Enamine

For more information
Please contact us at **libraries@enamine.net**

# FRAGMENT LIBRARIES
# 2024

**www.enamine.net**

Enamine **Fragments Collection** is the largest source of in-stock fragments and the only one constantly updated and enhanced with the latest advances in synthetic chemistry. Comprising **260k compounds** and covering over 80% of the accessible chemical space, this Collection provides an excellent background for library design. We collaborate with the leading experts in Fragment-based Drug Discovery (FBDD) to bring the best starting points to your Fragment screening campaign. *Here we represent 15 carefully designed pre-plated fragment libraries that are immediately available for shipping or screening at Enamine.*

We improve the quality of our fragment libraries by providing more assurance on their aqueous solubility, stability in DMSO and PBS solutions, and general quality.

All Fragment Libraries are supported with Hit Confirmation and Follow-up services:

• All compounds pass rigorous QC control and solubility checks in DMSO. Guaranteed resupply from dry stock, 10mg+.

• Close analog in Screening Collection of 4 million stock compounds and REAL Database of 39 billion molecules. Free substructure and similarity search services.

• Fast follow-up Library Synthesis with 85%+ success rate.

## Hit Follow up Support

*Looking for analogues of your fragment hits or novel fragments for your discovery?*

The success of a hit finding campaign heavily depends on the quality of a screening library and the ease of the hit follow-up process. We offer seamless support in following-up hits identified after screening of our Compound Libraries.

• **Hit Confirmation:** dry samples resupplied from the same batch, QC check, HPLC repurification, chiral resolution, impurities identification. Resynthesis following in-house synthetic protocols.

• **Analogs:** search within 4 million stock Collection, REAL Database, and REAL Space. Enumeration of new hit follow-up libraries.

• **FTE chemistry & MedChem support:** versatile synthetic chemistry with access to the latest technologies. Projects.

• **ADME/Tox:** on-site full panel ADME tests, fast turn-around time

# Protein-Protein Interaction Library

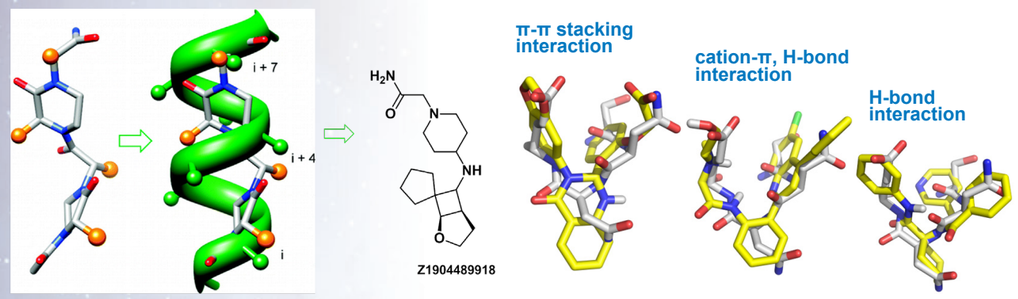
**• 3 600 compounds**

**• Fragments able to mimic protein structural motifs and hot-spot residues**

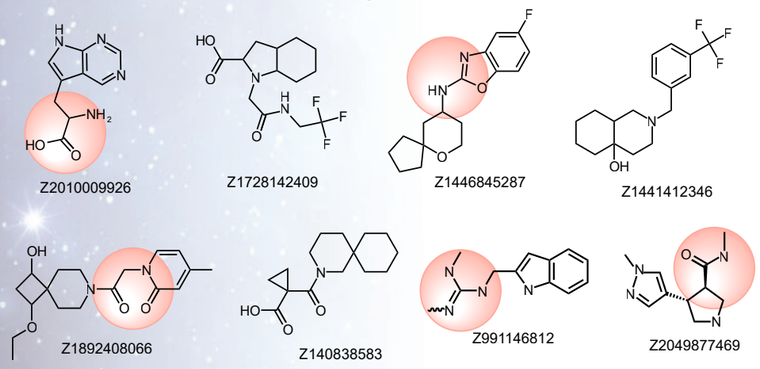
Protein-protein interactions regulate most aspects of the life cycle thereof being the most attractive and perspective target for contemporary drug development. Such intricate biological systems are often hard to tackle cost-efficiently using conventional HTS methods. However, the fragment-based approach showed fruitful results in the search for new PPI inhibitors. We created a PPI fragment library with a dedicated design that consists of systematical knowledge of common PPI inhibitors and selection by privileged structural motifs.

