April 2018

Key Organics Newsletter

Chemistry | Innovation | Quality

Key Organics and NTZ Lab Ltd. have recently entered into a development and marketing agreement focused on a class of novel CNS compounds discovered by Dr Nikolay Tzvetkov, founder and CEO of NTZ. The initial set of 9 target structures *(Figure 1)* have been synthesised by Key Organics and are available for screening by prospective licensees. They are part of a larger set which have been patented by NTZ and have demonstrated and selective MAO-B Inhibitor/Fe(II) chelation activity with potential indications in multiple CNS disease areas.

This screening collection with experimentally-determined bioactivity, lipophilicity (LogP/$D_{7.4}$), aqueous solubility, GIT and BBB permeability, chemical stability, toxicity addresses the need of new, robust, and multipotent small molecules for the treatment and diagnosis of CNS diseases, such as Parkinson´s disease, Alzheimer´s disease, dementia and/or other neurodegenerative diseases. The newly discovered and well-validated molecules are enriched in heterocyclic scaffolds and specifically substituted phenyl moieties commonly found in CNS drug candidates, and spans chemical space that minimally overlaps with existing commercial collections. The compounds are easily accessible and offer the possibility of broad structural diversities in order to further explore the chemical space within further biological screening on relevant CNS targets.

For more information please contact Dr Joe Carey at:
joec@keyorganics.net

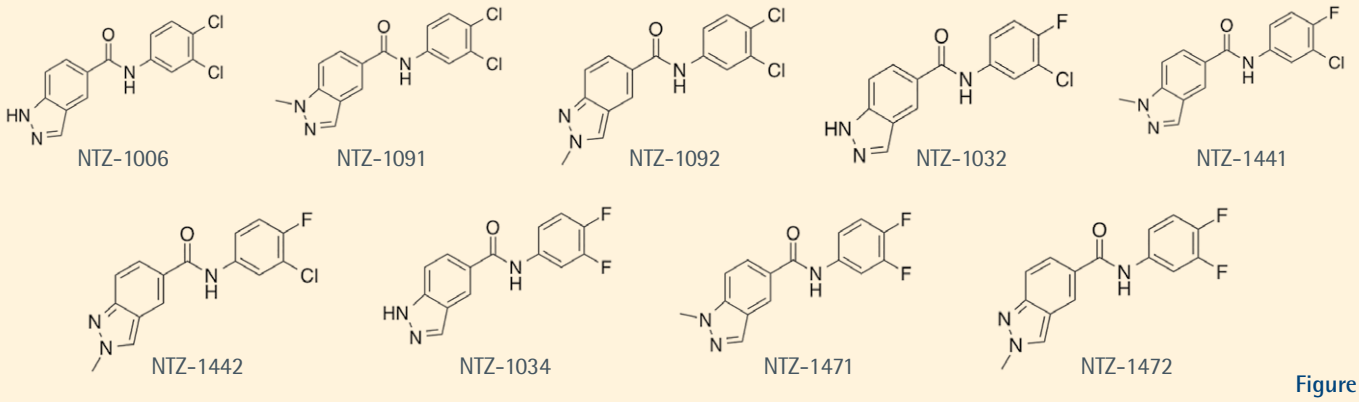


Figure 1.

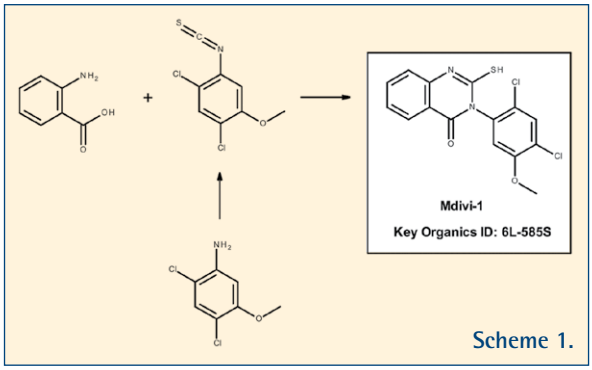
Bionet Biochemicals

The Bionet Biochemicals collection contains over 1100 diverse bioactives, metabolites and hormones, including deuterated and salt forms. They are in various stages of development, from pre-clinical through to approved market drugs, and are sold for research and development purposes.

