Issue 11 | July 2015

# Key Organics Newsletter

Chemistry | Innovation | Quality

Our Q3 Newsletter features the new co-marketing collaborations with Cancer Research Technology and Liverpool ChiroChem plus a profile of new product additions to our growing BIONET portfolio, that includes our new 2nd Generation Premium Fragment Collection. We also feature our capabilities in the synthesis of labelled compounds including the synthesis of Risperidone-d4.

## Continued Expansion of our BIONET Portfolio

**Key Organics' BIONET collection continues to expand. Since 2012 our intermediates and fragment product groups have grown by over 100%.** Our entire BIONET portfolio now stands at almost 100,000 products that are available for same day dispatch in both Europe and North America through our new Compound Handling Unit near Boston, MA. As well as our internal synthetic chemistry efforts, we continue to forge new mutually beneficial co-marketing programmes with selected partners that provide new products, methodology and customer-solutions that are applicable to both research and development across the markets we serve (i.e. pharmaceuticals, agrochemicals and material sciences). Our e-commerce approach, together with the expedient delivery of our BIONET products and outstanding customer service allows us to meet, and usually exceed our customers' needs.

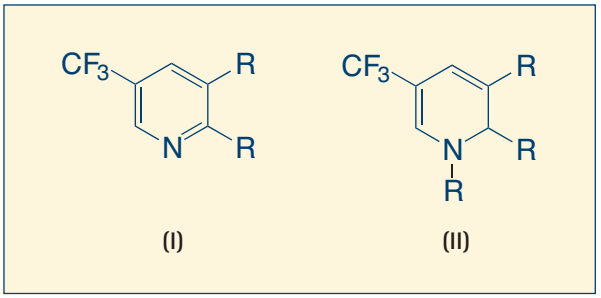
**We are therefore pleased to announce our new co-marketing collaboration with Cancer Research Technology (CRT), the development and commercialisation arm of Cancer Research UK.** The focus of this partnership will be to commercialize small molecule tool compounds developed by Cancer Research UK funded scientists across the UK. These products will be made available through our existing sales channels as well as CRT's new online portal, Ximbio (www.ximb.io). Broadening the range of tools available, through such partnerships, will benefit the wider scientific community and accelerate life science research.

**Through our new co-marketing agreement with Liverpool ChiroChem (LCC), we can now offer a range of novel chiral *N*-heterocycles.** These novel fragments form part of our growing fragment collection, further information is provided on the back page. The products will also be available in multi-gram quantities at affordable prices. LCC uses state of the art technology in the area of asymmetric catalysis to produce chiral *N*-heterocycles. The initial focus of our collaboration will be on the enantioselective synthesis of novel chiral piperidines that represent the most commonly occurring nitrogen ring found in FDA approved small molecule drugs.

## New 5-trifluoromethyl-2,3-disubstituted pyridines

Key Organics has synthesized a collection of over 600 5-trifluoromethyl-2,3-disubstituted pyridines-(II) and its *N*-substituted analogues-(II) that are now available within our BIONET portfolio. Compounds can be purchased as single entities or as functional group classes, please contact us for more information.

Both SD and PDF files are available for download from **www.keyorganics.net** or contact Joe Carey at: **joec@keyorganics.net** for further details.



# BIONET Fragment Libraries

**Through our collaboration with the Broad Institute, (Cambridge, MA) and NMX Research and Solutions, (Montreal, Canada) we are now pleased to report that our new 2nd generation BIONET Premium Fragment Library is now available for purchase. This unique library builds upon our previous CNS and Premium Fragment libraries and has the following features:**

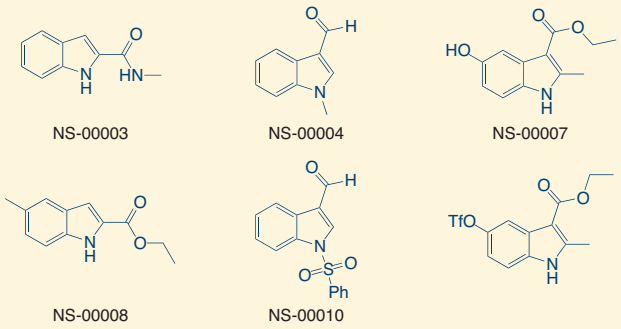
- 1166 compounds with experimentally assured aqueous solubility in PBS buffer.
- Excludes fragments deemed to aggregate as determined by 1H NMR spectra
- 1H NMR pdf and raw data files provided for all compounds purchased, chemical shifts provided for all compounds in an excel file.
- Strictly meet Astex Rule of 3 including polar surface area ≤ 60 and number of atoms ≤ 16
- Includes 445 fragments found in approved drugs and >1100 sharing cores found in drugs
- Filtered to exclude promiscuous and reactive substructures

The collection was established in consultation with our partners and based on a rational build strategy (*Figure 1*).