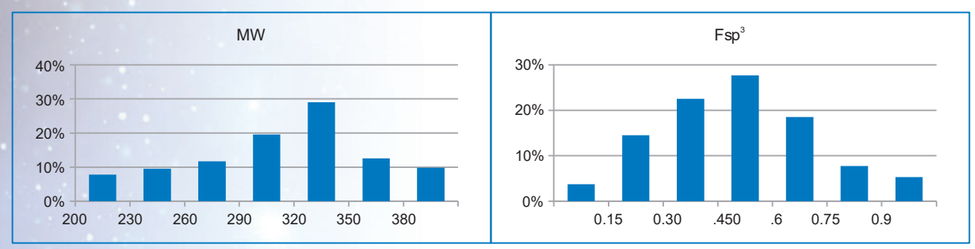
The library was designed with the main focus on molecules having alpha helix-like structures, able to mimic protein motifs. The “hot-spots” concept has also been used to select PPI fragments. Also since hydrogen bonds often play a crucial role in PPIs the preference was set for the molecules bearing at least one H-bond donor (> 70 %) and one H-bond acceptor (100%). In addition, we applied the “Decision tree” approach described previously in several papers.

**Traditional trhree residue approach**




**Examples of molecules in the library**






# High Fidelity Fragment Library

**• 1 920 pre-plated compounds**

**• Fragments of high MedChem tractability**

This fragment library was specially designed to feature high medchem tractability enabling researchers to grow interesting hits with confidence.

High medchem tractability of this set was achieved through structure review and selection by FBDD experts. We would like to thank Dr. Derek Cole, Dr. Dan Erlanson, Dr. David Lawson, and Dr. Xiaolun Wang for their involvement in the design of our **High-Fidelity Fragment Library**.

High quality: All compounds in the library passed turbidity tests to assure high solubility in water at 1 mM; all aggregators were filtered out. In addition, all fragments were screened by surface plasmon resonance (SPR) to remove any false positives.

Optimal molecular properties: Fragments in this set all have 9–16 heavy atoms, are moderately complex and have suitable physiochemical and shape profiles.

| Parameter | Range | Other restrictions |
|---|---|---|
| Heavy Atoms | **9 –16** | Heavy Ato No reactive groups or undesirable cores, PAINS and REOS filters |
| Mol Weight | 132 – 298 | |
| H-bond Donors | 0–2 | Turbidity at 1 mM in PBS and blank SPR assay filtering |
| H-bond Acceptors | 1–3 | |
| **ClogP** | **-1.0 – 2.5** | Chemotype control |
| TPSA | 20 –100Å$^2$ | Optimal and even distribution of molecular parameters |
| **logD$_{7.4}$** | **≤2.5** | |
| Aromatic rings | 0–2 | Purity of samples by LCMS/NMR ≥ 95% |
| Fused rings | ≤2 | |
| Scaffolds (BMLF) | 845 | No more than 1 S and 3 halogens, Cl and/or F only |

**110,500 Ro3 compliant** Enamine stock compounds

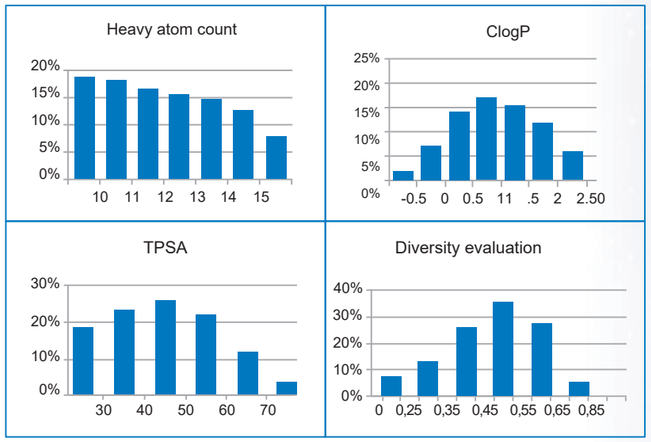
Strict structural filters and refinement by molecular parameters distribution

**Turbidity assay**, solubility measurements and filtering

**Diversity** improved through clustering

**SPR clean screen**

**High Fidelity Library 1,920 fragments**



# Essential Fragment Library

**• 320 compounds**

**• Elaborated tool for initial screen**

This small fragment library was designed and experimentally evaluated in collaboration with two research groups at the University of Cambridge for the primary screen *of novel or difficult targets*. All compounds passed solubility/turbidity and polarization measurements to remove any molecules that can interfere with the most common assays.

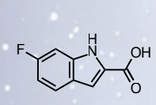
• *Increased hit probability* – the structures are based on frequently reported fragment hits and scaffolds derived from experimentally determined structures of protein-ligand complexes (PDB).

