Enamine PPI Fragments

1470 compounds

Deliverable as entire set or as selected compounds.

Protein–protein interactions (PPIs) play major roles in many biological processes including signal transduction, regulation of cellular function, muscle contraction, etc. [1,2] Therefore targeting PPIs is an emerging task for MedChem projects and is associated with treatment of such diseases as cancer, Alzheimer's disease, genetic disorders. [3,4] Fragment-based drug discovery (FBDD) revealed one of the most fruitful strategies in PPI targeting [5] and several fragments inhibiting different PPIs have already been identified. [6,7] In view of mentioned Enamine **PPI Fragment** library was designed by picking out from our screening compounds and building blocks collection.

Considering the variety of bond types (hydrogen, charged, hydrophobic) which take part in PPIs formation [6] several approaches were utilized at library formation. The **"hot-spots"** concept [5] implying in the use of "key" amino acid residues involved in PPIs [8] was applied at design. A significant amount of the selected fragments contains groups/moieties which correspond to these hot spots (see the Figure 1). According to literature data [2,5] the PPI fragment sets are characterized by higher number of **acid-** and **base-containing fragments** in compare with standard ones. Therefore marked part of compounds bearing carboxylic and amino functionalities was included (see the Figure 2). Also since hydrogen bonds often play a crucial role in PPIs the preference was given to compounds having at least one **HBD** (> 82%) and/or one **HBA** (100%).

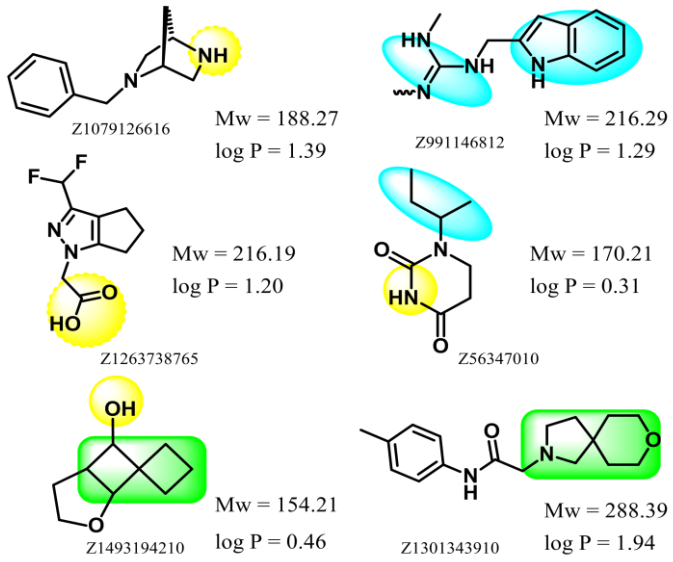

Figure 1. Representative set of Enamine **PPI Fragments**.

Parameter	Enamine **PPI Fragments**
MW	150 … 300
HAC	10 … 22
clogP	-2 … 3
HBD	≤ 3
HBA	≤ 3
RotB	≤ 3
TPSA, Å	≤ 95
Fsp^3	0.1 … 1
Purity	90+ %
Availability	10 mg

Novel chemotypes developed for PPIs include numerous examples of **3D-shape** molecules [9] corresponding to “Out-of-the-Flatland” concept. Therefore the 3D diversity was an additional selection criterion and significant number of picked out fragments posses features of 3D-shape structure (spiro-, bridged, fused bicyclic aliphatic motifs, see the Figure 3).

