Issue 12 | October 2015

Key Organics Newsletter

Chemistry | Innovation | Quality

Our Q4 Newsletter contains further details of our new Second Generation Premium Fragment Library of 1,166 fragments which has been developed, analysed and validated in close collaboration with The Broad Institute in Boston, USA and NMX Research (Montreal, Canada). We are also delighted to announce the introduction of several new BIONET reagents that are available from stock at our warehouses in the UK and USA. These include a range of chiral tert-butyl sulfinimines (sulfinyl imines) and enantiomerically pure sulfoximines, prepared by either the stereospecific imination of optically active sulfoxides or resolution of racemic sulfoximines.

BIONET Fragment Libraries

Pioneering New Fragment Library Design

Through continued investment and our innovative approach, Key Organics has established one of the worlds leading vendor fragment libraries and is a preferred supplier of proprietary libraries to the international Life Science industries. Our new "Second Generation BIONET Premium Fragment Library" has been constructed employing Rule of Three and industry standard substructure filtering that includes PAINS analysis. Diversity selection utilized methods in shape, scaffold, fingerprint and predicted property space have also been applied. All 1166 fragments within our new collection have been analysed by 1H NMR (Figure 1) for:

- Structure verification
- Purity
- Aqueous Solubility
- Aggregation.

Physiochemical Properties of the library:

- Heavy atoms ≤16
- cLogP ≤ 3,
- Hydrogen bond donors ≤3
- Hydrogen bond acceptors ≤3
- Polar surface area ≤ 60
- Rotatable bonds ≤ 3

In addition, we have undertaken substructure filtering and provided diversity statistics to support our product claims (Figure 2) and demonstrate the value of our new proprietary Second Generation Premium Fragment library.

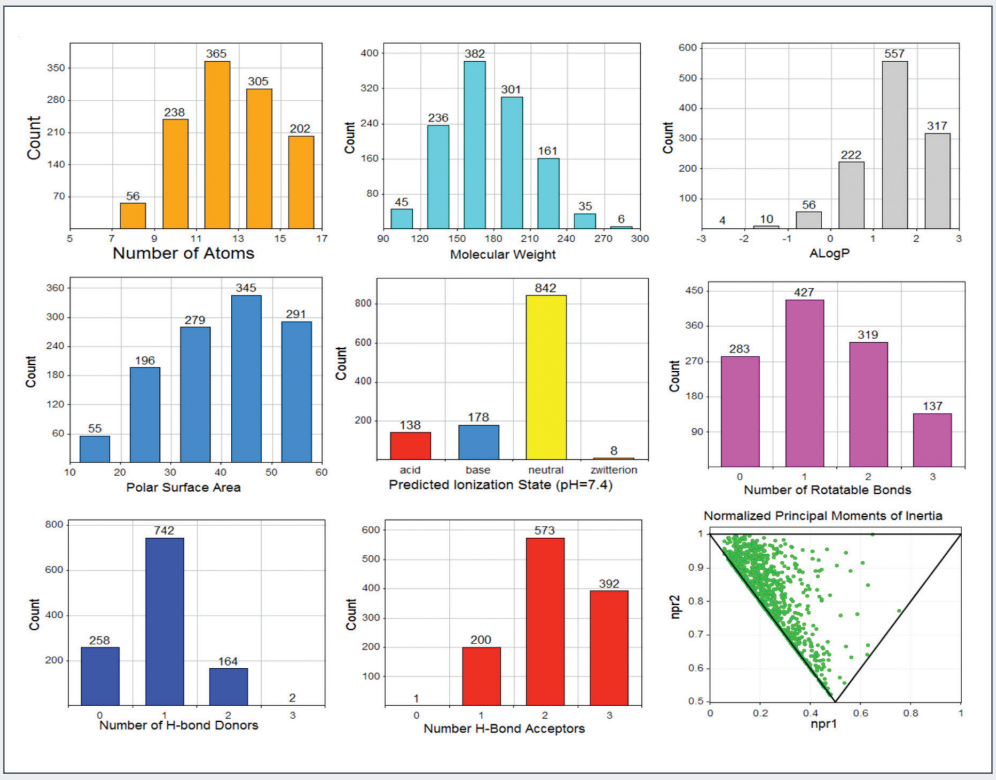


Figure 1: Overview of calculated properties of the final library

... Continued on page 2

BIONET Pioneering New Fragment design (Continued)

Fragment Libraries

Substructure Filtering:

- Lilly MedChem Rules[1]
- PAINS[2]
- BMS[3]

Diversity Statistics:

- Diversity coefficient (average distance using MACCS 166-bit keys) = 0.72
- # clusters at 0.85 Tanimoto similarity (MACCS 166-bit MOE) = 964 clusters