• *Suitable for different screening assays* such as fluorescence polarization anisotropy, SPR, ligand-based NMR, thermal shift etc.

• *Experimentally assured solubility* at 1 mM, 2mM concentrations in PBS buffer and at 200mM in DMSO. No aggregators.

• *Experimentally confirmed chemical stability* in aqueous buffer solution (pH 6.5–7.5) at 30 °C for 24 h (LCMS method)

| Molecular properties | Design | Filters |
|---|---|---|
| MW 110 - 250<br>ClogP -2,5 ▬ 2,5<br>HBA 0–5<br>HBD 0–3<br>TPSA, ≤ 75 Å$^2$ | Clustering-based diversity approach with manual review and structure analysis: indoles 20%, quinolines 18%, quinazolines 5%, morpholines 20%, pyrimidines 15%; fragments reported in PDB, CREDO, iPPI-DB | Reactive groups, toxicophores, groups with fluorescence interference at 488/520 nm and with affinity to CMD-coated surface |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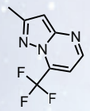
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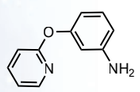
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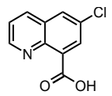
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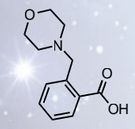
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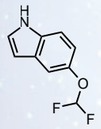
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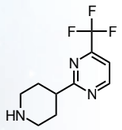
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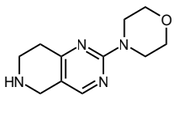
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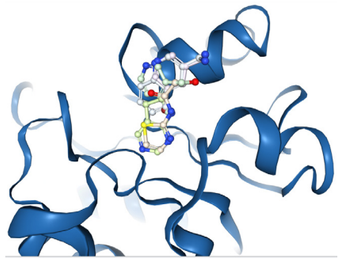


**Hit follow-up support:**

We provide hit resupply from dry powders with additional QC checks and unprecedented services for analogs search for all identified hits from our library including the following options:

• Analogs from 4M stock Screening Collection; substructure and/or 2D similarity search

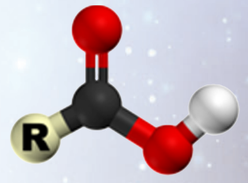
• REAL Database – substructure or similarity search in 38 billion compounds database



# Carboxylic Acid Fragment Library

**• 4 000 pre-plated fragments**

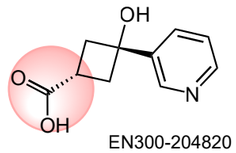
**• Designed for specific protein targets and sensible onset**



In response to the high demand for new and small carboxylic acids, we created a library of carefully selected molecules that strictly respond to FBDD requirements. This library mainly consists of compounds derived in the last three years from the previously established in-house program for designing and producing diverse carboxylic acids to enlarge the core Building Blocks Collection and diversification of coupling reagents.

Mainly this type of fragments has great potential for hit finding on new and difficult targets, e. g. protein-protein interactions (PPI), due to binding affinity to the so-called “hot-spot” residues. The Library has been pre-plated for most convenient access and prompt delivery in various customized formats.

**Representative examples of molecules in the Library**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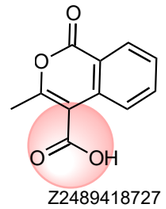
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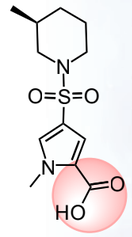
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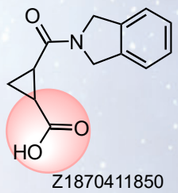
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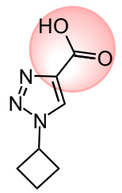
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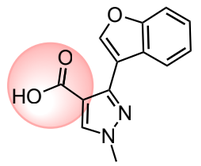
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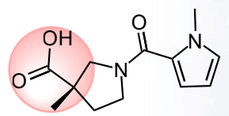
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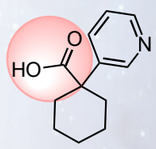
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HAC=15

The following molecular parameters were used to extract Enamine’s carboxylic acid fragments:

| Parameter | Range | Key Features |
|---|---|---|
| **MW** | 125 ,,, 300 | **High novelty and core diversity** |
| **HAC** | 9… 19 | |
| **Clog** | -2 …3 | **Fast follow-up with stock available analogues & synthesis** |
| **TPSA, Å$^2$** | 40,5… 80Å$^2$ | |
| **H-Acceptors** | ≤ 4 | |
| **H-Donors** | ≤ 3 | **Cherry-picking available, customer preferred delivery format** |
| **Ratable bonds** | 0… 3 | |