FEATURED PRODUCT

Mdivi-1

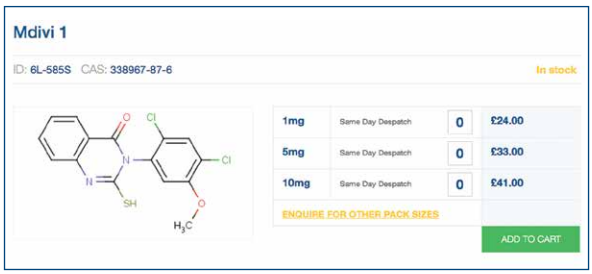
Mdivi-1 is a selective inhibitor of mitochondrial division in yeast and mammalian cells which acts via inhibiting the mitochondrial division dynamin. In cells, Mdivi-1 inhibits apoptosis by inhibiting mitochondrial outer membrane permeabilization. Mdivi-1 causes the rapid (<5 min) reversible and dose-dependent formation of net-like mitochondria in wild-type cells with an IC50= ~10μM. In yeast, time-lapse fluorescence microscopy revealed no detectable mitochondrial division after treatment with Mdivi-1. It inhibits Dnm1 GTPase activity in a dose dependent manner with an estimated IC_{50} of 1-10μM but is not a general inhibitor of GTPases.



Scheme 1.

SYNTHESIS

Mdivi-1 is synthesised in gram quantities in two synthetic steps at Key Organics UK site by our highly experienced Organic Chemists. The synthesis route employed to produce Mdivi-1d is summarised in Scheme 1. Chemical purity has been assessed using 1H NMR and LCMS experiments in Key Organics' own Analytical Department. All data is kept on file and available for inspection on request



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The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

University of Nottingham fluorescent ligands are available from our BIONET Biochemicals Collection

In looking for new avenues to expand our BIONET Biochemicals collection, we have extended our collaboration with the University of Nottingham by working with Professor Barrie Kellam from the School of Pharmacy.

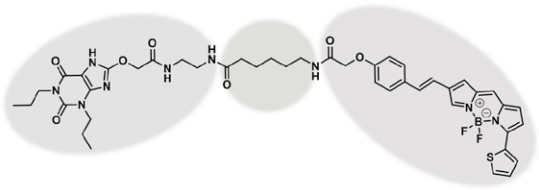

Figure 2 – A fluorescent ligand (exemplified by XAC-BY630)[3,4] comprising a pharmacophore (blue), linker (yellow) and fluorophore (red).

Professor Kellam and his team have well-established expertise in the design, synthesis and characterisation of fluorescently labelled small molecules, which are used to probe membrane receptor pharmacology.[1,2] These ligands will be soon available through Key Organics via Nottingham Research Chemicals – our ongoing collaboration with the School of Chemistry at Nottingham. The initial release will include fluorescent ligands of general structure presented in *Figure 2*. In addition to ligand binding experiments, fluorescent ligands have many applications including FRET/BRET assays, high content screening, and fluorescent correlation spectroscopy4 (*Figure 3*). These techniques can provide a more in-depth investigation into receptor pharmacology and the safety, handling and disposal issues associated with radio labelled ligands can be avoided. To enable the rapid and effective usage of the ligands, they will be accompanied by pharmacological characterisation data and key references. The release of the products coming from this collaboration will be announced in coming months, but please contact us if you need more information about these new additions coming to the BIONET catalogue.

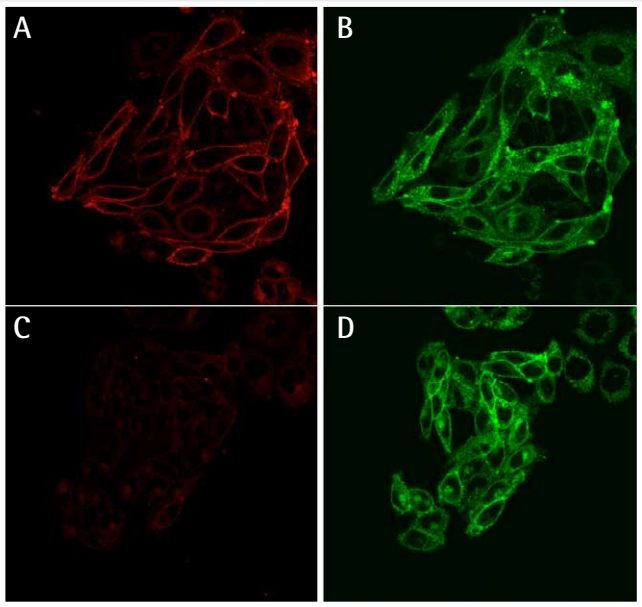

Figure 3 – Confocal images of CHO cells expressing the GFP tagged adenosine A_1 receptor (CHO-A1Tpz)[4] incubated with XAC-BY630 (50 nM, 15 mins) (A & B) or with the A1AR antagonist DPCPX (100 nM, 30 mins) followed by XAC-BY630 (50 nM, 15 mins) (C & D). Images taken after simultaneous excitation at 633nm and 488 nm.

