chemicals

MAYBRIDGE

Increasing success rates in your drug discovery research

Maybridge high-throughput screening and fragment libraries

ThermoFisher SCIENTIFIC

Introduction

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.

The Maybridge collection is widely recognized for its market leading diversity and quality. A highly diverse library of compounds that have the right chemical properties is much more likely to provide successful results than larger less diverse libraries with less suitable chemical properties.

In compound screening the size of your library is not as important as its diversity! After all why would you screen larger numbers of compounds at greater cost with less chance of getting positive results?

Maybridge libraries are designed to provide a high probability of discovering “hits” and thus accelerate your discovery campaigns!

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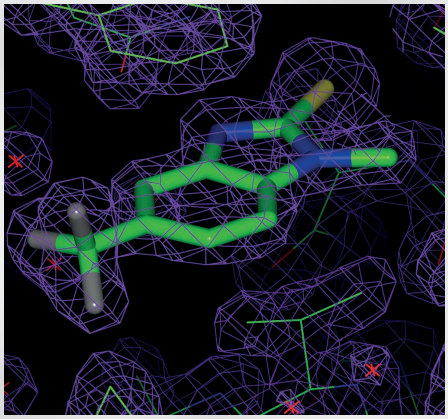
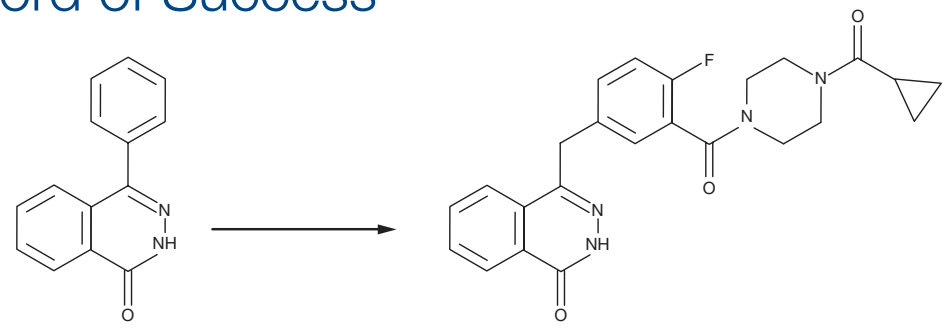


Track Record of Success



Maybridge Screening Compound

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.

Olaparib (Lynparza)

In 2019 the drugs advisory body NICE, the National Institute for Health and Care Excellence, said using olaparib at an earlier stage in treatment of ovarian cancer would bring the greatest benefit “and may have the potential to cure the disease”.

Lynparza is now also a “first-line” maintenance treatment for BRCA-mutated Metastatic Pancreatic cancer reducing the risk of disease progression or death by 47% in patients whose disease had not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

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.

Maybridge HitDiscover: the entire Maybridge Screening Collection pre-plated

A ready to screen collection of ~53,000 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 plates.

Maybridge HitCreator: The ultimate diversity screening library!

This library 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 500,000 compound library distilled to 14,000 molecules. Each HitCreator is conveniently supplied as dry films in 96 shallow-well plates or 384-well microplates.

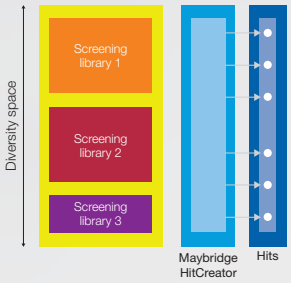


Figure 1. Importance of diversity in finding hits
The figure left illustrates how a highly diverse screening library will provide a greater hit probability than larger, but less diverse libraries.

Other specialty screening libraries available under the Maybridge brand in close collaboration with an external partner include:

- **Antiviral library:** over 8000 compounds chosen to facilitate the discovery of novel chemical entities with profound antiviral activity and improved safety profiles
- **Antibacterial library:** over 8,000 compounds that form a unique compound library for antibacterial research based on the proprietary natural product like scaffolds that provide great skeletal diversity combined with the presence of polar functional groups and multiple stereogenic centers.
- **Protein protein Interaction (PPI) library:** over 11,000 compounds selected through analysis of the PPI relevant chemical space and development of several strategies for building PPI-focused chemical libraries
- **GPCR library:** over 10,000 compounds selected for screening against G-Protein Coupled Receptors
- **Kinase library:** over 6,000 compounds chosen to facilitate the discovery of novel kinase inhibitors by providing access to our advanced collection of small molecules, fragments and macrocycles

Other focused libraries are available on request.

