August 2019

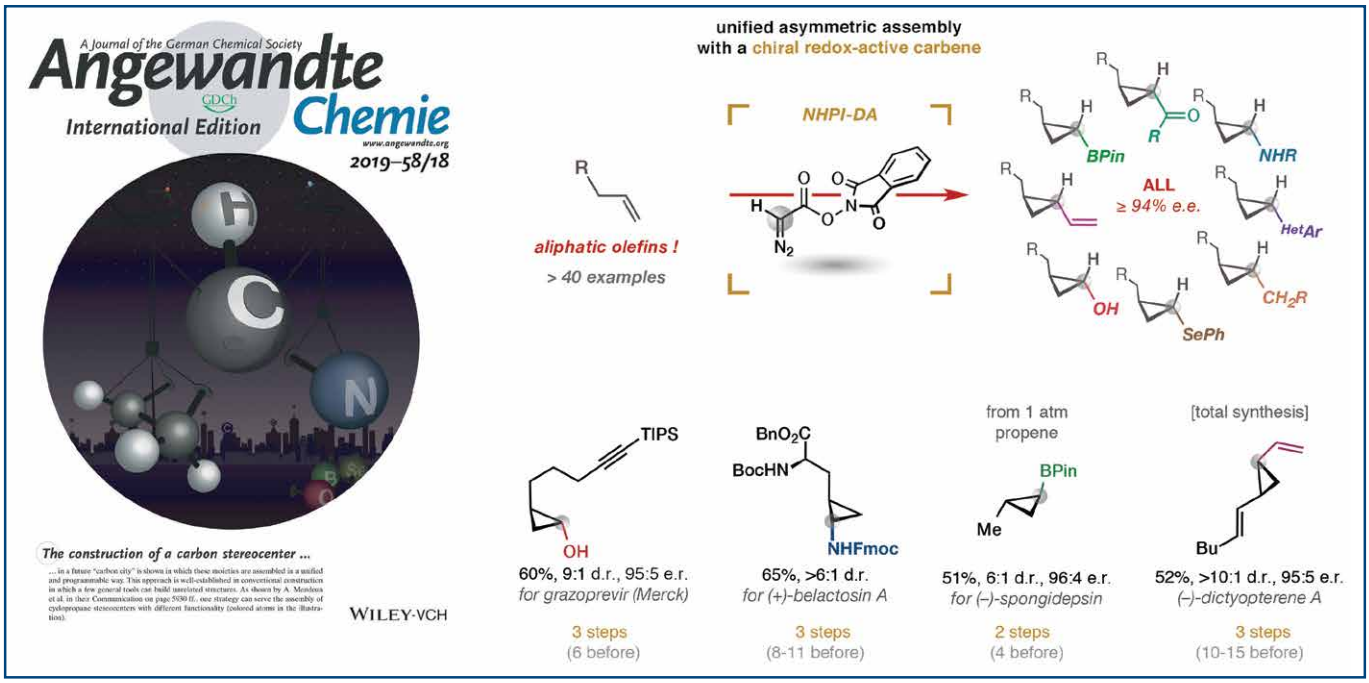
Key Organics Newsletter

Chemistry | Innovation | Quality

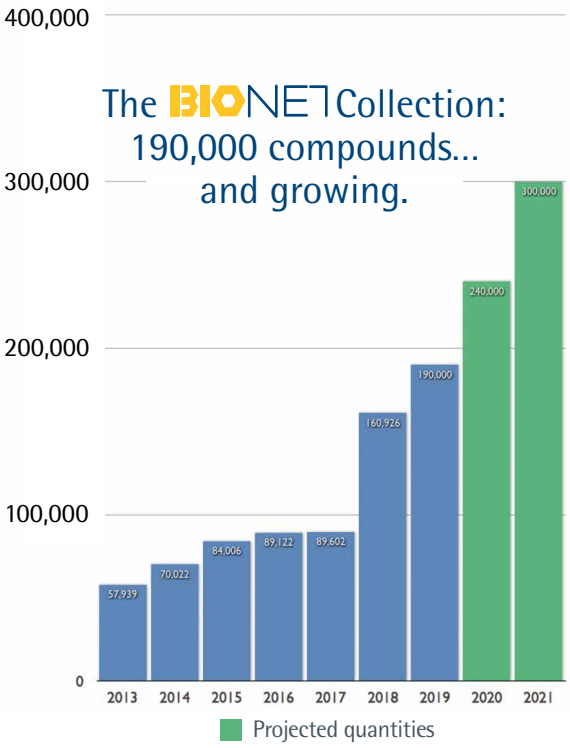
Enantioselective cyclopropane assembly

Key Organics is very pleased to exclusively offer a new reagent developed by Dr Abraham Mendoza and colleagues at Stockholm University as featured in the highly rated publication, *General Cyclopropane Assembly via Enantioselective Redox-Active Carbene Transfer to Aliphatic Olefins*

Marc Montesinos-Magraner, Matteo Costantini, Rodrigo Ramirez-Contreras, Michael E. Muratore, Magnus J. Johansson, Abraham Mendoza, Angewandte Chemie, Volume 131, Issue 18, Pages 5991-5996.



Within the paper, Dr Mendoza and colleagues introduce a practical and versatile diazocompound, and demonstrate its performance in the first unified asymmetric synthesis of functionalized cyclopropanes. NHPI-DA(13a) is available from Key Organics as SO-3001.



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Key Organics
Chemistry Services

Key Organics' Chemistry Services team offers bespoke synthesis solutions on an FTE/Research (fee-for-service) or one-off custom synthesis (fee-for-compound) basis. Offering a customer driven synthetic organic chemistry service on mg-small kg scale, our core competencies cover chemistries as diverse as heterocyclic chemistry, chiral chemistry, high pressure reactions, focused arrays for hit explosion or hit-to-lead optimisation, etc, and we undertake research projects in the areas of medicinal chemistry, agrochemistry, petrochemistry, aromachemicals, etc.

