MA. During the coming months we will present at several exhibitions, conferences and events that are profiled herein.

New Research Collaboration

Innovation is a critical aspect of our operation as we seek to further enhance and grow our successful BIONET product portfolio that now contains over 80,000 intermediates, fragments, biochemicals and screening compounds. As well as our internal innovation and co-marketing programmes with selected partners, we are also forging new R&D partnerships with leading academic institutions that facilitate new technology and new product development that provides Key Organics with further differentiation that can add value to the work we undertake for customers.

We are therefore pleased to announce a new research CASE studentship (formerly known as 'Collaborative Awards in Science and Engineering') with Professor Simon Woodward at the University of Nottingham.

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

The focus of this research programme will be to develop new synthetic methodologies to add to our current capabilities and develop new products for inclusion within our BIONET portfolio. Prof Woodward's research interest is primarily focused on catalysis and particularly asymmetric, C-C bond formation in Ni, Sn, and Cu catalysed reactions. The REF2014 exercise judged 95% of Nottingham's chemistry research to be 'internationally excellent' or 'world leading'.

BIONET Fragment Libraries

New BIONET 2nd Generation Premium Fragment Library

As reported in our last newsletter, Key Organics entered into a collaboration with the Broad Institute, (Cambridge, MA) and NMX Research and Solutions, (Montreal, Canada) in order 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
- 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 ^{1}H 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.

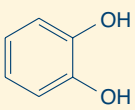
Focus on Pan Assay Interference Compounds[1] (PAINS) substructure filtering – a deciding factor in the quality of a fragment library.

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. However PAINS remain common in many vendors Fragment Libraries but have been removed from our BIONET fragment libraries.

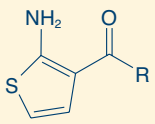
PAINS compounds have been identified and substructure filters constructed that recognise these compounds[1]. As part of our Fragment selection process, industry-standard substructure filtering - including PAINS filtering - was implemented and as a result the BIONET 2nd Generation Premium Library does not include substructures identified as promiscuous or reactive by empirically determined rules.

Examples of PAINS:

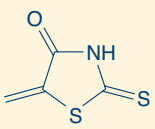
Catechols



2-Amini-3-carbonyl thiophenes



Rhodanines



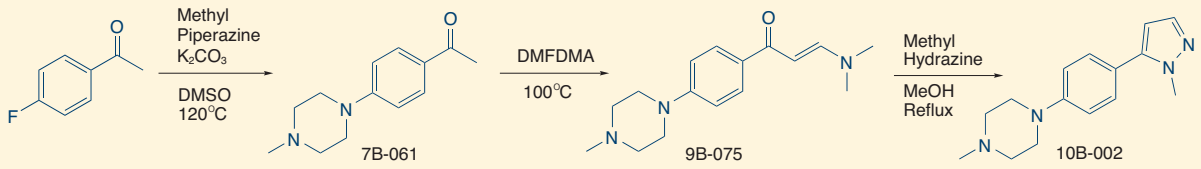
Our completed library also maintains a good diversity in scaffolds that are present in bioactive compounds and that have 3-dimensionality. Experimental data will avoid fragments that will aggregate or have poor solubility.

The BIONET 2nd Generation Premium Fragment Library is now due for release.
Please contact Andrew Lowerson andrewl@keyorganics.net for further details and to register your interest.

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.

BIONET Supporting Pyrazole Research for nearly 30 years

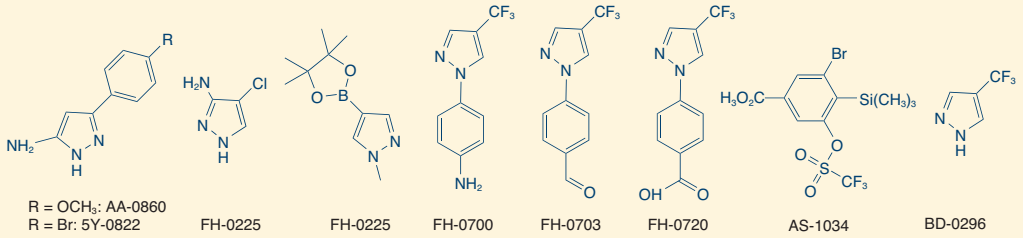
Pyrazoles and their derivatives have long been used as motifs and scaffolds in chemical research. In fact, the pyrazole core is prevalent in a variety of leading drugs such as Celebrex, Viagra and Rimonabant. Over nearly 30 years, Key Organics has been producing novel pyrazoles to support recent developments in pharmaceutical and agrochemical research. One of earliest pyrazoles (10B-002) to be added to the BIONET screening collection was back in early 1987. This simple and very robust approach to pyrazole formation, using dimethylamino methylene derivatives, which has been extensively explored by Key Organics over many years, is still widely used in chemical research groups worldwide[1].