Success story

There are a great many success stories of our customers accelerating their drug discovery programs with Maybridge Screening Libraries, one example is shown below:

Antimicrob Agents Chemother. 2012 Sep;56(9):4718-28. doi: 10.1128/AAC.00957-12. Epub 2012 Jun 25.
Severe Acute Respiratory Syndrome Coronavirus Replication Inhibitor That Interferes with the Nucleic Acid Unwinding of the Viral Helicase nucleic acid unwinding of the viral helicase.

Adedeji AO1, Singh K, Calcaterra NE, DeDiego ML, Enjuanes L, Weiss S, Sarafianos SG.

Severe acute respiratory syndrome (SARS) is a highly contagious disease, caused by SARS coronavirus (SARS-CoV), for which there are no approved treatments. We report the discovery of a potent inhibitor of SARS-CoV that blocks replication by inhibiting the unwinding activity of the SARS-CoV helicase (nsp13). We used a Förster resonance energy transfer (FRET)-based helicase assay to screen the Maybridge Hitfinder chemical library. We identified and validated a compound (SSYA10-001) that specifically blocks the double-stranded RNA (dsRNA) and dsDNA unwinding activities of nsp13, with 50% inhibitory concentrations (IC(50)s) of 5.70 and 5.30 µM, respectively. This compound also has inhibitory activity (50% effective concentration [EC(50)] = 8.95 µM) in a SARS-CoV replicon assay, with low cytotoxicity (50% cytotoxic concentration [CC(50)] = >250 µM), suggesting that the helicase plays a still unidentified critical role in the SARS-CoV life cycle.

Hence, it is possible that SSYA10-001 inhibits unwinding by nsp13 by affecting conformational changes during the course of the reaction or translocation on the nucleic acid. SSYA10-001 will be a valuable tool for studying the specific role of nsp13 in the SARS-CoV life cycle, which could be a model for other nidoviruses and also a candidate for further development as a SARS antiviral target.

Maybridge libraries contain diverse and hit-like compounds

The collection was mapped against the 400,000 known theoretical pharmacophores in the World Drug Index (WDI), by Oxford Molecular and it was found that ca. 87% are expressed in this collection therefore providing a far-reaching spread of active moieties, which can generate great value in screening programmes.

An independent study carried out by McGregor and Pallai comparing the diversity of 10 commercially available collections and the Available Chemicals Directory (ACD), 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.

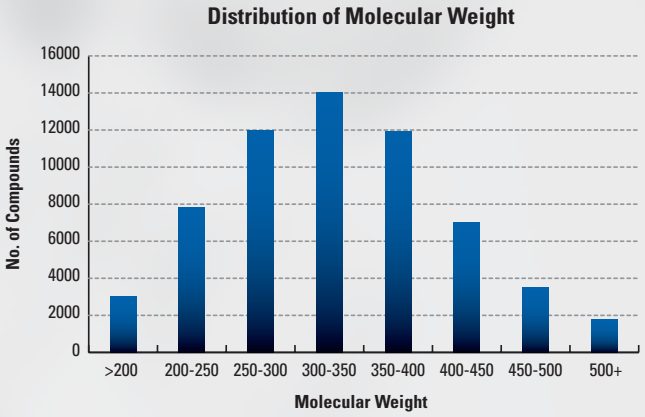
(Journal of Chemical Information and Computer Sciences; 1997; 37(3); 443-448.)

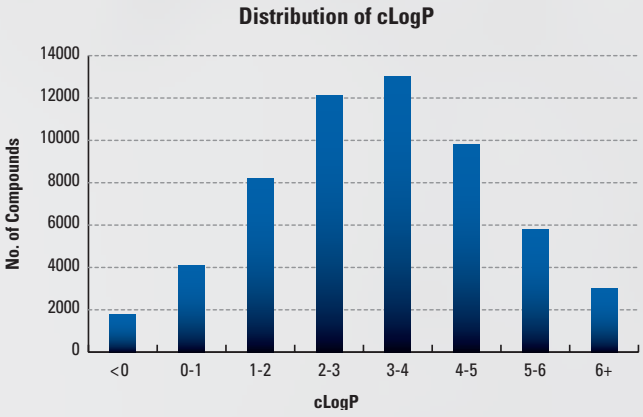
The Maybridge collection also has a high degree of 'hit-like' compounds. The paper by Teague et al*, summarises that the ideal hit profile of a compound is clogP 1-3 and molecular weight 100-350. The information in the table below illustrates that a large portion of the Screening Collection complies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

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

Benefits

- **Diverse –** A highly diverse library will provide a greater probability of obtaining "hits"
- **Hit-Like –** compounds containing the right chemical properties provide more successful results
- **Reliable –** High quality compounds ensure the hits you discover are an excellent starting point to accelerate your discovery campaigns