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1. Stoddart, L. A. et al., *Neuropharmacology* **2015**, 98, p 48-57
2. Vernall, A. J. et al., *British Journal of Pharmacology* **2014**, 171 (5), p 1073-1084.
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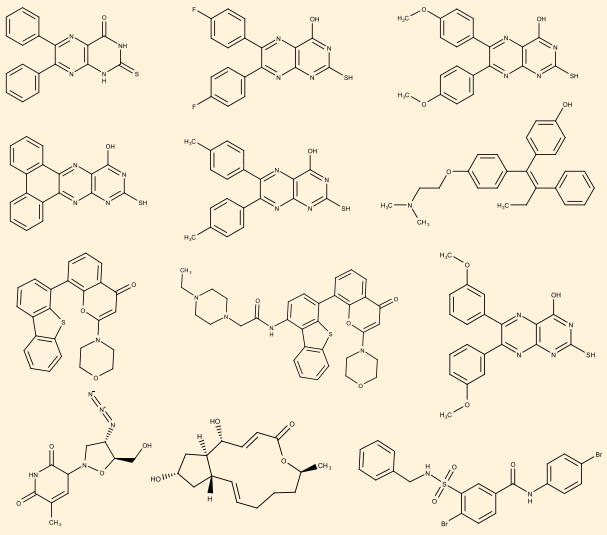
CRISPR-Cas9

According to the journal *Science*; CRISPR, the gene editing technology, was the breakthrough technology of 2015 due to ease of use, cost, speed and efficacy. CRISPR is short for 'cluster regular interspaced short palindromic repeats' which is a DNA sequence found in certain strains of bacteria and other microorganisms. These form an immune response along with an associated gene (CRISPR-Cas) to remove infectious DNA and viruses. There are a number of types, one of them being the Cas-9 protein, which is currently used in genome editing. The Cas-9 enzyme is guided to the specific site where cleavage is required by acting as a guide RNA. These guide RNA's make this a more specific method then previous.

The Cas-9 guides the CRISPR gene to the required sequence and cleaves the DNA with a double strand break. Cells are then repaired via two mechanisms, non homology end breaking (NHEJ) and homology directed repair (HDR). NHEJ is the most common method of repair but its outcome is unpredictable compared to HDR.

Studies have noted that certain small bioactive molecules enhance the efficiency and precision of the CRISPR Cas-9 mediated system by enhancing the HDR route.

We are proud to offer a number of these small molecules



Further background reading.

- https://fas.org/sgp//crs/misc/R44824.pdfYu et al (2015) Small molecules enhance CRISPR genome editing in pluripotent stem cells. Cell Stem Cell 16 142.
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Stockholm University