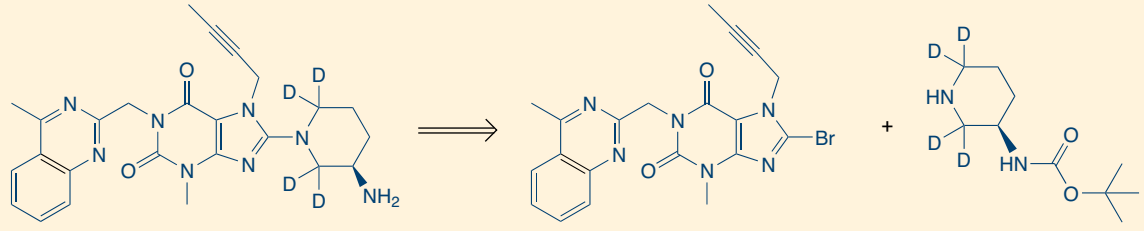
Our growing expertise in Stable labelled API's and Intermediates

One currently popular area for our clients is the synthesis of cold (non-radioactive) labelled reference standards. These materials are of use as tracers in the modeling of a number of chemical and biochemical systems, for example, in tracking the passage of an isotope, or an atom with a variation, through a reaction, metabolic pathway, or cell. The reactant is 'labeled' by replacing specific atoms by their isotope. The position of the isotopes in the products is measured to determine the sequence the isotopic atom followed in the reaction or the cell's metabolic pathway.

[$^2H_4$]-Linagliptin Case Study

We have developed considerable experience in the synthesis of ^2H- (deuterium) and ^{13}C-labelled materials. Whilst it is often possible to identify a suitably labelled commercially available building block with which to replicate the known non-labelled chemistry, there are instances where we need to devise an alternative synthesis route. Two such examples are to facilitate the late stage incorporation of the label, minimising the quantity – and cost – of material required, or where an appropriate building block is not available from the commercial pool.