# MiniFrag Library

**• 80 compounds**

**• Guiding optimisation of fragment-derived lead compounds**

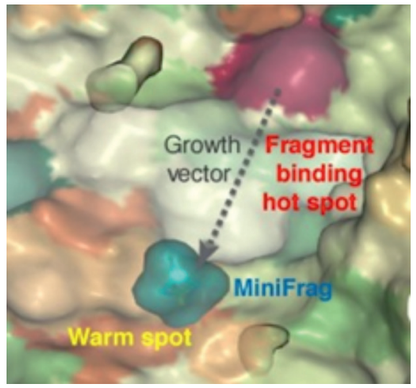
Reliable crystallographic data about the target protein is crucial for a successful drug discovery campaign. The combination of modern elaborated crystallographic methods with the smart design of chemical libraries can make a breakthrough in our understanding of protein structure changes and behavior. Novel crystallographic screening methodology reported by O'Reilly et al. in Drug Discovery Today 2019 was developed at Astex Pharmaceuticals, Cambridge, UK The high-concentration aqueous soaks were made with a chemically diverse and ultra-low-molecular-weight fragment library "MiniFrags" (heavy atom count 5–7). This allowed the identification of hot and warm spots on proteins. High screening hit rates reflect an enhanced sampling of chemical space. MiniFrag screening can represent thus a highly effective method for guiding the optimization of fragment-derived lead compounds.

We have collaborated with the Astex' scientists on making MiniFrag library available to the wide research community in the most convenient format. Screening at 1M suggests that the fragments would be provided dry, and ready for dissolution prior to protein soaking. Ultra-low molecular weight fragments (5-7 heavy atoms).

## Library format

| Catalog No. | Compounds | Amount | Format |
|---|---|---|---|
| **MiniFrag-10** | 80 | 10 mg | dry samples formatted in individual sealed glass vials suitable for dissolution |

| Parameter | Range |
|---|---|
| **MW** | 67 ,., 264 |
| **HAC** | 5,.,8 |
| **ClogP** | < 2 |
| **HBD** | ≤ 3 |
| **HBA** | ≤ 4 |
| **RotB** | ≤ 3 |
| **TPSA, Å²** | < 80 |




**Original paper:** *Drug Discovery Today*, Volume 24, Issue 5, 2019, Pages 1081-1086.



# CNS Fragment Library

**• 1280 pre-plated fragments**

**• CNS-friendly molecules capable of BBB penetration**

Despite intensive research, CNS drug discovery remains one of the most challenging areas for drug developers. Increased pollution, the aging population, and the pandemic all contribute to the increase in various CNS disorders. Regardless of great progress in diagnostics, this field remains in desperate need of new effective, and safe treatments for most serious and frightening disorders.

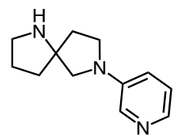
To help scientists at very early stages, we have developed a dedicated library of small fragments with the intention of progressing to potent CNS lead series. The analysis of all existing CNS drugs and drug candidates allows us to create special selection criteria and structural patterns to identify potentially active molecules. This algorithm has been applied to Enamine's Fragment Collection to reflect the most promising structures. The library was finalized with cluster-based diversity selections and manual review.

## Key features

**• High CNS scores: CNS MPO > 4.0 & QikProp CNS > 0**

**• Preferred scaffolds and chemotypes**

**• Rigorous MedChem filters and structure review**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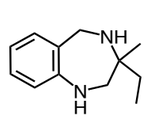
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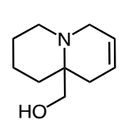
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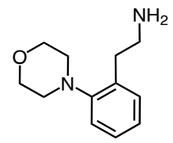
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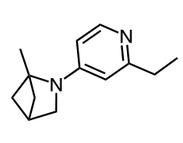
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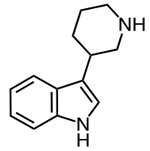
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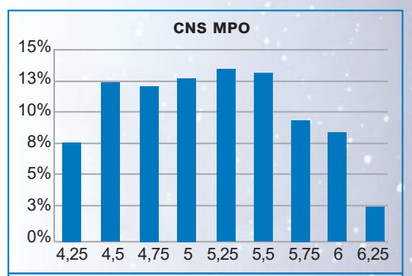
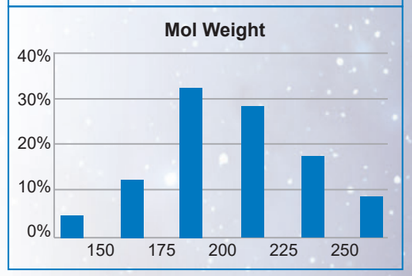