Rhodium catalysts summary – Key Organics

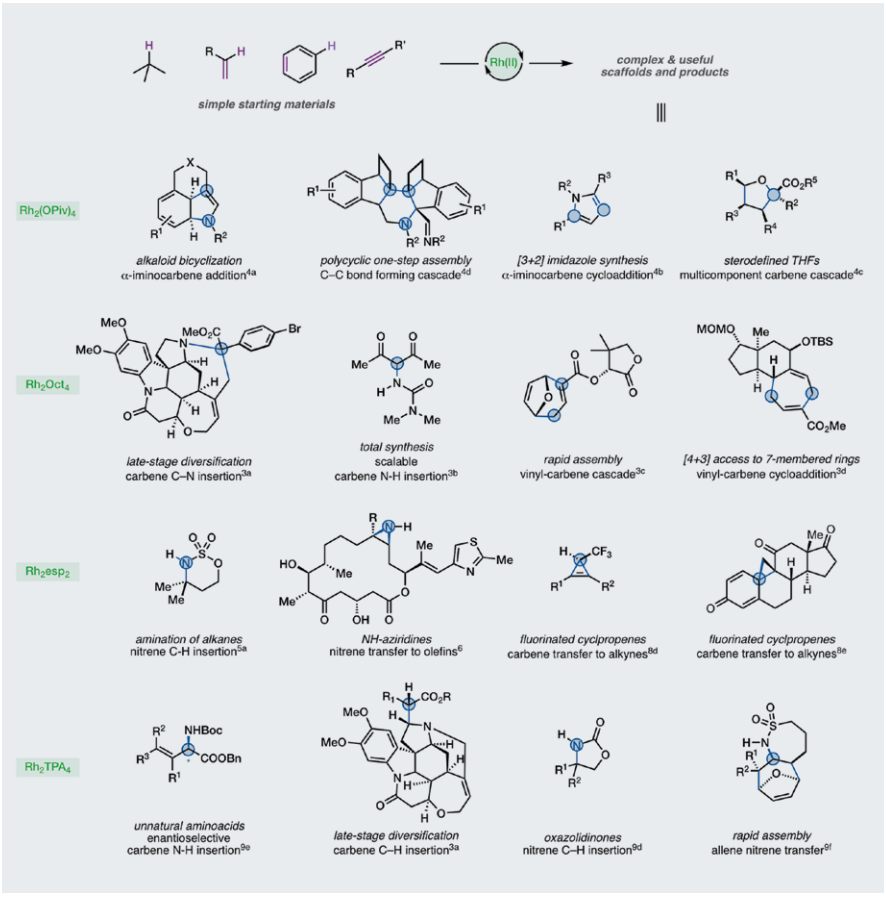
Elisa Martinez and Abraham Mendoza

Among the various families of catalysts that are used in carbene and nitrene transfer reactions, rhodium(II) paddlewheel complexes display a remarkable elasticity in their range of applications. Classic carbene transfer reactions such as cyclopropanation, ylide-promoted cycloadditions and intramolecular C–H insertions have been widely developed along this catalyst family.[1] Today they also excel in nitrene chemistry, delivering stereoselective and intermolecular C–H amination reactions of unactivated alkanes that allow the installation of nitrogen handles for further derivatization.[2] Although these reactions operate through distinct mechanisms, these catalysts offer an effective solution to this chemistry.

The catalysts **Rh_2Oct_4** (rhodium octanoate dimer)[3] and **Rh_2Piv_4** (rhodium pivalate dimer)[4] have an excellent track record in carbene transfer chemistry. They offer fine-tuned and distinct steric, electronic and solubility profiles that are screened to obtain optimal results.

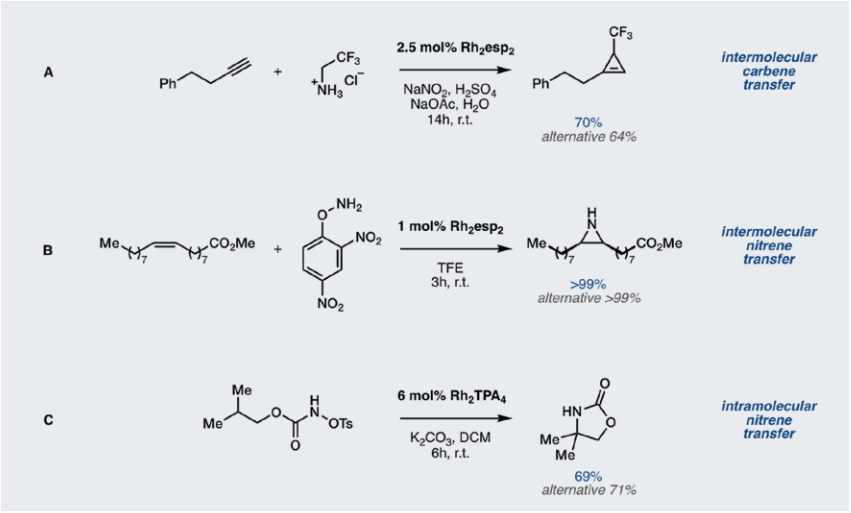
The C–H aminations developed by DuBois can be perfomed intra-[5a] or intermolecularly[5b] due to the excellent performance of the catalyst **Rh_2esp_2**. This catalyst displays a unique stability in the mild oxidative media used in the generation of electron-poor nitrenoids.[5c] It is also effective in nitrene transfer to olefins to produce *NH*-aziridines[6] and diamines.[5d] The catalyst is useful in the synthesis of heterocycles such as pyridines,[7a] a pyrroles,[7b] pyrrolidines,[7c] indoles,[7d],e indolines,[7f] and azetidines,[7g] to mention just a few. **Rh_2esp_2** is moreover an excellent and robust catalyst for challenging carbene transfer reactions[8a–c], that include access to fluoroalkylated cyclopropenes,[8d] and natural products.[8e]