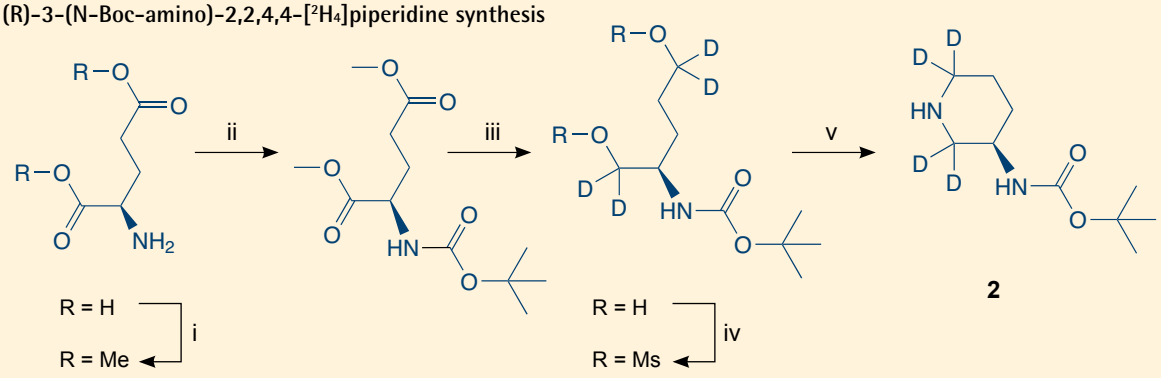
In one particular example, a customer required gram scale quantities of [$^2H_4$]-linagliptin. Linagliptin (CAS 668270-12-0) is a DPP-4 inhibitor developed by Boehringer Ingelheim for treatment of type II diabetes.[1] The availability of the late stage bromoimidazole building block **1** suggested placing the labelled atoms in the aminopiperidine component **2** (Scheme 3).



Scheme 3: [$^2H_4$]-Linagliptin retrosynthesis

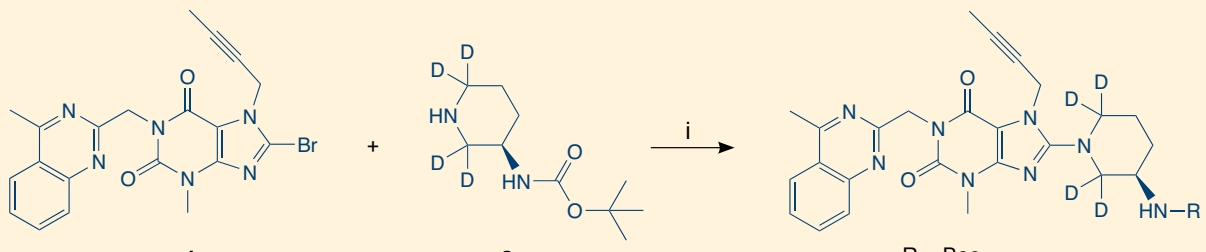
Adaption of a known method for the synthesis of enantiomerically pure 3-amino cyclic amines afforded the required building block (Scheme 4).[2] Commercial D-glutamic acid was esterified and N-Boc protected. Reduction of the two ester functions to the corresponding alcohols proceeded cleanly with sodium borohydride, and no loss of the Boc group was observed. Utilising the corresponding [$^2H_4$]-reductant afforded the chiral [$^2H_4$]-diol, which was converted to the bis-mesylate and cyclised to (R)-3-(N-Boc-amino)-2,2,4,4-[$^2H_4$]piperidine on treatment with ammonia.

Scheme 4: (R)-3-(N-Boc-amino)-2,2,4,4-[$^2H_4$]piperidine synthesis



Reagents: (i) c. H_2SO_4, MeOH; (ii) Boc_2O, Et_3N, Dioxane, H_2O; (iii) $NaBD_4$, $CaCl_2$, EtOH; (iv) MsCl, Et_3N, CH_2Cl_2; (v) NH_4OH, MeCN

With gram quantities of the labelled building block in hand, the synthesis of [$^2H_4$]-linagliptin was completed via reaction of the customer supplied bromoimidazole building block **1** with the aminopiperidine component **2**, followed by Boc-deprotection (Scheme 5).[1]



Scheme 5: [$^2H_4$]-Linagliptin synthesis

Reagents: (i)K_2CO_3, DMF; (ii) TFA, CH_2Cl_2

References:

1. M. Eckhardt, E. Langkopt, M. Mark, M. Tadayyon, L. Thomas, H. Nar, W. Pfrengle, B. Guth, R. Lotz, P. Sieger, H. Fuchs and F. Himmelsbach, *J. Med. Chem.*, 2007, **50**, 6450-6453
2. S.-H. Moon and S. Lee, *Syn. Commun.*, 1998, **28**, 3919-3926

NEW BRAIN PENETRANT COMPOUNDS IN ADVANCED *IN VIVO* STUDIES

Key Organics Ltd. & NTZ Lab Ltd. entered into advanced *in vivo* studies in relevant Parkinson´s and Alzheimer´s disease models

A new collection of structurally optimized compounds addressing the central nervous system (CNS) diseases, which have been recently entered into a development and marketing agreement between Key Organics Ltd. and NTZ Lab Ltd., is now available in the BIONET collection. The aim of the collaboration is to explore global markets for new generation of structurally optimized compounds addressing CNS diseases. This screening collection with experimentally-determined bioactivity, ADMET, bioavailability, and toxicity will address the need of new, robust, and multi-potent 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 initial set of nine target indazole-5-carboxamides (subclasses I–III) is part of large number CNS active compounds. Importantly, the newly discovered molecules are virtually and experimentally evaluated as multi-target acting monoamine oxidase (MAO)/histone deacetylase 2 (HDAC2) inhibitors by using a well validated, combined X-ray/modeling technology platform (Fig.1). In addition, the neuroprotective effects on TH-positive dopaminergic neurons and the induction of the neurite network outgrowth of the most promising compound **NTZ-1441** have been investigated in a Parkinson´s disease model (Fig. 2). These effects are associated with a good BBB penetration of all presented compounds that was confirmed in several *in vitro* assays.*

Due to the excellent ADMET profile combined with experimental confirmed "Proof-of-Principle" biological activity, selected representatives of this next generation multi-target compounds are now advanced for further *in vivo* studies in relevant Parkinson´s and Alzheimer´s disease models.

Fig. 1: Multipotency Screening (A) and estimated binding affinity ($K_{i\ HYDE}$ ranges) at hMAO-B (B) and hHDAC2 (C).