**Figure 1.** Build Strategy for BIONET 2nd Generation Premium Fragment Library

All structural and physiochemical data are available in an SD file format that is now available for download from **www.keyorganics.net** or please contact Andrew Lowerson at: **andrewl@keyorganics.net** for further details.

**Figure 2.** New BIONET Indoles now available from Key Organics




## New additions to the BIONET Indoles library

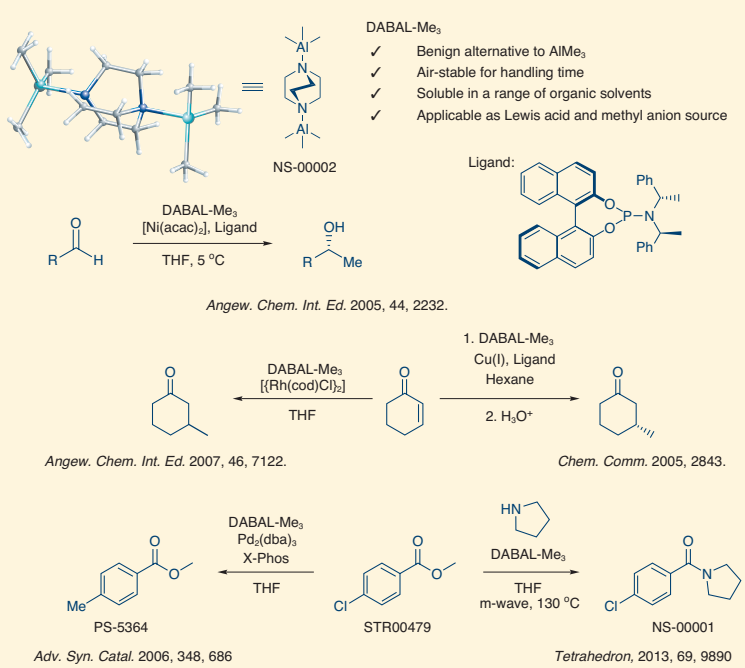
Our collaboration with the University of Nottingham brings more indoles to our BIONET library of fragments and screening compounds (*Figure 2*). Prof. Chris Moody's research focuses on new methods in heterocyclic chemistry, especially new routes to indoles which are one of the most abundant and important heterocycles in nature.[1] Consequently, new additions to BIONET include functionalised indoles coming from his research, such as esters, aldehydes and other derivatives open for further modifications. Please contact us for more information.

# New BIONET Reagents

## DABAL-Me$_3$ – a versatile tool for modern chemistry

Through our new co-marketing collaboration with the University of Nottingham we have now added DABAL-Me$_3$ (NS-00002 , see figure 3 opposite) to our BIONET collection. As explored by Prof. Simon Woodward's group, DABAL-Me$_3$ being a complex between DABCO and AlMe$_3$ is a white solid that is air-stable for short periods of time and soluble in a range of organic solvents; there is no requirement for a glove box or Schlenk line and in some cases additional drying of solvents is avoided. Consequently, it serves as a great alternative to air and moisture sensitive pyrophoric AlMe$_3$. DABAL-Me$_3$ can be applied as a Lewis acid as well as a source of methyl nucleophile required by methylation of aldehydes, conjugate addition to enones, or methyl cross-coupling to aryl halides (*Figure 3*). Additionally, synthesis of amides from coupling esters with a range of amines can be conveniently achieved in the presence of DABAL Me$_3$; recent advance in the area include preparation of benzimidazoles from diamines.[2] DABAL-Me$_3$ amide couplings have recently been demonstrated at up to 0.1 Kg scales,[3] and therefore larger pack sizes of this reagent are available from the BIONET range. A product of this research, amide NS-00001, is also available from our BIONET Fragment Libraries, please contact us for more information.

