Issue 6 | April 2014

# Key Organics Newsletter

Chemistry | Innovation | Quality

# Coming to America!

## We are delighted to announce the expansion of our operations into the USA.

Our new office and BIONET compound handling unit/warehouse will be based in Bedford, Massachusetts in close proximity to the growing biotechnology and pharmaceutical communities in Boston and Cambridge, MA. With same day dispatch, guaranteed quality and reliability, this expansion will provide our North American customers with more competitive pricing and the expedient delivery of our 74,000 and growing BIONET product range.

We are also pleased to announce our alliance with Prosarix Ltd. and the launch of our new Key Finder™ library generation service. These 'ready to run' virtual libraries are supported with follow-on synthesis that combine a number of advantageous features including support from Prosarix's strong computational capabilities and Key's extensive library design services.

Within this edition we profile our BIONET biochemicals capabilities with an interesting case study and review the versatility of the 1,8-diaminonaphthyl (DAN) boronamide protecting group which can be considered complimentary and advantageous to the wider known MIDA boronate.

Our staff interview is with Colin Swinburne who heads up our BIONET Intermediates Group and we present our event attendance this quarter.

# The Key Finder™ Concept:

**Key Finder™ is our new product and drug discovery service developed by Key Organics and Prosarix. These 'ready to run' virtual libraries, with follow-on synthesis combine a number of advantageous features:**

- Novel and large drug-like chemistry space designed to a specific target family
- Library designs based on in-house reagents and templates, enables rapid synthesis
- Virtual screen of library client's requested pharmacology profile
- Design and synthesis of compounds delivered to client
- Provides unique service capability for target class - bespoke design and chemistry

*Figure 1* profiles the salient aspects of the service which can be supported by additional computational or synthetic support by Prosarix and Key Organics.

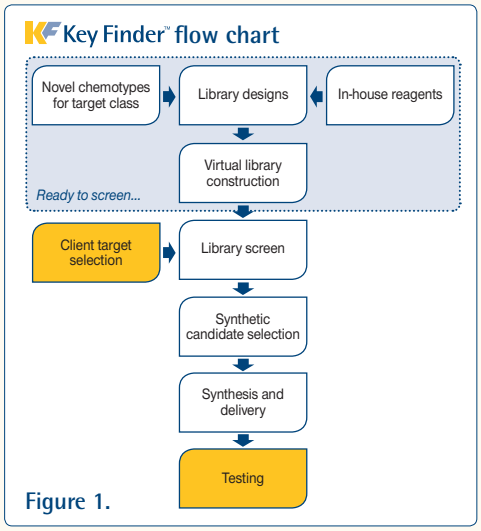



Figure 1.

## New Offerings:

**Our first offering** is a sphingosine-1-phosphate receptor (S1Px) library that consists of >800K enumerated compounds utilising >10 different chemotype cores. For the S1Px Key Finder™ library, S1P2-5 receptor models were constructed, based on the S1P1 structure, and have been validated by the docking performance of known modulators before being used to screen prospective chemotypes as fragments across the subtypes (agonist and antagonist forms). High scoring novel chemotypes have then been decorated in virtual library schemes with available reagents in-house from Key Organics.

**Our second offering** will be a Kinase library and will combine state of the art virtual library construction, virtual screening and follow-on 'in house' synthesis for client targets. Our approach offers several unique selling points:

- Our chemical space is significantly greater (*i.e.* > 1000x larger) than currently available focussed libraries
- Designed chemical space has been validated against kinome inhibitor binding modes (*e.g.* DFG-out *vs* DFG-in targets)
- Includes novel and known hinge binding groups and other chemistries
- We design in clients required selectivity during the structure based screening processes
- ALL library reagents are in house, therefore rapidly implemented
- Seamless transition from LI to LO phase because chemistry and in *silico* design has been worked through at hit stage

## Our new alliance with Prosarix

Prosarix is a privately-owned biotechnology company based in Cambridge, UK. The Company develops computational approaches and products to assist pharmaceutical and biotechnology companies in the drug discovery process. Prosarix developed ProtoDiscovery™, a validated, state-of-the-art computational platform with which it is pioneering novel approaches for the identification and optimisation of small molecules.