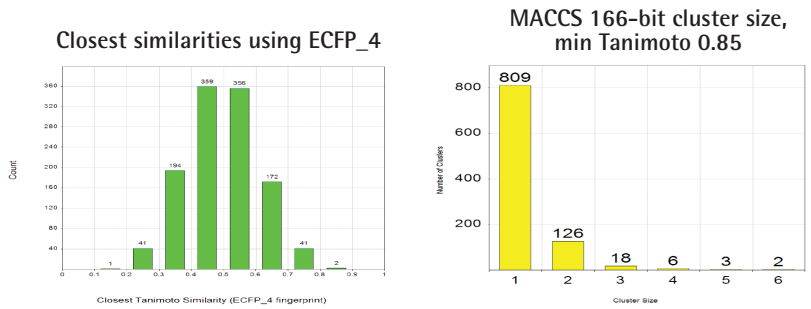


Figure 2: Diversity statistics of the final library.

DMSO Solubility:

All 1,166 Fragments are soluble in DMSO at 200mM

All customers will be supplied with the following data package for each aqueous soluble fragment purchased:

- Aqueous buffer 1H NMR pdf
- Aqueous buffer 1H NMR raw data file
- ^{1}H NMR chemical shifts supplied in an excel file

A comprehensive review of the design process employed in constructing the 2nd Generation BIONET Premium Fragment Library is available from Andrew Lowerson (andrewl@keyorganics.net).

References:

1. Bruns, R. F.; Watson, I. *A. J. Med. Chem.* **2012**, 55 (22), 9763–9772.
2. Baell, J. B.; Holloway, G. *A. J. Med. Chem.* **2010**, 53 (7), 2719–2740.
3. Pearce, B. C.; Sofia, M. J.; Good, A. C.; Drexler, D. M.; Stock, D. A. *J. Chem. Inf. Model.* **2006**, 46 (3), 1060–1068.

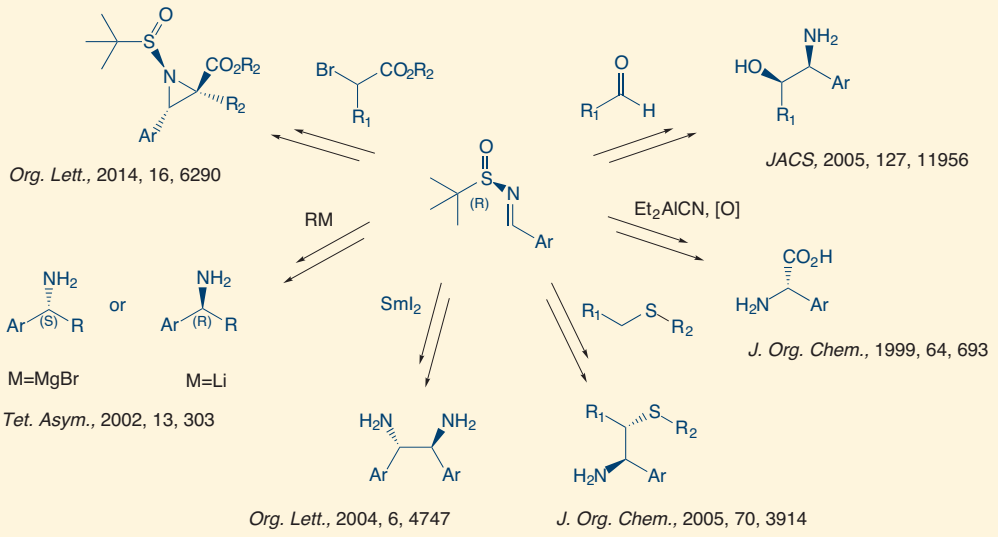
BIONET Innovative Reagents for R&D

New Chiral *Tert*-Butyl-Sulfinimines

Our BIONET collection has been recently expanded by a unique selection of chiral *tert*-butyl sulfinimines (sulfinyl imines) via our co-marketing collaboration with the University of Nottingham. From the research by R. Stockman and co-workers, these compounds were elegantly utilised as chiral intermediates for synthesis of cyclic adducts[1] and multisubstituted aziridines.[2]

Sulfinimines are applicable as both *N*-auxiliaries for synthesis of enantiopure amines and ligands for asymmetric synthesis. Moreover, further synthetic elaboration can lead to a diverse range of chiral skeletons desired in modern organic chemistry (Scheme 1).[3,4] Our emerging collection consists of 19 aromatic *tert*-butyl sulfinimines substituted with various functional groups ready for further derivatisation. Both (*S*)- and (*R*)-enantiomers are available to purchase from our BIONET Library to provide immediate answers when studying asymmetric reactions. Please contact us for more information.