Scheme 1. Early synthesis of BIONET pyrazole; 10B-002.

There are currently over 4,800 products in the BIONET collection that contain the pyrazole substructure. Many of these have been cited in the scientific literature. Numerous patents describe the use of the 3-aminopyrazoles as building blocks to potential drug candidates[2]. 5-Aminopyrazoles (AA-0860 and 5Y-0822) have been used in heterocyclizations involving N-arylmaleimides[3], or β,γ-unsaturated γ-alkoxy-α-keto esters[4]. Suzuki coupling of a 7-bromo-1,4-benzoxazine derivative with pyrazole boronate esters (AS-3002) led to a series of potential PI3 kinase inhibitors for the treatment of chronic inflammatory diseases[5].

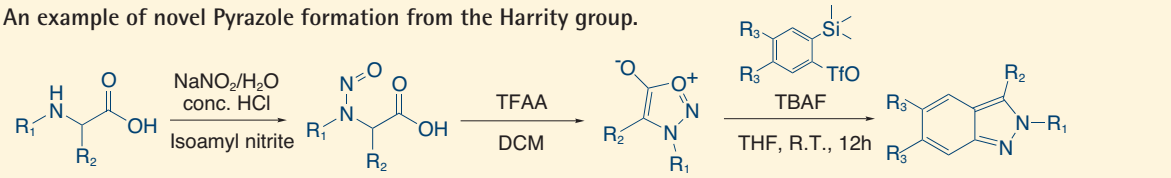
Figure 1: Examples of BIONET Pyrazoles and drug candidates.



One of our more popular products over the last few years has been BD-0296. This has been utilised in a wide range of interesting applications. We routinely repeat this challenging synthesis in batches of several hundred grams. We now stock a range of other products which also contain the 4-(trifluoromethyl)-1H-pyrazole moiety.

While several classical synthetic methods for pyrazole formation exist, recently the Harrity group at the University of Sheffield have been involved in their preparation via alkyne cycloadditions with the unique, mesoionic class of compounds called sydnones (*Scheme 2*)[6,8].

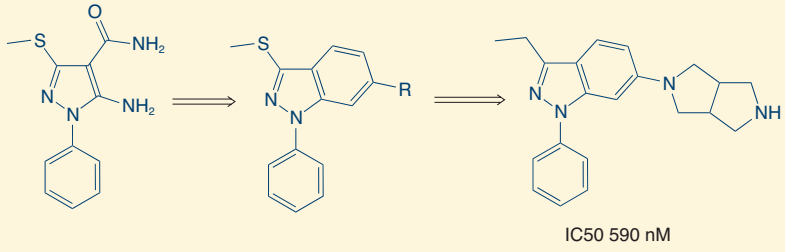
Scheme 2. An example of novel Pyrazole formation from the Harrity group.



Sydnones[7] are synthesised in 2 simple steps from *N*-substituted-amino acids, and are commonly isolated as air-stable solids. Through our exclusive partnership with Farapack Polymers, a spin out from the University of Sheffield, we stock a range of interesting Pyrazoles, Sydnones, and Benzyne precursors (AS-1034).

In the last four years[9], Zhang *et al.* described a series of indazoles that have been discovered as KHK inhibitors from an initial pyrazole hit identified through fragment-based drug discovery (FBDD). The optimization process was guided by both X-ray crystallography and solution activity, which resulted in lead-like compounds with good pharmaceutical properties.

Figure 2. KHK Inhibitor Optimisation Process.



As a world-leading supplier of high quality fragments libraries, and through our Keyfinder platform (in partnership with Prosarix), Key Organics is well placed to provide lead identification through both fragment approaches and virtual screening of large, designed, *in silico* libraries (can be >14.5 million) derived from our in-house compound collection (>80,000) and robust chemistry protocols. We can also take hits from either of these approaches and carry out Hit to Lead and Lead Optimisation work, all the way up to the preclinical stage.

For more details please email: enquiries@keyorganics.net or visit our BIONET shop.

