Accelerate Your Drug Discovery Process

Maybridge Screening Collections and Fragment Libraries

Diversity.
Quality.
Reliability.

MAYBRIDGE

Introduction and Index

The search for bioactive molecules in early-stage drug discovery using rapid compound screening and fragment-based design should not be like looking for a needle in a haystack. Selecting a highly diverse screening collection containing many drug-like compounds can reduce the element of chance and shorten the drug discovery process.

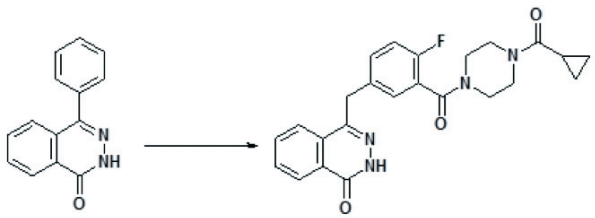
For over 50 years, Maybridge has been at the forefront of innovative screening compound design, fuelled by the desire to access novel molecules of pharmaceutical interest.

The Maybridge portfolio is driven by a keen understanding of the needs of the drug discovery scientist and designed to expedite the drug discovery process.

Track Record of Success

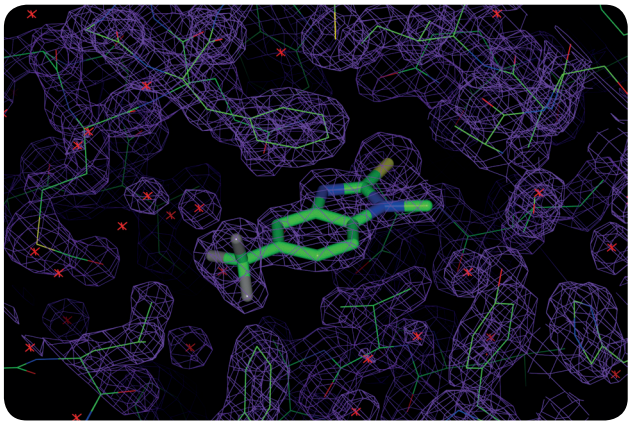
Over our 50+ year history in the screening business we have had numerous success stories documented in the peer reviewed literature and there are many available references across many therapeutic categories. The highlights are of course actual drugs that got their starting points from the Maybridge Screening Collection, including Celebrex, Nexavar, Stutent and most recently Olaparib:

Olaparib, trade name **Lynparza** was approved by the FDA in December of 2014 for the treatment of ovarian cancer. The compound from which this drug was developed came from the Maybridge Screening Collection. It is an inhibitor of poly ADP ribose polymerase (PARP), an enzyme involved in DNA repair. It acts against cancers in people with hereditary BRCA1 or BRCA2 mutations, which includes many ovarian, breast, and prostate cancers. This is the fourth drug that has been identified as being developed from the Maybridge Screening Collection.



Starting Maybridge Screening Compound → Olaparib

Index



Screening Libraries

Maybridge Screening Collection: A highly diverse set of over 53,000 hit-like and lead-like molecules widely acknowledged as a critical tool in screening campaigns.

When mapped against the World Drug Index (WDI), it was shown that the Maybridge Screening Collection expresses ca. 87% of the 400,000 theoretical drug pharmacophores, indicating a far-reaching coverage of active moiety space which can generate a high impact in any screening program.

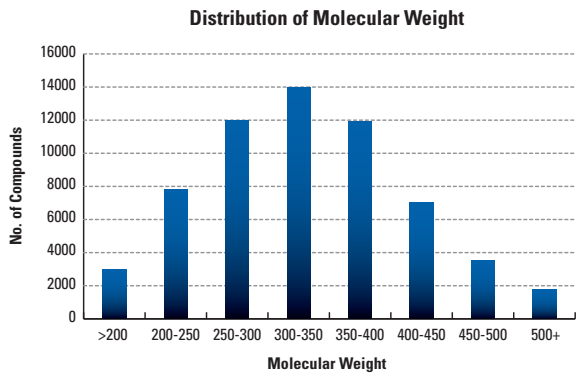
An independent study carried out by McGregor and Pallai comparing the diversity of 10 commercially available collections showed that out of those that were produced in-house, Maybridge had the most diverse library i.e. the most singletons (clusters with one member), and the highest number of clusters.