**Figure 3.** Profile of applications of DABAL-Me$_3$ (NS-00002)



# Isotope Labelled Compounds

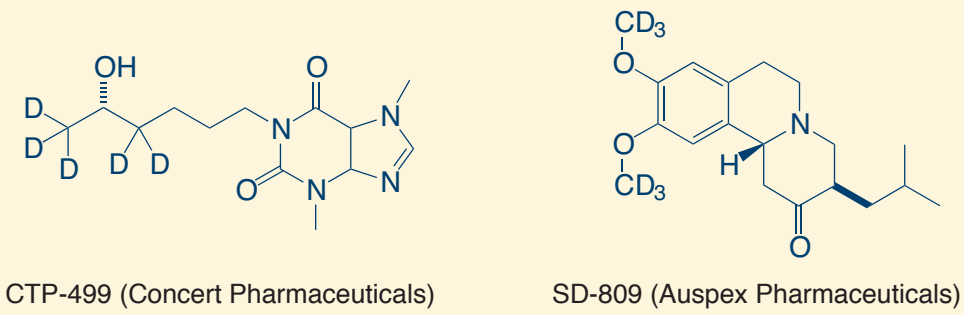
Custom synthesis of isotope-labelled compounds has been a major growth area for Key Organics over the last two years. We have built up considerable experience in incorporating deuterium and carbon-13 labels in a diverse range of target molecules for customers in the pharmaceutical industry. In this brief review, we give an overview of this exciting area of synthetic chemistry and profile one of our recent successes.

## Uses of isotope labelled compounds

Traditionally, isotope labelled compounds have been used to elucidate reaction mechanisms and biosynthetic pathways, and for the identification of metabolites. However, several pharmaceutical companies have drugs in late stage development that contain deuterium (*figure 4*). The carbon-deuterium bond is between 6 and 10 times stronger than the carbon-hydrogen bond, offering considerable advantages in metabolic stability. The pharmacokinetic properties of existing drugs can often be improved by selectively deuterating sites of metabolism.

Two examples of deuterated drugs in development are shown in figure 4 opposite. CTP-499 is in phase II clinical trials for diabetic nephropathy. It is the deuterated analogue of the active metabolite of pentoxifylline, a phosphodiesterase inhibitor used to treat peripheral artery disease. SD-809 is the deuterated analogue of tetrabenazine, a drug used to treat hyperkinetic disorders. It is in phase III trials for the treatment of chorea associated with Huntingdon's disease.

**Figure 4.** Examples of deuterium-containing drugs in development




CTP-499 (Concert Pharmaceuticals)

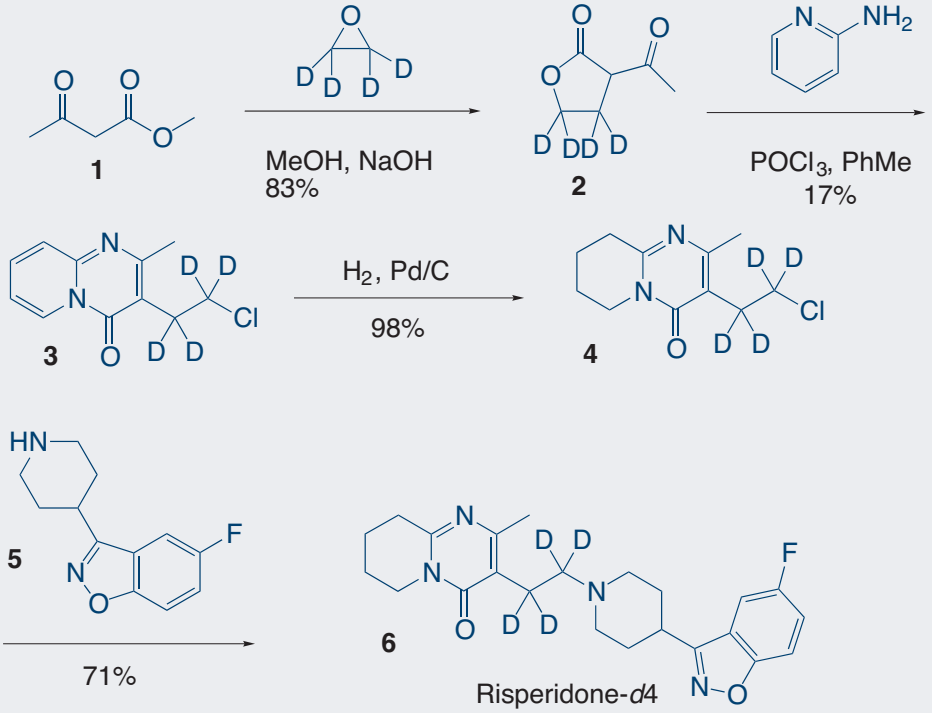
SD-809 (Auspex Pharmaceuticals)

## Case Study: The Synthesis of Risperidone-*d*4

**Risperidone is an antipsychotic drug used to treat schizophrenia and bipolar disorder. The synthesis of the tetradeuterated compound (6, *scheme 1*) was recently carried out at Key Organics.**