Further information can be found at: http://www.prosarix.com

For more information please contact us at: keyfinder@keyorganics.net

# BIONET Biochemicals

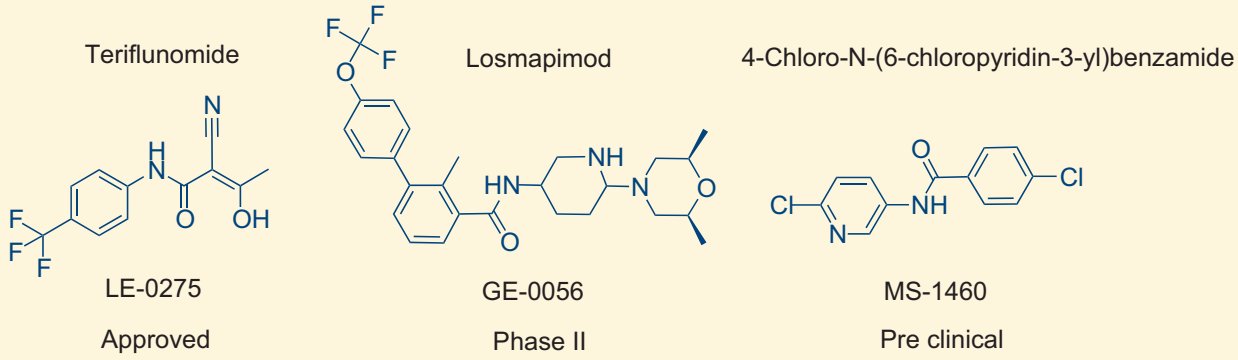
## Our expanding BIONET Biochemicals collection now contains over 1,000 diverse bioactive compounds which are directly available for research and development purposes.

As well as our usual BIONET advantages (*Figure 2*), we are also able to supply bioactive compounds in various stages of development from pre-clinical through to Phase III, some examples of our new products are provided in Figure 3. We can also offer some intermediates to a variety of final API's either from our BIONET collection or as custom synthesis projects. Please contact us for more information at: **enquiries@keyorganics.net**

**Figure 2.** BIONET Advantages:

- ☑ Extensive, growing compound collection
- ☑ Next day courier delivery in EU
- ☑ Dedicated customer support
- ☑ >90% deliverable in-stock
- ☑ Novelty and diversity
- ☑ Full CoA, NMR and LC Analysis
- ☑ Assured quality guaranteed

**Figure 3.** Selected BIONET Biochemicals



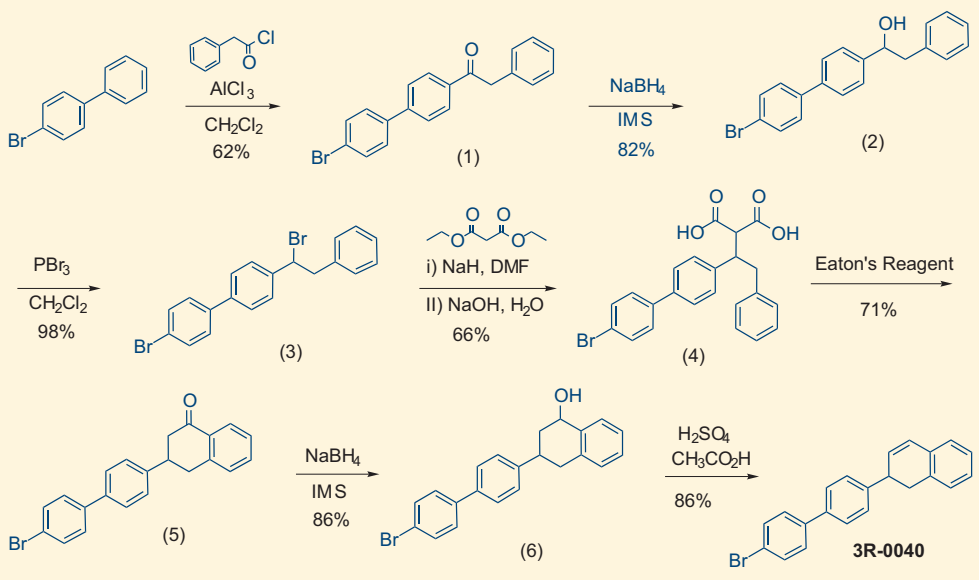

## Custom Re-Synthesis Case Study – Agrochemical by-product 3R-0040

2-(4'-Bromo-biphenyl-4yl)-1,2-dihydronaphthalene **(3R-0040)** is a by-product from the total synthesis of rodenticide, brodifacoum.