| Parameter | Range | Parameter | Range |
|---|---|---|---|
| MW | < 200 | RotBonds | ≤ 3 |
| ClogP | < 3.0 | ClogP-(N+O) | > -2.0 |
| PSA | ≤ 60 Å2 | F*sp*³ | 0.15 ... 0.8 |
| Hb Donor | ≤ 3 | Ring count | ≤ 3 |
| Hb Acceptor | ≤ 5 | Basic Nitrogen | ≤ 2 |
| Total H-bonding | < 8 | S, Cl atoms | ≤ 2 |
| Carboxylic acids | ≤ 1, no more than 10% of CA | | |
| No more than 2 amide bonds, 87% only with one amide bond | | | |
| No quaternary Nitrogen, no NO2, Br, I, P | | | |

## 3D Shape Diverse Fragment Library

**• 1 200 compounds**

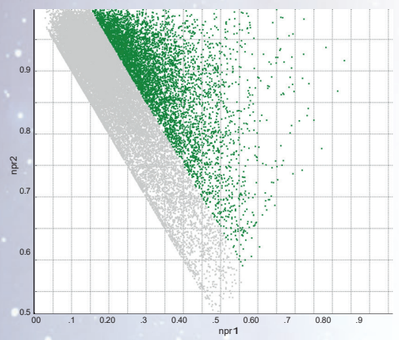
**• Unique 3D diversity among shaped molecules**

Enamine has been working on the synthesis of new *sp*³-rich heterocycles and expanding spirocyclic chemistry for already over 20 years. Our research in this area enabled the synthesis of a large variety of 3D-shaped molecules that are well-represented in Enamine's Screening Collection. Design and synthesis of aliphatic conformationally restricted core molecules, often exclusive to Enamine, followed by parallel chemistry modification led to many readily available analogs in REAL Database and REAL Space. Fast-accessible analogs are crucial in fragment-to-lead optimization and follow-up.

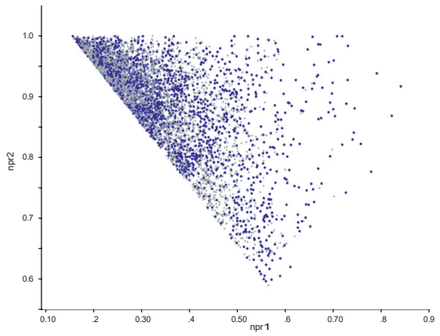
• Ro3 compliant molecules (>120k compounds) was refined with strict MedChem filters (FAF-Drugs3) and F*sp*³ cut off 0.35.

• Elimination of flat molecules and selection of shaped structures. 3D-dimensionality criteria: NPR1 ≥ 0.15; NPR2 ≥ 1.15 - value of npr1 (PMI plot 1).

• K-mean clustering of preselected 14,000 3D fragments has been carried out using NPR1/2 values. Only centroid molecules were included in the library, PMI plot 2.

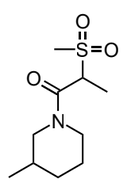



**PMI plot 1:** 8,000 3D Fragments (green dots) compared to other Enamine in-stock Ro3 compliant molecules (grey dots)




**PMI plot 2:** Final 3D Shape Diverse Fragment Library (blue dots) compared to other 3D Fragments (grey dots)

| Parameter | Range |
|---|---|
| MW | 120 ,,, 300 |
| Heavy atoms | 8… 19 |
| ClogP | -1.5 …3 |
| HBD | 0… 3 |
| HBA | 0… 3 |
| RotB | 0… 3 |
| TPSA, Å$^2$ | ≤ 80 |
| Aromatic rings | ≤ 2 |
| Chiral centers | ≤ 2 |
| S, Cl, Br counts | ≤ 1 |
| Nitrile, amide, sulfonamide counts | ≤ 1 |



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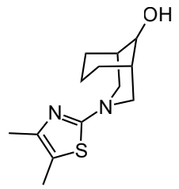

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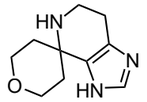

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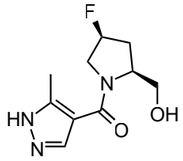


Z2060926323

## Single Pharmacophore Fragments

**• 1,500 compounds**

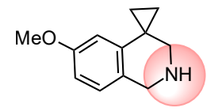
**• Simple interpretation of key binding with a protein target**

Recently, it was proposed that fragments with a single pharmacophore (*i. e.* polar group or other moiety for binding to a protein) have advantages over those with multiple, distally separated functional groups. This design approach is believed to maximize the advantages of FBDD, first of all through increasing synthetic capabilities of the fragment growth at the hit follow-up step. Applying these guidelines, we have created a library of single pharmacophore fragments.