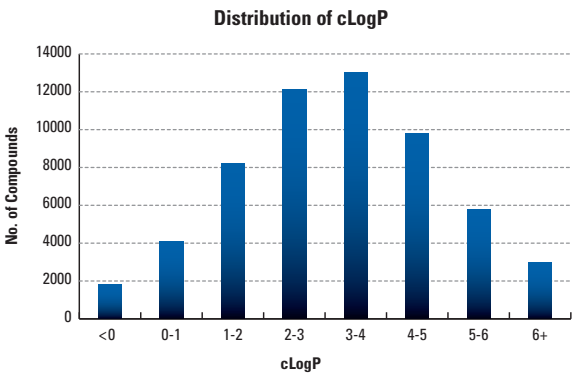
(Journal of Chemical Information and Computer Sciences; 1997; 37(3); 443-448.)

Using Daylight finger printing and Tanimoto Clustering at .9 similarity gives a total of 40,000 clusters and single compounds, which demonstrates the exceptional diversity of the library.

The Maybridge collection also has a high degree of 'hit-like' compounds. The paper by Teague et al.* summarises that the ideal hit profile of a compound is cLogP 1-3 and molecular weight 100-350. The information in the table below illustrates that a large portion of the Screening Collection complies with these hit-like characteristics.

(* S.J. Teague et al., Angew. Chem. Int. Edn., 1999, 38, No.24, pp3743-3748)





The collection also demonstrates classic characteristics of drug-like molecules, as defined by Lipinski's so-called 'Rule of 5'. These rules are essentially a pragmatic reduction of the common features of the drugs represented by the WDI. The collection is highly compliant with Lipinski's guidelines as the table shows.

Lipinski Rule** Maybridge Screening Collection

< 5 H-bond donors - 99.7% ≤5

< 10 H-bond acceptors - 99.8% ≤10

cLogP <5 mean log P 2.83 - 95% in range -0.11 to 6.3

Mol. Weight <500 mean mol. weight 308 - 95% in range 146-498

(** Lipinski, C.A., Lombardo, F., Dominy, B.W. and Feeney, P.J. (1996). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews 23 3-25.)

Success story

There are a great many success stories of our customers accelerating their drug discovery programs with Maybridge Screening Libraries. One of the most recent is shown below:

J. Biomol. Screen. 2015 Apr 16. pii: 10870571 - 15579637.
Novel Scaffolds of Cell-Active Histone Demethylase Inhibitors Identified from High-Throughput Screening. Wang W, Marholz LJ, Wang X.
Abstract

Jumonji C domain-containing histone demethylases (JHDMs) are epigenetic proteins capable of demethylating methylated lysine residues on histones proteins and for which high-quality chemical probes and eventual therapeutic leads are highly desirable. To expand the extent of known scaffolds targeting JHDMs, we initiated an unbiased high-throughput screening approach using a fluorescence polarization (FP)-based competitive binding assay we recently reported for JHDM1A (aka KDM2A). In total, 14,400 compounds in the HitFinder collection v.11 were screened, which represent all the distinct skeletons of the Maybridge Library. An eventual three compounds with two new scaffolds were discovered and further validated, which not only show in vitro binding for two different JHDMs, JHDM1A and JMJD2A (aka KDM4A), but also induce hypermethylation of their substrate in cells. These represent novel scaffolds as JHDM inhibitors and provide a basis for future optimization of affinity and selectivity.

Maybridge HitDiscover: the entire Maybridge Screening Collection pre-plated

A ready to screen collection of 52,160 Maybridge Screening compounds in dry film format, the compounds are of minimum 90% purity and pre-plated as 1umol dry films in 96 well plate format, offering exceptional diversity and outstanding value! Immediate re-supply is available on the majority of the compounds.

Maybridge HitFinder: representing the diversity of the entire Maybridge Screening Collection

HitFinder Compounds are selected from the Maybridge Screening Collection using a clustering algorithm employing standard Daylight fingerprints with the Tanimoto similarity index (J.Chem.Inf.Comput.Sci.,1999, 39, 747-750), clustering at 0.7 similarity. All compounds fit Lipinski guidelines for "Drug-likeness" (cLogP ≤5, H-bond acceptors ≤10, H-bond donors ≤5, Molecular Weight ≤500), and all have purity greater than 90%.