Scheme 1. Synthetic elaboration can lead to a diverse range of chiral skeletons



References:

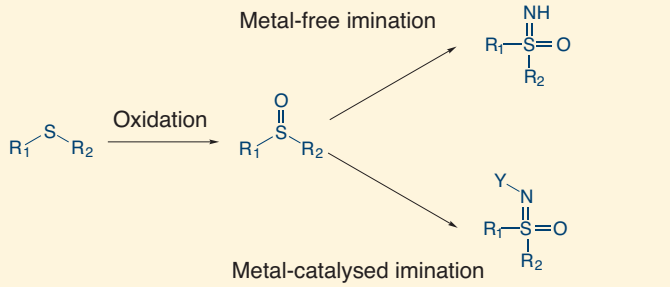
1. Procopiou, G.; Lewis, W.; Harbottle, G.; Stockman, R. A. *Organic Letters* **2013**, 15, 2030.
2. Moragas, T.; Churcher, I.; Lewis, W.; Stockman, R. A. *Organic Letters* **2014**, 16, 6290.
3. Dong, H.-Q.; Xu, M.-H.; Feng, C.-G.; Sun, X.-W.; Lin, G.-Q. *Organic Chemistry Frontiers* **2015**, 2, 73.
4. Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, 62, 8869.

Sulfoximines – A new opportunity for Drug discovery

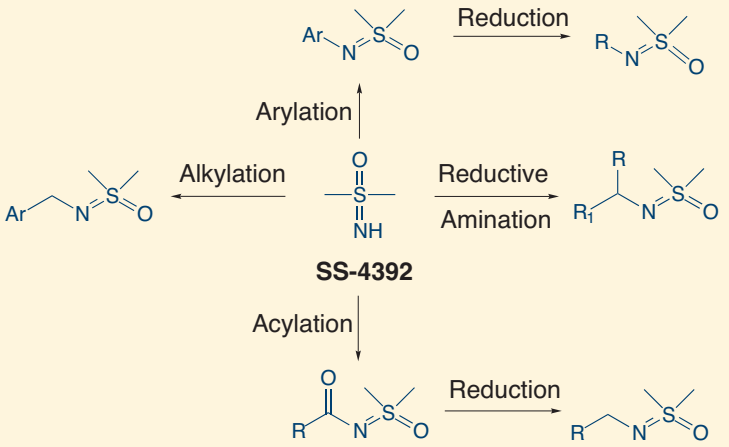
The sulfone group is commonly used in drug discovery. One disadvantage with the sulfone group, however, is that it can introduce poor solubility due to intermolecular interactions in the solid state. The isosteric sulfoximine group; discovered at the end of the 1940s, can provide improved solubility compared to the sulfone group. These stable mono-aza analogues of sulfones have several interesting features including a stereogenic sulfur atom, nucleophilic nitrogen and an acidic hydrogen. In general, they are synthesized from sulfides in two steps involving oxidation and imination (Scheme 2). Enantiomerically pure sulfoximines are also accessible by either the stereospecific imination of optically active sulfoxides or resolution of racemic sulfoximines.

Sulfoximines have rarely been used in medicinal chemistry, possibly due to their perceived toxicity and potentially hazardous synthesis. This has resulted in less than a handful of sulfoximine based compounds entering clinical trials. However, given some recent developments in the area[1,2,3], this would seem to be a neglected opportunity[4]. In the discovery of the pan-CDK inhibitor BAY 1000394[5], the unconventional proposal to introduce a sulfoximine group into the lead series allowed many of the fundamental issues of the project to be overcome, culminating in the identification of a potent new lead compound.

Scheme 2. Traditional Sulfoximine synthesis



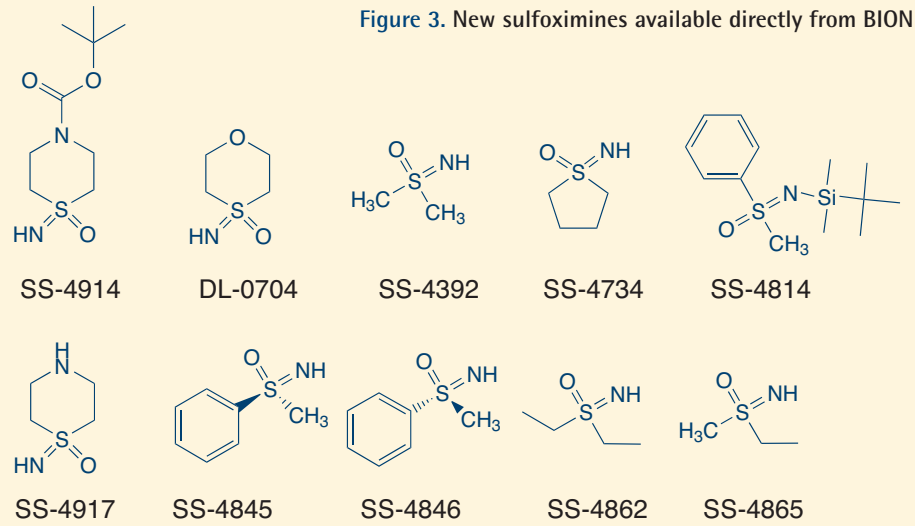
Scheme 3. Proposed use of Dimethylsulfoximine to synthesise *N*-alkyl sulfoximes.