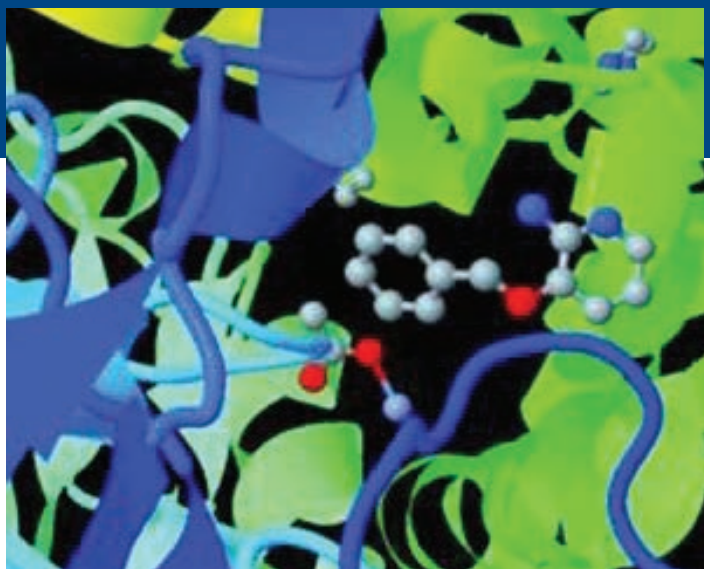
The collection also demonstrates classic characteristics of drug-like molecules, as defined by Lipinski's so-called 'Rule of 5'. These rules are essentially a pragmatic reduction of the common features of the drugs represented by the WDI. The collection is highly compliant with Lipinski's guidelines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

Lipinski Rule** Maybridge Screening Collection

< 5 H-bond donors 99.7% <5
< 10 H-bond acceptors 99.8% <10
cLog P <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.)**

Fragment Libraries



Maybridge 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 DMSO **AND Aqueous conditions**
- **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 → **2020**

The Maybridge Fragment Library

One of the first commercially available fragment libraries.

- 500 compounds cherry picked from the pharmacophorerich Maybridge building block portfolio

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
  - > Pharmacophorerich fragments containing "linkerfriendly" 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

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 benefi t to the Ro3 and diversity advantages of the original library

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

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

Redesigned the Maybridge Ro3 Library to be PAINS free

PAINS free – filtered to remove pan assay interference compounds

- Aqueous NMR for every compound
- Data for 5 fragment cocktails
- Optimized for Surface Plasmon Resonance (SPR) – clean screen carried out on 3 different probes

The Maybridge 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 fi nd a hit.
A **core set** the entire library with **1000** compounds	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:

Antimicrob Agents Chemother. 2018 Mar; 62(3): e01571-17.

Negatu DA1,2,3, Liu JJJ2, Zimmerman M4, Kaya F4, Dartois V4, Aldrich CC5, Gengenbacher M6,4, Dick T7,4.

Tuberculosis (TB) remains a global health threat, killing 1.34 million people in 2016. The high prevalence of drug-resistant Mycobacterium tuberculosis strains is a medical urgency and calls for the development of new drugs active against TB.

Several key antituberculosis drugs, including pyrazinamide, with a molecular mass of 123.1 g/mol, are smaller than the usual drug-like molecules. Current drug discovery efforts focus on the screening of larger compounds with molecular masses centered around 400 to 500 g/mol. Fragment (molecular mass < 300 g/mol) libraries have not been systematically explored for antitubercular activity. Here we screened a collection of 1,000 fragments, present in the Maybridge Ro3 library, for whole-cell activity against Mycobacterium tuberculosis.

Twenty-nine primary hits showed dose-dependent growth inhibition equal to or better than that of pyrazinamide. The most potent hit, indole propionic acid [IPA; 3-(1H-indol-3-yl)propanoic acid], a metabolite produced by the gut microbiota, was profiled in vivo. The molecule was well tolerated in mice and showed adequate pharmacokinetic properties. In a mouse model of acute M. tuberculosis infection, IPA reduced the bacterial load in the spleen 7-fold. Our results suggest that IPA should be evaluated as an add-on to current regimens and that fragment libraries should be further explored to identify antimycobacterial lead candidates.