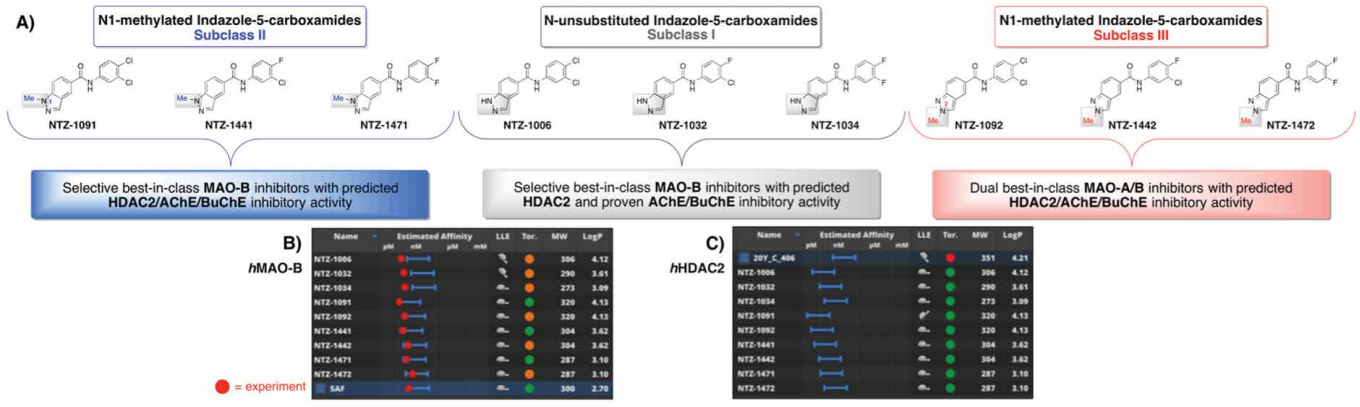
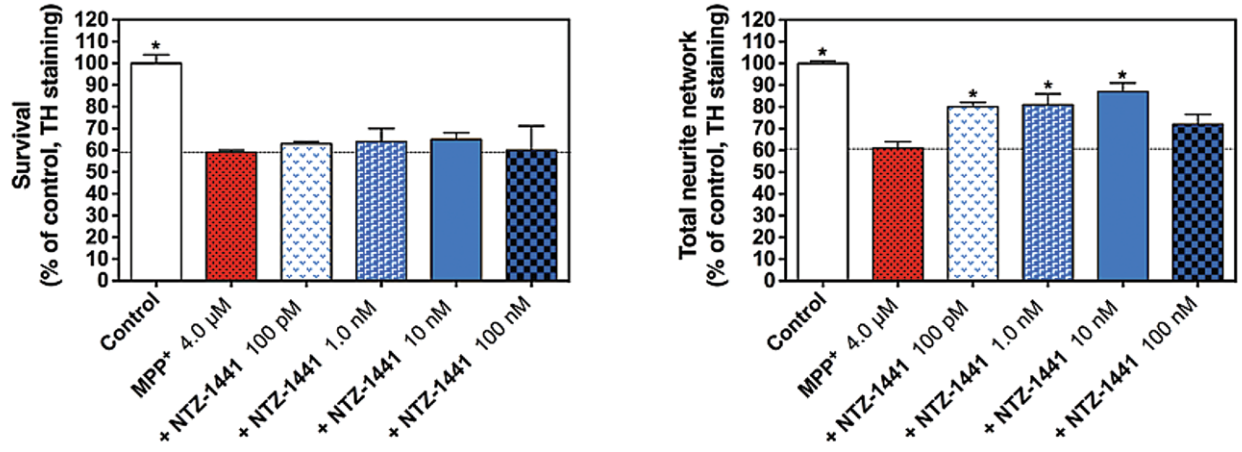


Fig. 2: Effect of **NTZ-1441** on dopaminergic neurons and neurite network after 48 hrs injury with MPP+.



* $p < 0.05$ *vs.* MPP* condition. Data are expressed as the mean ± SEM ($n = 4–6$) and were analyzed using one-way ANOVA followed by Dunnett´s test.

References:

*Carboxamides vs. methanimines: Crystal structures, binding interactions, photophysical studies, and biological evaluation of (indazole-5-yl)methanimines as monoamine oxidase B and acetylcholinesterase inhibitors. *European Journal of Medicinal Chemistry*, Volume 179, 1 October 2019, Pages 404-422. The article is available online at: https://authors.elsevier.com/a/1ZJ3xoqiQ0RRP

We will be exhibiting and/or attending the following exhibitions and conferences in the coming months:

August 21st	27th Annual GP2A Medicinal Chemistry Conference	Nottingham, UK
September 8th	20th RSC / SCI Cambridge MedChem symposium	Cambridge, UK
September 16th	Discovery On Target	Boston, US

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

Staff Interview Lorna Bankole, Analytical Chemist

Q: Please tell us a bit about yourself?

A: I have a BSc Honours degree in Applied Biochemistry from the University of Paisley with an MSc degree in Pharmaceutical Analysis from the University of Strathclyde along with 22 years of experience (& still counting) in the pharmaceutical/chemical industry. I have a good background in chromatography (HPLC/GC) & spectroscopy (UV, IR, NMR, mass spec). My hobbies/interests include roller skating, watching TV (quiz shows & hospital dramas), listening to music & playing computer games. I am particularly passionate about Morris Minor cars & am pleased to say that after around 30 years of interest in the Morris Minor I am now the proud owner of a 1959 Morris Minor 4 door saloon *(as seen in the photo above).*

Q: What is your role within Key Organics?

A: I am an analytical chemist & my main role is to test samples (either internal or external) by LCMS, NMR, GC.

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

A: The people I work with are great & I get a lot of interaction & involvement within my role in addition to the varied aspect of the role.

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

A: We strive to maintain on time delivery, providing a good quality service for both internal & external customers.

Key Organics

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