We recently prepared 3R-0040 and had the opportunity to improve the synthetic approach. Its synthesis from commercially available tetrahydronaphthol (6) can be achieved in one step, however this material became unavailable and an alternative approach was sought. We opted to begin the synthesis from inexpensive and commercially available 4-bromobiphenyl and phenyl acetyl chloride (scheme 1). The ketone (1) was readily prepared by treatment of 4-bromobiphenyl with phenyl acetyl chloride under Friedel-Crafts conditions and was reduced to the corresponding alcohol (2) with sodium borohydride. The alcohol (2) was treated with phosphorus tribromide to give 4-bromo-4'-(1-bromo-2-phenylethyl) biphenyl (3) which on heating with diethyl sodiomalonate followed by hydrolysis afforded the malonic acid (4) in moderate yield. The malonic acid could be decarboxylated by heating to 180˚C to give the corresponding butyric acid which was treated with Eaton's reagent to give the dihydronaphthalenone (5). Reduction of the dihydronaphthalenone (5) with sodium borohydride afforded the tetrahydronaphthol (6) which was dehydrated to obtain 3R-0040.

We were able to complete the eight step synthesis within our desired timeframe, delivering the required batch of 3R-0040 with a purity of 97%. As with all BIONET products, it is available directly with full CoA and supporting analytical data.

**Scheme 1.** Synthesis of 3R-0040



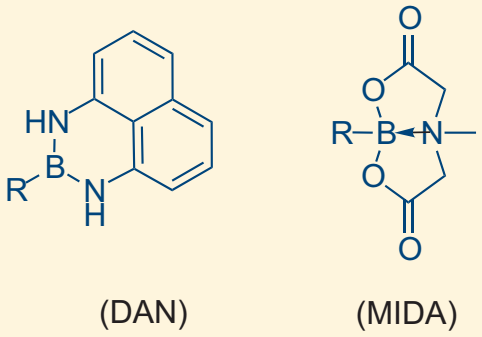
# Protected Boronic Acids – DAN Boronamides

**In September 2013 we announced our co-marketing agreement with Advanced Molecular Technologies (AMT) of Melbourne, Australia. In this review, we highlight a range of protected boronic acids that are available from our BIONET product portfolio.**

The Suzuki-Miyaura coupling reaction is well established in synthetic chemistry and is arguably the most famous and widely applied carbon-carbon bond forming reaction known.[1] There has been major advancement and understanding into the scope and development of this coupling reaction with respect to substrate, catalyst, and reaction conditions.[2-4] In particular, the ability to protect the organoboron reagent allows for elaboration and distal manipulation of the substrate to provide a range of multifunctional building blocks for SMC reactions.

Here we profile the 1,8-diaminonaphthyl (DAN) boronamide protecting group which can be considered complimentary, and also has some distinct advantage to the wider known MIDA boronate5 (*Figure 4*).

**Figure 4. The DAN and MIDA Reagents**

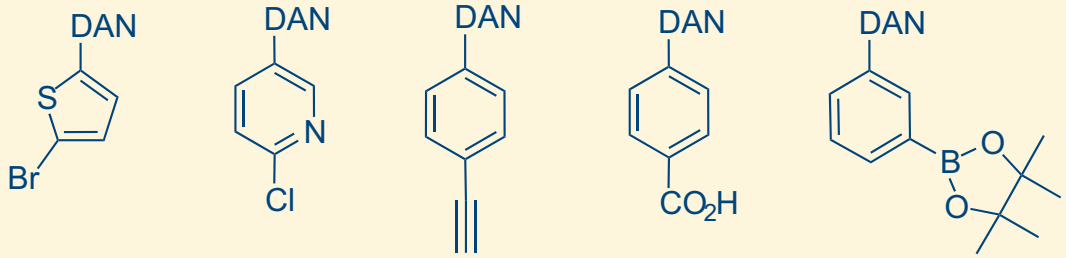



The discovery that DAN boronic acids (DAN Boramides) could be used as protected boronic acids in cross-coupling reactions was established at the same time as the more well known MIDA boronates.[6-8] The boron centre is very unreactive in the DAN ligand which makes them suitable towards aqueous work-up and column chromatography. They are stable to basic Suzuki-Miyaura coupling conditions and are readily deprotected with mild acid treatment. This acidic deprotection makes them chemically distinct from the MIDA boronates, which require basic conditions. Unlike MIDA protected boronic acids, strictly anhydrous conditions are not required to retain the protected boronic acid during cross-coupling and other reactions. DAN boronamides have good functional group compatibility (amide, amino, cyano, ether, ester, hydroxy, nitro) and generally have higher solubility in organic solvents than the corresponding MIDA protected boronic acids and potassium trifluoroborates.

DAN reagents can also be used in a wide range of organic transformations including, Suzuki-Miyaura coupling reactions,[5,6,8] Heck reactions,[9] Sonigashira,[10] Hiyama cross-coupling[10] and click chemistry reactions.[10]

A selection of multifunctional DAN protected boronic acids are available in Key Organics "BIONET" catalogue is represented in Figure 5.