• All the compounds pass both strict *"Ro2-like"* physicochemical and most stringent in-house *structural filters* excluding PAINS, highly reactive and toxic motifs.

• High variety of both pharmacophores and scaffolds bearing them

• Rapid follow-up/fragment growth using both readily available in-stock and synthetic analogs from Enamine Fragments, Screening Collection and REAL Database



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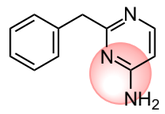

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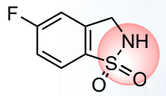

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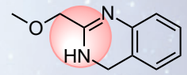

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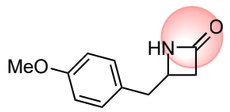

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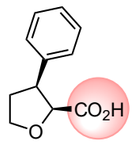

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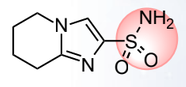

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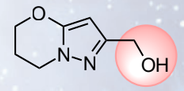

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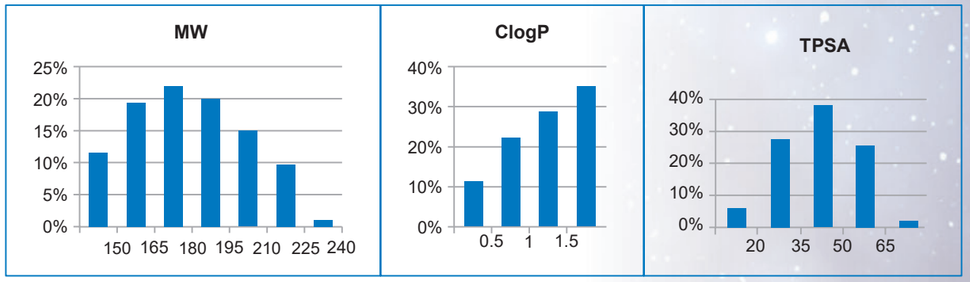


## Natural Product-like Fragments

**• 4 160 compounds**

**• Source of biologically validated starting points**

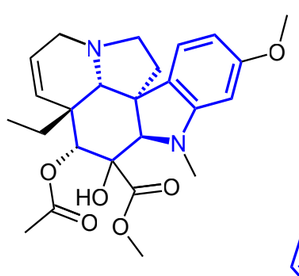
Screening of natural products has inspired discovery of remarkable number of drugs. Enrichment of small libraries with compounds possessing structural motifs validated by nature allows reaching better molecular profile and improves biological response. A special place in drug development should belong to Natural Product-like Fragments as promising starting points within attractive chemicals space.

• *The Scaffold Tree approach* was applied to the Universal Natural Product Database (UNPD) comprising over 200K compounds to extract initial Scaffold Set.

• MedChem structural filters and refinements were used in order to remove trivial chemotypes, PAINS and overpopulated cores resulting in the *Reference Scaffold Set* with *550 structures*.

• Substructure and similarity searches were applied to extract compounds bearing natural-like cores and moieties. *Scaffold frequency analysis* was carried out to finalize and optimise the library.

| Parameter | Range |
|---|---|
| MW | 100 …300 |
| HAC | 7... 22 |
| ClogP | < 3 |
| HBD | ≤ 3 |
| HBA | ≤ 4 |
| RotBonds | ≤ 4 |
| TPSA, Å$^2$ | < 115 |



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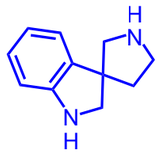

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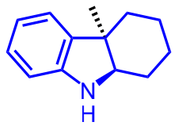

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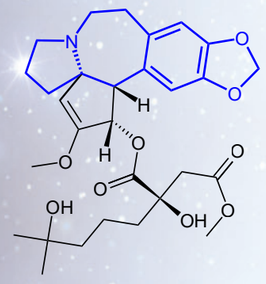
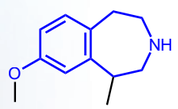


**Omacetaxine mepesuccinate**



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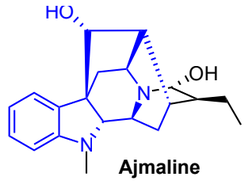
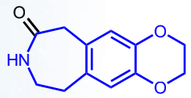


**Ajmaline**



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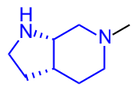

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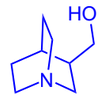

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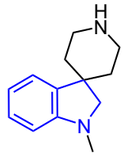