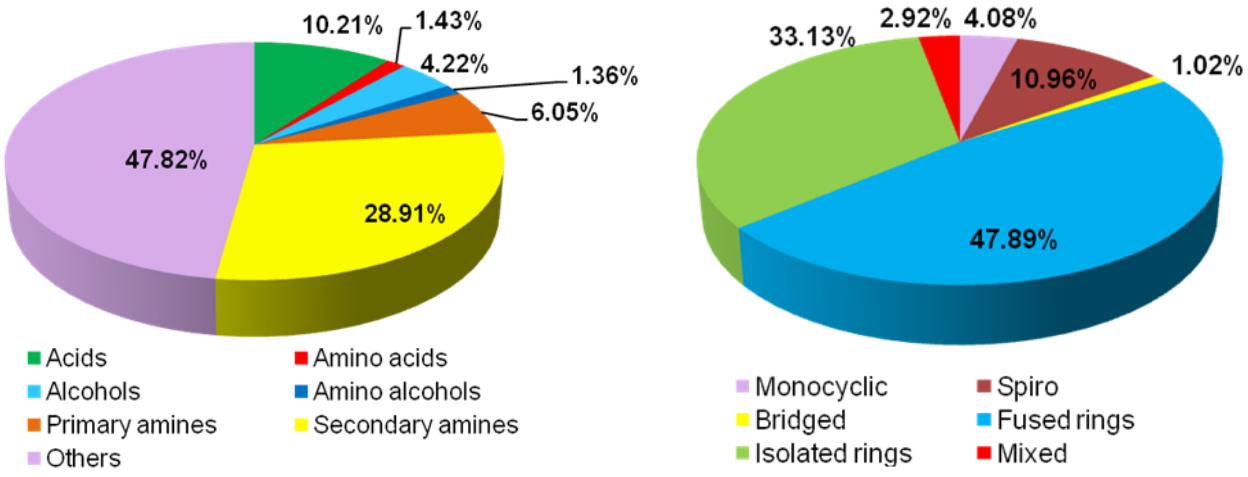

Figure 2. Chemical and structural diversity of Enamine **PPI Fragments**.

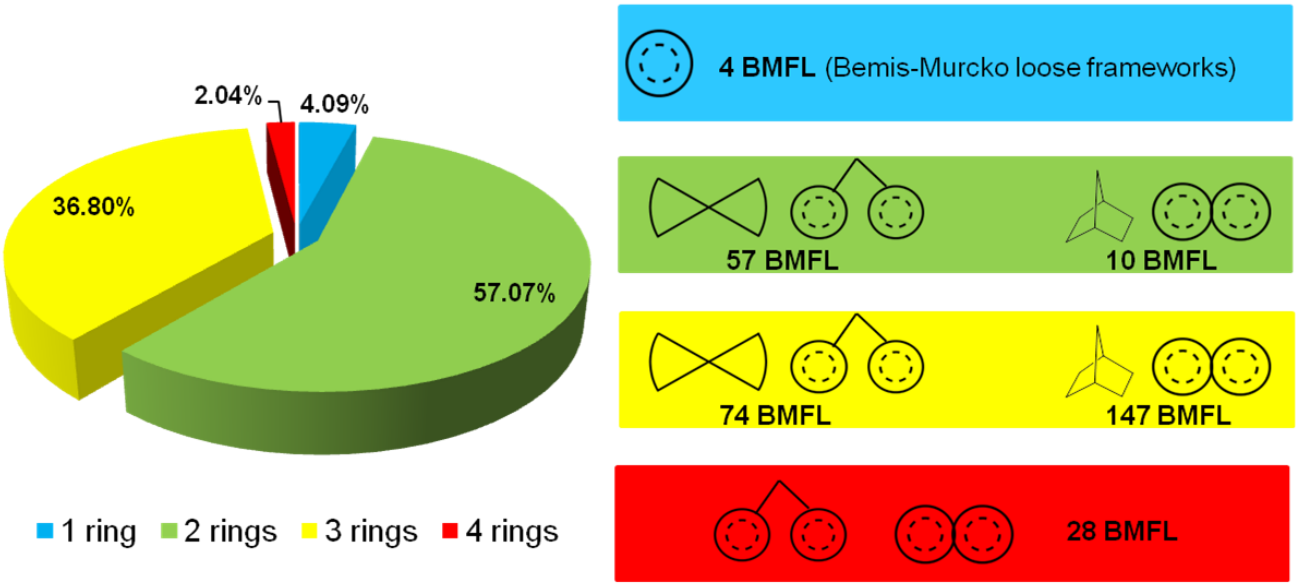

Figure 3. Analysis of structural diversity of Enamine **PPI Fragments**.

As far as for many potent PPI-ligands a balance of aromatics/ heteroaromatics and aliphatic is observed in their cores the Enamine **PPI Fragments** contains similar diverse set with different combination of heteroaromatic and aliphatic rings. The majority of selected fragments are characterized by high **Fsp^3**, the preference to compounds containing aliphatic cycles was given.

Enamine **PPI Fragments** are characterized by high diversity (the diversity coefficient is **0.90**). Included compounds are described with **320** different Bemis-Murcko loose frameworks [12], as far as each fragment contains at least one ring the structural diversity starting from ring count is described on the Figure 3.