Each plate represents a unique sample from this selection, is diverse in its own right and available pre-plated at 1µmol in 96-well plates or .25µmol in 384-well microplates.

Maybridge HitCreator: The ultimate diversity screening library!

Our new offering takes away the need to choose between different libraries by providing the ultimate coverage of drug-like chemical space with a single library. Building on over 50 years of expertise in designing industry leading screening libraries the pre-plated HitCreator represents the diversity of a 550,000 compound library distilled to 14,000 molecules. Each HitCreator is conveniently supplied as dry films in 1μmol in 96 shallow-well plates or .25μmol in 384-well microplates.

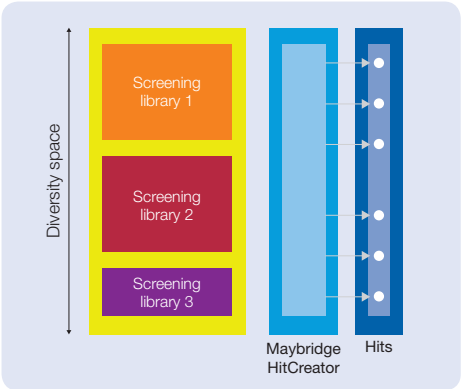


Figure 1. Importance of diversity in finding hits
The figure above illustrates how a highly diverse screening library will provide a greater hit probability than larger, but less diverse libraries.

Maybridge Fragment Collection

We offer 30,000 chemical fragments as well as world-leading pre-selected libraries to accelerate structure-based lead identification, from which our customers can select any combination of fragments to suit their own program.

Maybridge PAINS Free Fragment Library: the industry-leading library for fragment-based drug screening

Fragment screening has become a method of choice in the quest for rapid identification of new lead molecules in drug discovery due to the higher hit probability and fewer fragments needing to be screened.

The Maybridge fragment library is a proven, industry-leading library due to its diversity, pharmacophoric content and novelty.

Key Features and Benefits

- **Rule of Three (Ro3) compliance** delivers superior ADME attributes
- **Exceptional diversity** – Tanimoto similarity index of 0.66 based on standard Daylight fingerprinting
- **PAINS Free** – The library has been filtered to remove pan assay interference compounds (PAINS) avoiding false hits
- **Experimentally measured solubility** – guaranteed solubility of fragments in PBS buffer (1mM) ensures robust screening data and minimizes candidate attrition
- **Assured quality of >95%**, NMR spectrum available for each of the 2,500 compounds in both neat DMSO and Aqueous PBS with 1% DMSO
- **Optimised for SPR** – in collaboration with GE Healthcare a "Clean Screen" was run on a Biacore instrument to remove promiscuous binders
- **Chemically "clean"** – filtered to remove toxic and reactive groups
- **Pharmacaphore rich**, but not too complex to allow simpler interpretation of the results

Fragment hopping is facilitated with the entire Maybridge portfolio, for the full range visit www.maybridge.com

Leading the way in fragment library design since 2005

2005

The Maybridge Fragment Library

One of the first commercially available fragment libraries.

- 500 compounds cherry-picked from the pharmacophore-rich Maybridge building block portfolio

2007

The Maybridge Ro3 Fragment Library

The first commercially available Ro3-compliant library.

- 1,000 compounds computationally selected to provide:
  - Full "Rule of Three" compliance
  - High structural diversity
  - Pharmacophore-rich fragments containing "linker-friendly" groups for hit evolution

The Maybridge Fragment Collection

- 30,000+ compounds
- Convenient access to the extensive Maybridge portfolio
- Powerful tool for building bespoke fragment screening libraries or searching for hit analogues

2009

The Maybridge Ro3 Fragment Library Solubility Upgrade

The first commercially available fragment library with assured solubility.

- Experimental solubility data acquired for each of the 1,000 Ro3 library compounds
- Each member of the library has been shown to dissolve in:
  - DMSO at 200mM
  - PBS buffer (0.5% DMSO) at 1mM
- The solubility assurance is an additional benefit to the Ro3 and diversity advantages of the original library

2010

The Maybridge Ro3 Diversity Fragment Library

Developed with fragment screening practitioners to provide the most practical and powerful fragment library available.