References:
1. F. A. Rosa *et al*, Synlett, **2008**, 1673-1678.
2. Examples include (a) Pfizer Inc. Patent: US2008/280875 A1, 2008; (b) Merck GmbH Patent: WO2009/46784 A1, 2009; (c) Novartis AG Patent: WO2009/150230 A1, 2009; (d) AstraZeneca UK Ltd Patent: WO2006/40528 A1, 2006.
3. R. V. Rudenko *et al*, Synthesis, **2011**, 5, 783.
4. O. O. Stepaniuk *et al*, Synthesis, **2013**, 45, 925-930.
5. B. Perry *et al*, Bioorg Med Chem Lett, **2008**,18, 5299.
6. D. L. Browne, J. B. Taylor, A. Plant, J. P. A. Harrity, J. Org. Chem., **2010**, 75, 984.
7. J. C. Earl *et al*, J. Chem. Soc., **1935**, 899
8. D. L. Browne, J. P. A. Harrity, Tetrahedron, **2010**, 66, 553; and references within
9. X. Zhang *et al*, Bioorg Med Chem Lett, 21, **2011**, 4762 – 4767.

Key Organics
Chemistry Services

A Focus on Parallel Synthesis

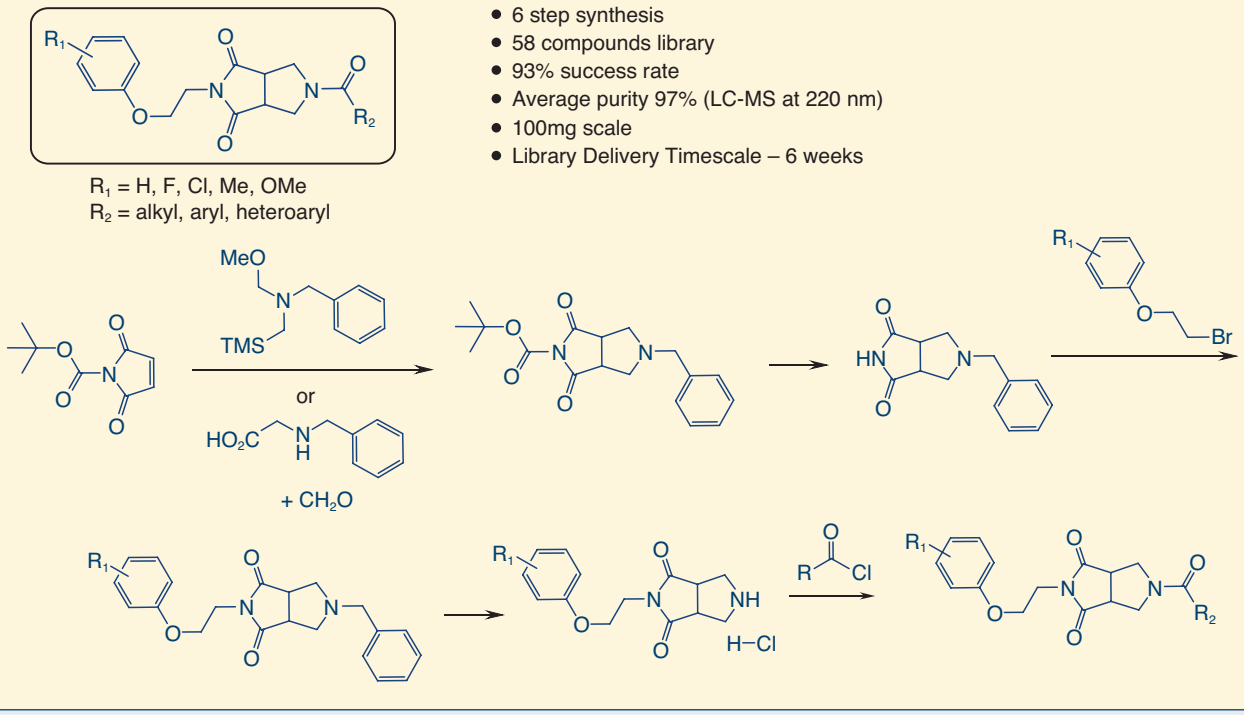
Key Organics has over twenty years experience synthesising bespoke compound libraries for both the pharmaceutical and agrochemical industries. Increasingly, these libraries are of smaller size (20-30 compounds) and more focussed around known SAR rather than large (100's or 1,000's of compounds). With our large collection of scaffolds and experience of this type of work, we are well placed to propose and synthesise these focussed arrays to quickly move clients projects forward. We are equally at home working with the client's in-house scaffold, proposing and synthesising analogues, typically in 20-30mg quantity and of >95% purity, ideal for most primary screening needs.