All fragments correspond to “Rule of three” criteria specifying the fragments [10] and are constricted by internal structural filters accounting PAINS [11], toxic and reactive motifs. Structural and physical chemical profile of Enamine **PPI Fragments** is summarized in the Table and on the Figure 4.

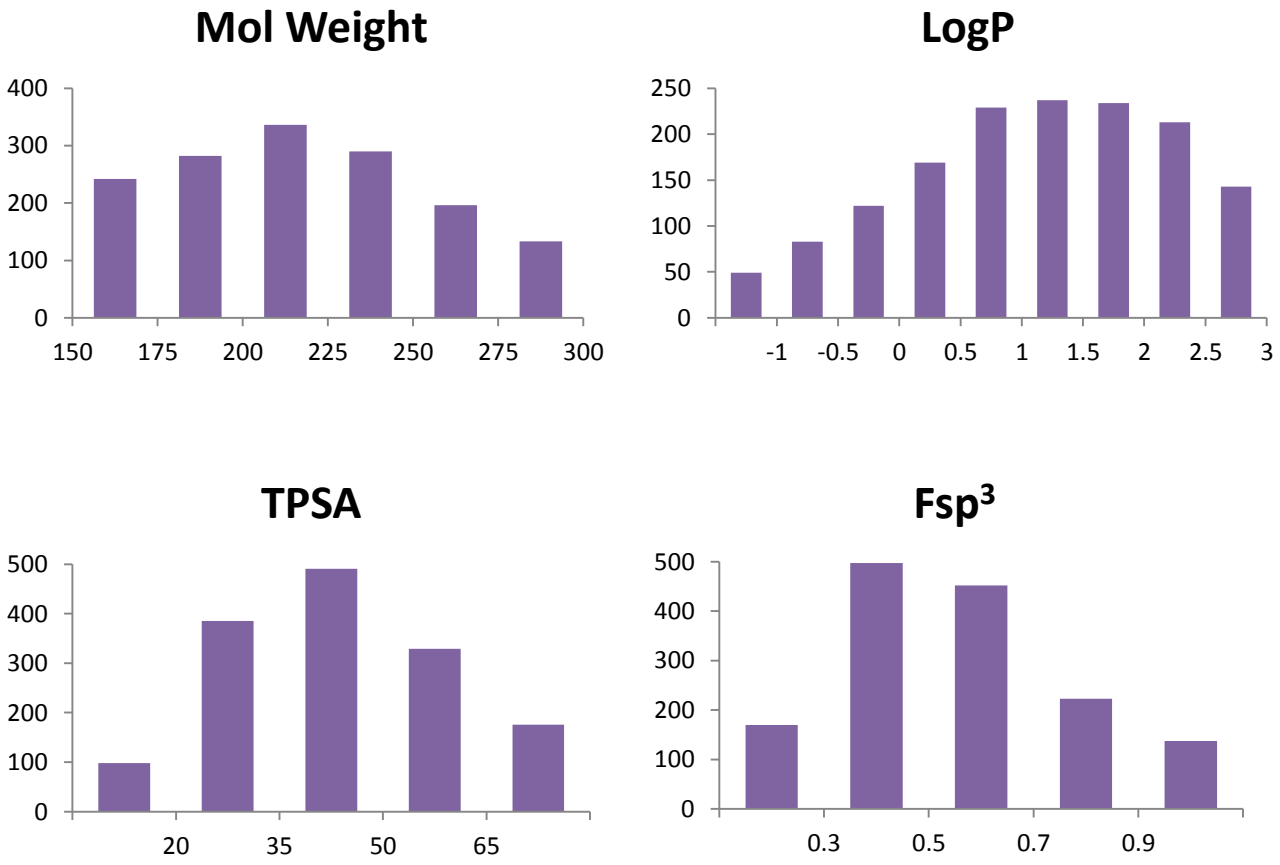

Figure 4. Physical chemical profile for Enamine **PPI Fragments**.

Also **Enamine Golden Fragment Library**, general **Enamine Fragments** as well as different focused fragment libraries (**Enamine Fsp^3-enriched, Flourinated, Brominated Fragments**) were developed exploiting the same filters and approaches. Furthermore the database of **Enamine Feasible Fragments** calculating near 465 k compounds and representing the biggest offered on the market “fragment space” was prepared by applying fragment identifying criteria to Enamine REAL DataBase collection. For further information please visit www.enamine.net.

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