Z2900773053

## DSi-Poised Library

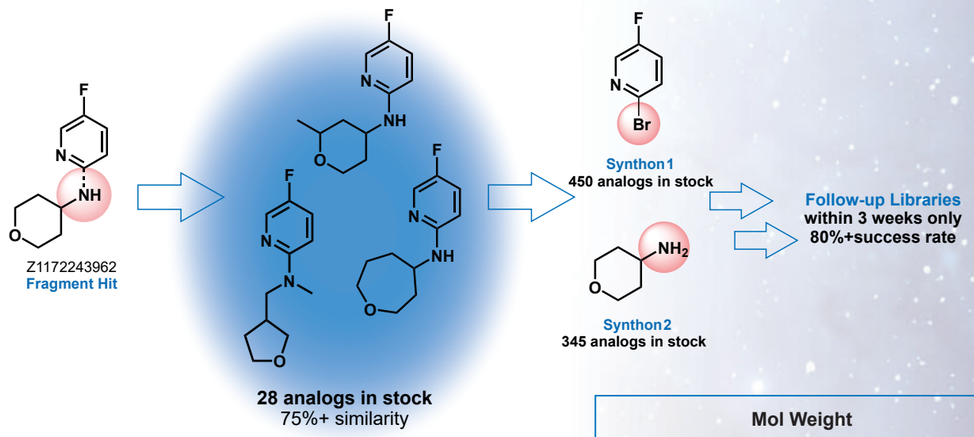
**• 860 compounds**

**• Designed for easy and rapid hit follow-up**

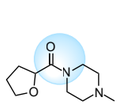
Fragment screening is an efficient way of establishing initial points for drug discovery. However, seemingly simple small molecules don't necessarily mean that their chemistry is not complex. Quite the contrary, fragment hits may be challenging to follow up and progress into a lead series.

It was shown by Cox et al., in Chem. Sci. 2016 that the compounds synthesised from a robust and general synthetic reaction can be prioritized for building a fragment library. Identification of so-called "poised" bonds in a fragment means that a library of analogs can be rapidly elaborated using standard parallel chemistry. The first poised library was developed at Diamond Light Source, UK (Diamond) and Structural Genomic Consortium, UK (SGC) in the frame of one of the iNEXT Joint Research Activities. Enamine collaborated with the joint research alliance in the design of a next-generation DSi-poised Library. DSI stands for Diamond, SGC, and iNEXT. On January 10, 2018 Diamond and SGC announced that Enamine would become a key supplier of poised fragment and analog libraries to the XChem Facility in Oxford, UK. All fragments contain "poised" bonds of one of the types defined in the original paper.

• *Guaranteed analogs in stock and REAL Database*
• *Rapid follow-up synthesis based on the initial hit*




### Examples of compounds in the library



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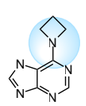
**Amide Coupling**



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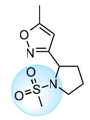
***N*-Arylation**



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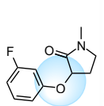
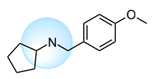
**Sulfonamide Coupling**

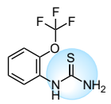


Z1217960891
**Ether synthesis**



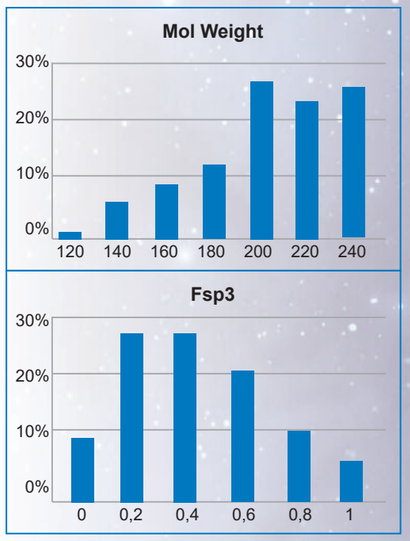
Z2856434940
**Reductive Amination**

Z274554872
**Ureas**



Z291279160
**Thioureas**

Z744754722
**Suzuki Coupling**



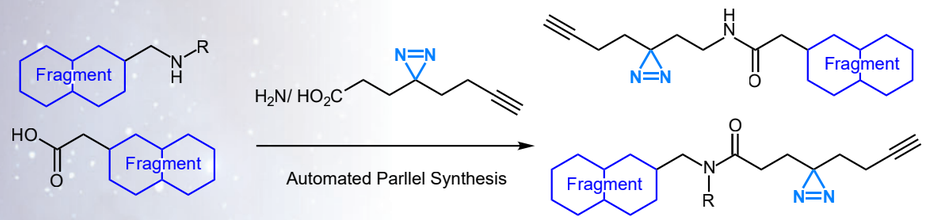
# Fully Functionalized Probe Library

**• 640 pre-plated compounds**

**• Designed for easy and efficient exploration of novel protein targets**

**Fully functionalized probes** are designed to speed up and simplify the early stages of drug development. The introduction of the diazirine photocrosslinking moiety along with the presence of a functional acetylene group allows screening of compounds directly in cells. Initially described in the Cell paper by Ben Cravatt this approach has been adopted by other research groups to a number of successful project, including reported by GSK researchers 'direct-to-biology' high-throughput chemistry screening platform.