- 1,500 compounds selected from the Maybridge and Acros Organics portfolios to provide:
  - Improved structural diversity
  - Access to a broader, pool of analogues for "fragment hopping"
  - "Linker-friendly" groups allow for rapid hit evolution
  - Full "Rule of Three" compliance
  - Experimental solubility assurance for each compound in the library

2011

Expansion of the Maybridge Ro3 Diversity Fragment Library

As the number of fragments that can be screened during assays increases due to the development of higher throughput biophysical techniques such as surface plasmon resonance, we have added additional fragments.

This has enabled us to:

- Increase the diversity by 30%
- Redesign the library to maximize the diversity across all the subsets
- Offer a greater number of high quality fragments for custom selection

2015

Redesigned the Maybridge Ro3 Library to be PAINS free

PAINS free – filtered to remove pan assay interference compounds

- Aqueous NMR for every compound
- Optimized for Surface Plasmon Resonance (SPR) – clean screen carried out on 3 different probes

The Maybridge Ro3 Diversity Fragment Library is available in the following formats

Available format	Comments
Entire library with **2,500** compounds	Highly recommended. It provides the highest probability to find a hit.
A **core set of 1000** compounds selected from the entire library	It encompasses the diversity of the entire library. Suitable for rapid and exploratory work.
A **supplement set** of the entire library with **1,500** compounds	For those who have screened the core set. It provides an additional probability to identify more hits.
Customised set	A selection of any number of fragments. Our searchable database allows rapid selection of fragments based on substructure and calculated Ro3 parameters.
Complete convenience	Custom weighed to your requirements in milligram or micromolar quantities, neat, in DMSO, in D6DMSO, in plates or vials.

Success story

The Maybridge Ro3 Fragment library has been the source of many successful fragment screening projects, for example:

Screening the Maybridge Rule of 3 Fragment Library for Compounds that interact with the Trypanosoma brucei myo-Inositol-3-Phosphate Synthase and/or show Trypanocidal Activity

Louise L.Major and Terry K. Smith

Biomolecular Science, The North Haugh, The University of St. Andrews, Fife, Scotland, KY16 9ST, UK
Correspondence should be addressed to Terry K. Smith, tks1@st-andrews.ac.uk

Received 31 December 2010; Revised 23 February 2011; Accepted 23 February 2011

Academic Editor: Wanderley De Souza

Inositol-3-phosphate synthase (INO1) has previously been genetically validated as a drug target against *Trypanosoma brucei*, the causative agent of African sleeping sickness. Chemical intervention of this essential enzyme could lead to new therapeutic agents.

Unfortunately, no potent inhibitors of INO1 from any organism have been reported, so a screen for potential novel inhibitors of *T. brucei* INO1was undertaken. Thus, an alternative approach of differential scanning fluorimetry to identify compounds that interact with *T. brucei* INO1 was employed to screen 670 compounds from the Maybridge Rule of 3 Fragment Library. This approach identified 38 compounds, which significantly altered the Tm of TbINO1. Four compounds showed trypanocidal activity with ED50s in the tens of micromolar range, with 2 having a selectivity index in excess of 250. The trypanocidal and general cytotoxicity activities of all of the compounds in the library are also reported, with the best having ED50s of approx. 20 μM against T. brucei.

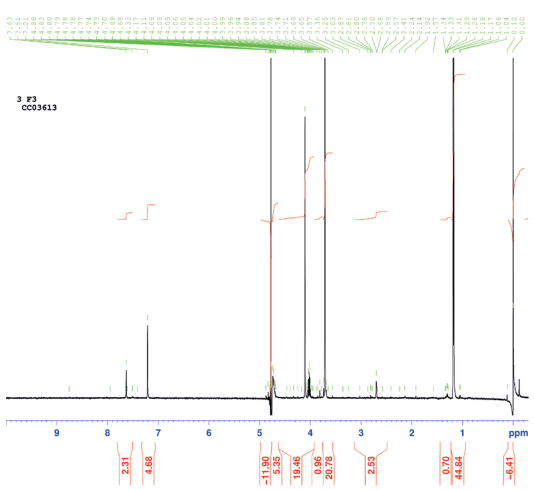
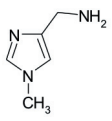


Figure 1. An example of an NMR spectra in PBS with the chemically encoded shift data of all of the compounds in the Fragment Library.