**Figure 5. A Selection of multifunctional DAN protected boronic acids**




## The DAN protected boronic acids, Key Features:

1. Have good functional group compatibility (amide, amino, cyano, ether, ester, hydroxy, nitro, etc.)
2. Are stable to the basic conditions used in many cross-coupling reactions
3. Are complementary to the MIDA protected boronic acids (removed by mild acid treatment/ MIDA removed by mild base treatment)
4. Generally have higher solubility in organic solvents than the corresponding MIDA protected boronic acids and potassium trifluoroborates
5. Unlike MIDA protected boronic acids, strictly anhydrous conditions are not required to retain the protected boronic acid during cross-coupling and other reactions
6. Are stable to aqueous work-up
7. Can be purified by column chromatography
8. Unlike many boronic acids they are monomeric species

For these and more products, please visit our BIONET shop at: www.keyorganics.net/bionet


References:

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3. H. Doucet, Eur. J. Org. *Chem*, **2008**, 2013-2030
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6. H. Noguchi et al. J. *Am. Chem. Soc.* **2007**, 129 , 758-759
7. E.P. Gillis et al. J. *Am. Chem. Soc.* **2007**, 129, 6716-6717
8. S. Borman, "Masks unveil new synthetic routes" *Chem. Eng. News* **2007**, 85, 63-64
9. Ding J et al *Organics Letters* **2012**, 14, 4462-4465
10. S.M. Marcuccio et al, AMT Internal research **2014**

## Events that we will attend during Q2 2014

**2 – 4 April**
SCI Process Development Symposium; Cambridge, UK
www.soci.org/Membership-and-Networks/Technical-Groups/Fine-Chemicals-Group/Process-Development-Symposia

**9 April**
Organic Materials: New Opportunities for Synthetic Chemists; London, UK
www.nature.com/natureevents/science/events/22715-Organic_Materials_New_Opportunties_for_Synthetic_Chemists

**9 – 11 April**
CPhI Japan; Tokyo, Japan
www.cphi.com/japan/home

**23 – 25 April**
Drug Discovery Chemistry; San Diego, CA USA
www.drugdiscoverychemistry.com

**5 May**
MassBio Massachusetts CRO/CMO Symposium
Burlington, MA USA
www.massbio.org/events/calendar/2303-massachusetts_cro_cmo_symposium/event_detail

**12 – 14 May**
Biotrinity; London, UK
www.biotrinity.com/silverstripe

**19 – 20 May**
Kinase 2014; Cambridge, UK
www.rsc.org/ConferencesAndEvents/conference/alldetails.cfm?evid=113298

**2 – 3 June**
15th Annual Drug Discovery Summit 2014;
Geneva, Switzerland
www.drugdiscovery-summit1.com

**18 – 19 June**
Chemspec Europe; Budapest, Hungary *(UKTI Pavillion)*
www.chemspecevents.com/europe

**23 – 26 June**
Bio USA; San Diego, USA *(UKTI Pavillion)*
www.onhelix.com

# Staff Interview

Colin Swinburne,
Head of BIONET Intermediates

**Q: Please tell us a bit about yourself?**

**A: I have always been keen on science subjects, but it was my A-level teacher who sparked my interest in chemistry. I studied at the University of Leicester, obtaining a BSc (Class I, Hons) in Chemistry and then spent a year at AstraZeneca in Loughborough, before heading to Australia for 7 months of back-packing experience. On my return and looking for employment, I worked for a company making activated carbon cloth for medical dressings. Then in 1999 I joined Key Organics as a junior chemist and have progressed to my current position. I am married with three young children and we lead active lives enjoying swimming, cycling and the spectacular countryside and coastline here in Cornwall.**

**Q: What is your role within Key Organics?**

**A:** I have worked with the BIONET Intermediates catalogue almost exclusively since joining Key Organics. Having had many years of laboratory experience my role now oversees all management aspects of the department, such as inventory and quality control, customer service, team performance, internal and external chemistry resources and occasionally getting back in the lab. We are currently in setting up an office and distribution in the USA which involves a great deal of planning and increase in travelling.

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

**A:** I think that most people who work in research chemistry will recognise the enjoyment that comes from the variety of work, daily challenges and problem solving that chemistry brings and this is no different at management level. With our global customer base, it is great knowing and meeting many people who share the same interests.

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

**A:** Quality is our greatest strength. We have a large amount of repeat business in both our BIONET product and the services side of Key Organics, our quality and reliability have been imperative and underpinned our growth of ca. 30% last year and continue to be differentiators as we further grow in international markets.

Key Organics

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## New Satellite Offices, Let's Meet-up!

We are now able to meet with customers at our new satellite offices at BioCity Nottingham and BioCity Scotland. Of course everyone is still welcome to visit HQ in Cornwall!



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