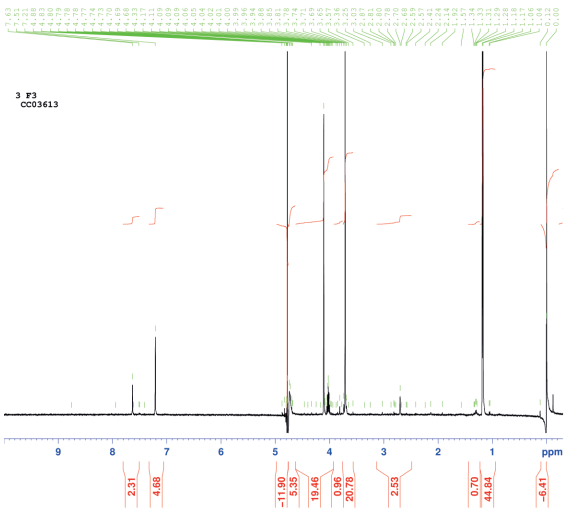
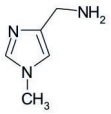


Figure 1. An example of an NMR spectra in PBS with the chemically encoded shift data of all of the compounds in the Fragment Library.



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

1H-NMR spectra in aqueous conditions is available on request and accelerates your screening workflow by avoiding having to run an 1H-NMR baseline

Other specialty fragment libraries include:

The Maybridge Fluoro-Fragment Collection

More than 5,300 fluorine containing fragments ideal for 19F 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 480 compounds, designed 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.

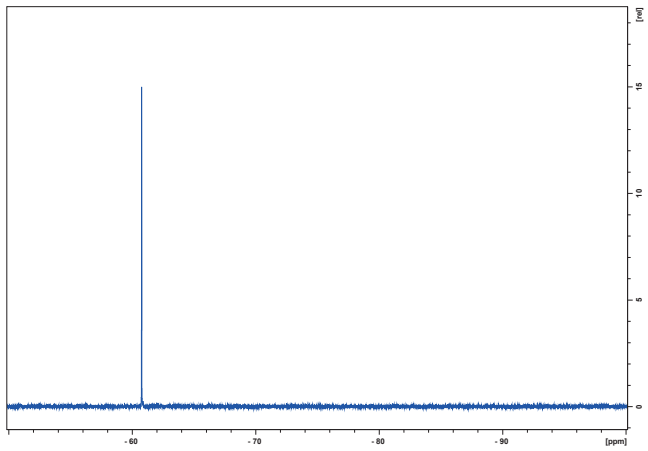
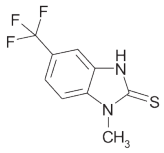


Figure 2. An example of a ^{19}F NMR spectra.

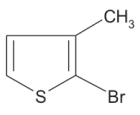


TG00013:
1-Methyl-5-(trifluoromethyl)-2,3-dihydro-1Hbenzo[d]imidazole-2-thione

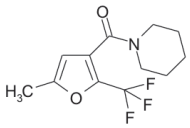
19F NMR spectra simplifies the interpretation of the spectra and thus facilitates the use of 'cocktailing' allowing multiple compounds to be screened together

Examples of Maybridge Fragments

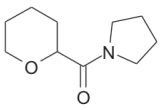
1. SPB08396:
2-Bromo-3-methylthiophene



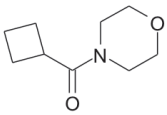
2. MO08143:
1-[5-Methyl-2-(trifl uoromethyl)-3-furoyl] piperidine



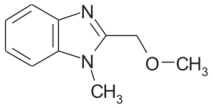
3. MO08161:
1-(Tetrahydropyran-2-ylcarbonyl)pyrrolidine



4. MO08170:
4-(Cyclobutylcarbonyl) morpholine

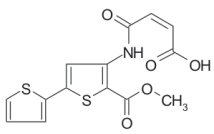


5. MO08563:
2-(Methoxymethyl)-1-methyl-1H-benzimidazole

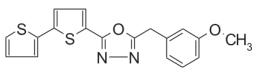


Examples of hits from high-throughput screening compounds

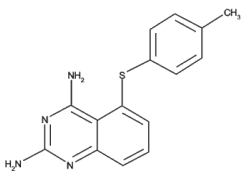
1. HTS01037:
4-{[2-(Methoxycarbonyl)-5-(2-thienyl)-3-thienyl]amino}-4-oxo-2-butenoic acid



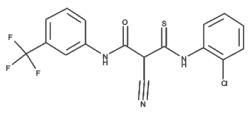
2. HTS11125:
2-(3-Methoxybenzyl)-5-[5-(2-thienyl)-2-thienyl]-1,3,4-oxadiazole



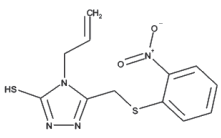
3. MWP01127:
5-[(4-Methylphenyl)thio] quinazoline-2,4-diamine



4. DP00477:
N1-[3-(Trifl uoromethyl) 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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