Oxirane-*d*4 gas was passed through a cooled basic methanolic solution of methyl acetoacetate **1**, giving the lactone product **2** in 83% yield (F. Turicek *et al., J. Am. Chem. Soc.,* **2002**, 124 (44), pp 13282–13289). The mechanism of this step is presumably ring-opening of the epoxide by the stabilised anion of methyl acetoacetate, followed by ring closure. The lactone **2** was then reacted with 2-aminopyridine in the presence of phosphorous oxychloride, giving the pyridopyrimidine **3**. Reduction of **3** with hydrogen and catalytic palladium on carbon gave **4** in excellent yield. Coupling of **4** with the commercially-available piperidine intermediate 5 gave risperidone-*d*4 **6** in 71% yield and >98% purity by LCMS and $^1$H NMR.

**Scheme 1.** Synthetic route to Risperidone-*d*4




References:

1. Inman, M.; Moody, C. J., Indole synthesis - something old, something new. *Chemical Science* 2013, *4* (1), 29-41
2. Pinder, J. L.; Davis, R. E.; Charrier, J.-D. *Tetrahedron Letters* 2014, 55, 4853.
3. Lee, D. S.; Amara, Z.; Poliakoff, M.; Harman, T.; Reid, G.; Rhodes, B.; Brough, S.; McInally, T.; Woodward, S. *Organic Process Research & Development* 2015, Article ASAP (DOI: 10.1021/acs.oprd.5b00101).

## Key Organics will be exhibiting or attending the following events and conferences in the coming months

| | | |
|---|---|---|
| **July 13th** | **Innovations in Healthcare Conference 2015.** | The University of Sheffield, Sheffield, UK. |
| **September 2nd** | **3rd Drug Discovery 2015.** | Telford International Conference Centre, Telford, UK. |
| **September 13th – 16th** | **Cambridge Med Chem Symposium** | Cambridge, UK |
| **September 14th – 17th** | **Chem Outsourcing** | Long Beach NJ, USA |

# BIONET

Through our co-marketing agreement with LCC, we are now able to offer a range of chiral *N*-heterocycles that have been synthesised by a new, and more direct, high yielding asymmetric synthesis (*Scheme 2*). The route is robust and amenable to further scale-up, please contact us for more information.

**A selection of products available are shown in Figure 5. All are available from stock for immediate delivery.**

**Scheme 2.** Asymmetric Synthesis of chiral N-heterocycles (ex LCC)

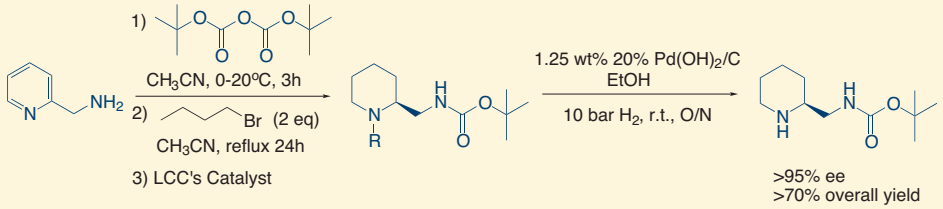
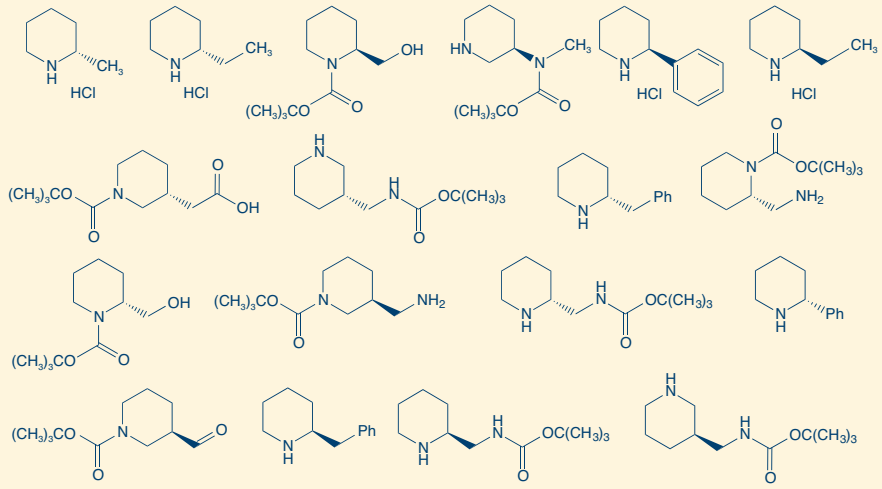



**Figure 5.** Selection of chiral *N*-heterocycles now available from our BIONET Portfolio



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