CC03613: (1-Methyl-1H-imidazol-4-yl) methylamine

Other specialty fragment libraries include:

The Maybridge Fluoro-Fragment Collection

More than 5,300 fluorine containing fragments ideal for ^{19}F NMR based fragment screening a diverse set of which is offered as the Maybridge ^{19}F Fragment Library

Maybridge ^{19}F Fragment Library - with ^{19}F NMR spectra for every compound

A fluorine labelled fragment library of 400 compounds, based on the Maybridge collection of fluorinated compounds. This library has been developed in collaboration with Argenta and the University of Kent and has been shown to have appropriate properties for fragment screening using biophysical methods.

The Maybridge Bromo-Fragment Collection

More than 1,500 bromine containing fragments for X-ray based fragment screening.

The Maybridge Pre-Fragment Collection

A valuable source of reactive "pre-fragments" for synthesising your own fragments or evolving your hits.

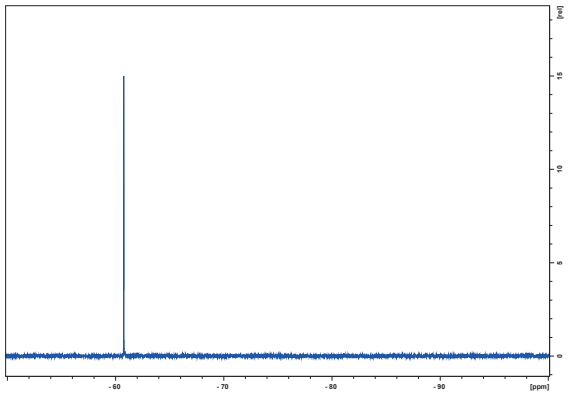
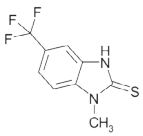


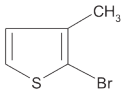
Figure 2. An example of a ^{19}F NMR spectra.



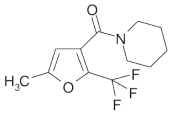
TG00013:
1-Methyl-5-(trifluoromethyl)-2,3-dihydro-1H-benzo[d]imidazole-2-thione

Examples of Maybridge Fragments

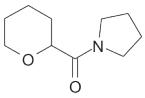
1. SPB08396:
2-Bromo-3-methylthiophene



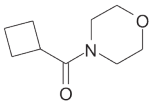
2. MO08143:
1-[5-Methyl-2-(trifluoromethyl)-3-furoyl] piperidine



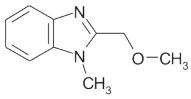
3. MO08161:
1-(Tetrahydropyran-2-ylcarbonyl)pyrrolidine



4. MO08170:
4-(Cyclobutylcarbonyl) morpholine

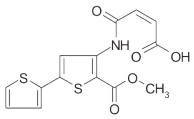


5. MO08563:
2-(Methoxymethyl)-1-methyl-1H-benzimidazole

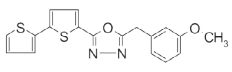


Examples of hits from HTS Compounds

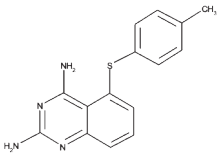
1. HTS01037:
4-{[2-(Methoxycarbonyl)-5-(2-thienyl)-3-thienyl]amino}-4-oxo-2-butenoic acid



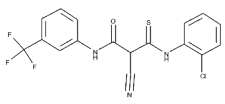
2. HTS11125:
2-(3-Methoxybenzyl)-5-[5-(2-thienyl)-2-thienyl]-1,3,4-oxadiazole



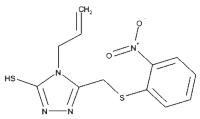
3. MWP01127:
5-[(4-Methylphenyl)thio] quinazoline-2,4-diamine



4. DP00477:
N1-[3-(Trifluoromethyl) phenyl]-3-(2-chloroanilino)-2-cyano-3-thioxopropanamide



5. DSHS00884:
4-Allyl-5-{[(2-nitrophenyl) thio]methyl}-4H-1,2,4-triazole-3-thiol



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To enquire about focussed libraries, such as kinase and protein-protein interaction libraries, please contact us for further information at Maybridge.Sales@thermofisher.com.

To place an order, contact your local distributor.

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