Enamine currently has almost 3,000 fully functionalized compounds in stock and over 50,000 molecules in REAL Database. The most diverse compounds have been selected and sorted into a small library, which has been pre-plated for the most convenient and fast delivery to our clients

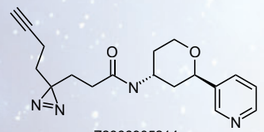



2 993 compounds in stock
56 693 REAL Photoaffinity fragments

**Key features**

- **Discovery of novel tractable protein targets**
- **Identification of the binding site of the POI**
- **Screening directly in cells**
- **Easy hit confirmation *via* LC-MS**
- **Next generation libraries can be rapidly synthesized through parallel chemistry**

This fully functionalized library has been designed based on the fragments with experimentally confirmed solubility in aqueous PBS at 1 mM concentration. In addition, we try to cover as much structural diversity as possible to have different chemotypes and pharmacophores within a limited number of compounds.

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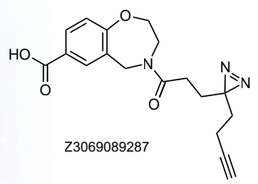


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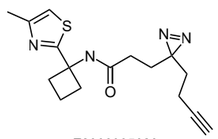


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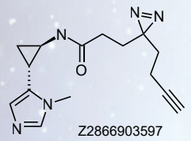


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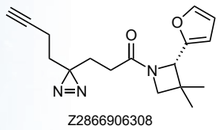


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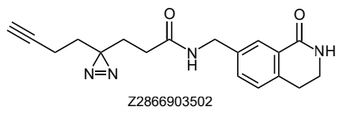



Z2866903502



# Fluorinated Fragment Library


**• 1 280 compounds**

**• Special set for $^{19}$F NMR-ligand based screening**

Enamine holds expertise in Fluorine chemistry with over 50 scientific papers in this synthetic research area published in the last 15 years. Our chemists are heavily involved in research on new synthetic methodologies for introducing fluorine atoms into a wide range of aliphatic/aromatic heterocyclic cores and various side chains.

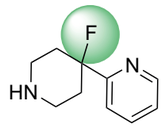
The fragment selection has been made with emphasis on the high structural quality of molecules and easy performance and interpretation of 19F NMR screening results. Very simple/trivial cores with widely populated chemotypes; compounds having more than two stereocenters, showing rotamers, diastereoisomeric mixtures, as well as molecules prone to aggregation have been removed from the library.

**Key features**

- **Experimentally confirmed solubility in aqueous PBS at 1 mM concentration and in DMSO at 200 mM.**
- **$^{19}$F NMR chemical shifts are provided for all compounds in DMSO and aqueous PBS.**
- **Full Ro3 compliance, no reactive and unstable compounds, stability in DMSO solution has been tested.**
- **15,200 in-stock analogues are available (MW 160…400)**

**Examples of the molecules Fluorinated Fragment Library**

Single-fluorine Fragments

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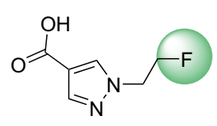
HAC=13

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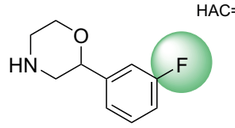


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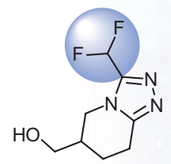
HAC=13

Difluoromethyl-substituted Fragment

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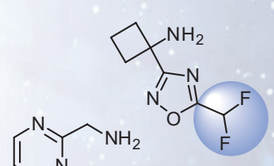


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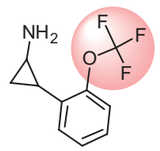
Z2092370865
HAC 11

Trifluoromethyl-substituted Fragments

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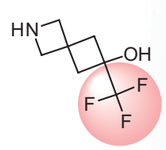


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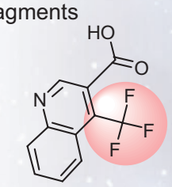


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