Dimethylsulfoximine (SS-4392) is an extremely versatile starting material for synthesising a variety of S- and N-alkyl sulfoximines. Although S-alkyl sulfoximines are fairly well precedented in the literature, *N*-alkylsulfoximines, by contrast, have not thus far had the same degree of interest in medicinal chemistry. Recently Goldberg et al[6], have reported the synthesis of a diverse range of novel N-alkyl sulfoximine building blocks on practical (>10 g) scale, using dimethylsulfoximine in a variety of applications (scheme 3).

Drawing upon a wealth of expertise in this area, Key Organics is pleased to highlight the introduction of a growing range of these extremely interesting new products to the BIONET portfolio. We hope that this will further enhance the usage of the sulfoximine group in drug discovery. A number of new compounds (Figure 3) are now available direct from stock and are ready for same day shipping. Similar custom analogues are available on request within a few weeks.

Figure 3. New sulfoximines available directly from BIONET

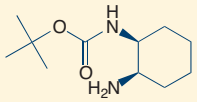


References:
1. Dixon *et al.* PCT Int. Appl. (2015), WO 2015095048 A1 20150625
2. Blum *et al.* PCT Int. Appl. (2015), WO 2015082324 A1 20150611
3. Nugent et al. *Pest Management Science* (2015), 71(7), 928-936.
4. U. Lücking. *Angew. Chem. Int. Ed.* 2013, 52, 9399 – 9408
5. U. Lücking. *Mol. Cancer Ther.* 2012, 11, 2265.
6. F.W. Goldberg *et al. Tetrahedron* 70 (2014) p6613-6622

Key Organics will be attending or exhibiting at the following events:

October 20th	Pharma Venture Creation	Alderley Park, UK
November 3rd	The Chemistry of Collaboration	Sedgefield, UK
November 13th	MassBio CRO/CMO Symposium	Boston, MA, USA

New Products available from our BIONET Product Group: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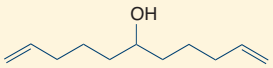
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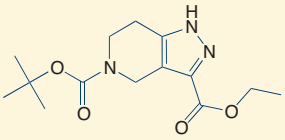
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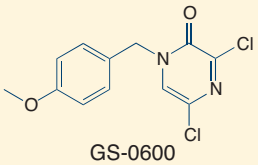
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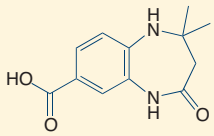
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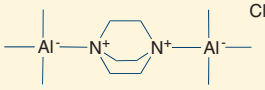
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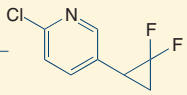
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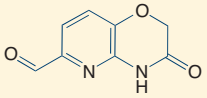
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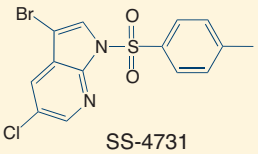
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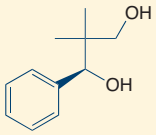
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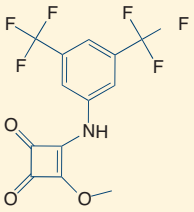
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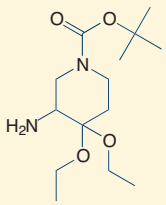
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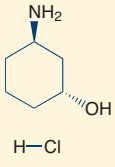
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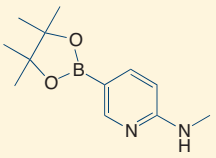
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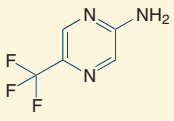
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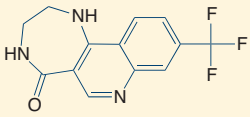
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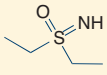
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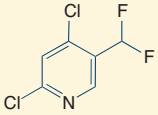
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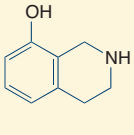
DS-2445

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