Rh_2TPA_4 developed by Hashimoto,[9a] a is one of the largest achiral dirhodium catalysts and it has been found to provide unique performance and stereocontrol. This catalyst is particularly successful in carbene transfer reactions towards cyclopropenes,[9b] alkane C-H functionalization,[9c] and late-stage functionalization of complex alkaloids.[3a] Moreover it has also found potential nitrene transfer to C-H bonds,[9d] N-H bonds,[9e] and allenes.[9f]



Catalyst benchmarking

We have compared the activity of some of our catalysts with current suppliers and found no difference between them (within experimental error). Namely, we have selected an intermolecular carbene transfer[8d] towards fluorinated cyclopropenes **(A)** and both inter-[6] and intramolecular[9d] nitrene transfer reactions towards aziridine intermediates **(B)** and oxazolidinone products **(C)**, respectively.



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4 (a) *J. Am. Chem. Soc.*, **2014**, 136, 2272; (b) *Angew. Chem., Int. Ed.*, **2013**, 52, 1507; (c) *J. Am. Chem. Soc.* **2009**, 131, 1101; (d) *Angew. Chem., Int. Ed.*, **2014**, 53, 6645.
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6 (a) *Science*, **2014**, 343, 61; (b) *Angew. Chem., Int. Ed.*, **2017**, 56, 9886; (c) *J. Am. Chem. Soc.*, **2017**, 139, 7318.
7 (a) *Angew. Chem., Int. Ed.*, **2013**, 52, 2212; (b) *J. Am. Chem. Soc.* **2013**, 135, 11712; (c) *Angew. Chem., Int. Ed.*, **2016**, 55, 3749; (d) *J. Am. Chem. Soc.*, **2011**, 133, 4702; (e) *Angew. Chem., Int. Ed.* **2011**, 50, 1702; (f) *J. Am. Chem. Soc.*, **2012**, 134, 7262; (g) *Nat. Chem.*, **2014**, 6, 872. (f) *Angew. Chem., Int. Ed.* **2016**, 55, 13240.
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We will be exhibiting and/or attending the following exhibitions and conferences in the coming months:

April 2nd-6th	Drug Discovery Chemistry	San Diego, CA, USA
April 26th	29th Symposium on Medicinal Chemistry in Eastern England	Hatfield, UK
May 3rd	Swiss Biotech Day 2018	Basel, Switzerland
May 14th-15th	Kinase 2018: towards new frontiers - 8th RSC / SCI symposium on kinase inhibitor design	Cambridge, UK
September 2nd-6th	XXV EFMC International Symposium on Medicinal Chemistry	Ljubljana, Slovenia
September 17th-19th	ChemOutsourcing	Ocean Place Resort, Long Branch, NJ, USA
September 26th-28th	Discovery on Target	Boston, MA, USA

For more information, please visit: https://www.keyorganics.net/about/exhibition-conference-attendance/

Staff Interview Bonnie Ober, U.S. Operations Manager

Q: Please tell us a bit about yourself?

A: I grew up in Newton, Massachusetts, USA and have lived in this New England state my entire life. At Bentley University I chose a Marketing and Management course with a focus in Communications. I initially started working in the construction industry; but I found the work mostly unfulfilling and was very lucky to fall into the healthcare industry in several capacities in the last decade. That overall experience combined with a good business acumen brought me to this Operations position at Key Organics, Inc.

I have lived in several towns in MA but recently settled in Westford which is northwest of Boston. Westford affords me spectacular trails to hike and mountains to climb with my kids & dog in Northern Mass. And nearby New Hampshire.

Q: What is your role within Key Organics?

A: My position at Key is varied - and constantly evolving - which is very exciting! I have all the regular duties of managing the office; stocking our warehouse in the US with our growing inventory of BIONET products to supply the North American market, processing orders and enquiries and packing and shipping those orders out to our customers. I am lucky enough to be extremely close in proximity to the hub of the Biotech industry clustered in Cambridge/Boston - which allows me to be very hands-on with our quick turn around on delivery and exceptional service to the entire US and North American markets. I most look forward to meeting more of our customers and finding our what their individual needs are. The plan is to continue to build these relationships and help our customers with their unique and varied needs!

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

A: The opportunity to grow our business means that ultimately, we may contribute in changing the course of disease - which makes our work so essential and worthwhile. To have that passion to want to do great things - coupled with the freedom within a company that encourages new ideas and thought processes is remarkable, and very special.

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

A: Our staff in every capacity, is the greatest strength of Key Organics. Our drive to offer the best service, products and information to our customers is the focus of everything we do.

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