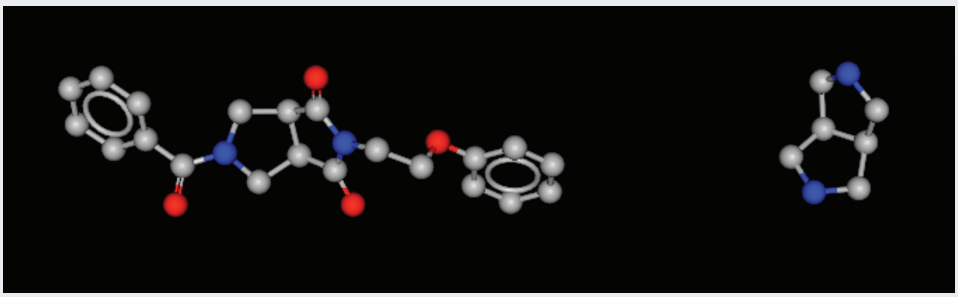
Case Study:

Emergence of 3,7-diazabicyclo[3,3,0]octane in modern therapeutic literature has led to the development of a novel screening set. Owing to its fixed spatial geometry and bifunctionality it has proven a suitable core molecule for library expansion and application in potential lead drug studies[1].

The aza bicyclicdione was accessed from a one pot cycloaddition of *N*-benzylglycine, formaldehyde and *N*-Boc protected maleimide via the formation of an azomethine yilde intermediate yielding a differentially protected core scaffold in one step (*Figure 3*). Subsequent BOC de-protection and installation of a range of phenoxyethyl alkyl bromides yielded intermediates which were debenzylated and elaborated via acylations with carbonyl chlorides using polymer-supported *N*-methylmorpholine providing a matrix of 58 lead-like compounds, exploring different vectors in 3D chemical space.

Figure 3. One Pot Synthesis of the aza bicyclicdione.





Such versatile scaffolds could also be useful for a plethora of variation. An example of this would be the reduction of the aza bicyclicdione using $LiAlH_4$ to furnish octahydropyrrolo[3,4-c] pyrrole allowing for further scope for elaboration and providing an isostere for the piperazine system albeit with a more ridged special geometry.

Figure 4: Molecule on the left is the bicycle dione and on the right is the octahydropyrrolo[3,4-c]pyrrole.

Key Organics has over 28 years of providing interesting screening compounds to the pharmaceutical and agrochemical industries; its highly experienced, skilled customer oriented team of chemists are able to rapidly synthesise novel core scaffolds and provide subsequent library elaboration on 5-100mg scale utilising resin technologies in concert with Bohdan Block reactor technology as well as solution phase approaches and using automated purification including mass directed prep HPLC to provide rapid and efficient access to targets.

References: 1. WO 2006/137791 A1
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2891-2894

Events that we will attend during Q1 2015

3rd – 5th February	Informex USA	New Orleans	http://www.informex.com
17 – 18th February	Discovery Chemistry Congress,	Berlin	http://selectbiosciences.com/conferences/index.aspx?conf=DCC2015
22 – 24th March	Fragments 2015	Cambridge UK	http://www.maggichurchouseevents.co.uk/bmcs/fragments_2015.htm

Staff Interview Steven Brouillette, Office Manager, Bedford (USA)

Q: Please tell us a bit about yourself?

A: I grew up in Salem, New Hampshire, before moving to Lowell, Massachusetts to attend University. There I studied at the University of Massachusetts: Lowell campus with a concentration in Business Management. I received my Bachelors Degree in Management and also gained some work experience at a property management company. I then met my girlfriend and we still live in Lowell. I enjoy hiking with my dog in the woods around my lake house in the northern part of New Hampshire. It is extremely relaxing exploring up in the mountains with nothing but a compass and a backpack for the day. I also enjoy travelling, watching the Boston Bruins hockey team every chance I get, and going to live concerts whenever possible.

Q: What is your role within Key Organics?

A: The US office opened last year and is now fully operational based in Bedford, MA. As Office Manager my main duties include stocking the warehouse with our growing BIONET product inventory for supply to the North American market, processing orders and inquiries, as well as packaging and shipping orders to our customers. An additional aspect of my role is focused on supporting our US business development activities and to help further establish the Key Organics and BIONET brands within the vast cluster of Biotech companies in the Boston area and wider US market. With our new US-based BIONET warehouse, we are can now offer our North American customers next day delivery and with reduced shipping costs. I believe this gives us an advantage over our Competition, especially given the proven quality of our BIONET product portfolio. Our Fragment, Screening, Biochemicals, and Intermediate BIONET collection now contains over 80,000 compounds, with new products being added every week.

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

A: I enjoy the freedom that Key Organics has given me in order to help grow the business in North America. Using my experience together with the knowledge I attained in University, I can apply this practically and help build growth and success. It is also exciting be in a growing company and part of an international team.

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

A: The greatest strength we possess is the Key Organics Team. We have a highly skilled staff of chemists, deliver quality products and provide an unrivalled service for our international customer base.

Key Organics

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