Fragment Library with Experimental Solubility

Solubility is one of the essential physicochemical properties of drug candidates, and its measurement is an important component in the *in vitro* profiling of drug-like properties. An early assessment of this property in drug discovery projects provides valuable information for better interpretation of screening results and the design of new molecules.

Compounds with low aqueous solubility can often produce erroneous results during functional assays, thus, increasing the risk of obtaining false hits or leads. Besides, compounds with low aqueous solubility tend to be highly bound to plasma proteins with poor tissue distribution and increased potential of CYP enzyme inhibition. Measuring solubility at the early stages of the drug discovery process can identify potentially ambiguous activity data, such as false negatives due to poor solubility, therefore, improving the overall efficiency of activity screening and hit identification.

Taking into account the fact that solubility of fragments is the crucial feature that limits their use in various screening techniques of FBDD, Life Chemicals developed its in-house high-throughput technique of kinetic and thermodynamic determination of aqueous solubility of fragments from its proprietary Fragment Compound Collection [1-7].

There are almost **22,500** readily available fragments with confirmed aqueous solubility in the Library. Additionally, **6,500** fragments are soluble at high concentrations and included in the High Solubility Fragment Subset.

The solubility measurement method is indicated for each compound. The Library is regularly updated and expanded, mainly with newly synthesized compounds that are rigorously filtered by physicochemical and structural parameters.

The compound selection can be customized based on your requirements, cherry-picking is available.

Please, contact us at orders@lifechemicals.com for any additional information and price quotations.

For a **pre plated set** based on this Screening Library, please, explore our Pre-plated Fragment Screening Sets.

DMSO solubility measurement

The procedure includes visual determination of solubility by observing scattering of solutions at different concentrations in DMSO, and the results are presented as DMSO solubility intervals:

- ≥ 200 mM
- < 200 mM ≥ 100 mM
- < 100 mM ≥ 50 mM
- < 50 mM ≥ 20 mM

Thermodynamic Experimental Solubility Data in PBS

Almost **10,500** fragments possess experimental thermodynamic solubility data in PBS (Phosphate Buffer Saline) at pH = 7.4. The procedure includes quantity measurement of solubility, using HPLC for a compound solution at varying concentrations (up to 200 mM) in PBS. [7]

Note: Solubility results obtained by this method might be different from similar kinetic solubility measurements, where DMSO was used as a co-solvent, which may exponentially increase compound solubility.

Kinetic Experimental Solubility Data in PBS

The procedure includes visual determination of solubility by observing scattering of solutions under the following conditions:

- 5 mM in phosphate buffer with 2.5 % DMSO
- 1 mM in phosphate buffer with 0.5 % DMSO

It is measured for over **12,000** compounds, mainly from the Life Chemicals Advanced Subset of General Fragments. Approximately 81 % of these fragments are soluble in phosphate buffer at 1 mM, and 66 % – at 5 mM.

High Solubility Fragment Subset

All compounds included in the High Solubility Fragment Subset (**6,500** fragments) possess minimum experimentally confirmed solubility in PBS at 1 mM and in DMSO at 200mM, measured by the thermodynamic method using HPLC.

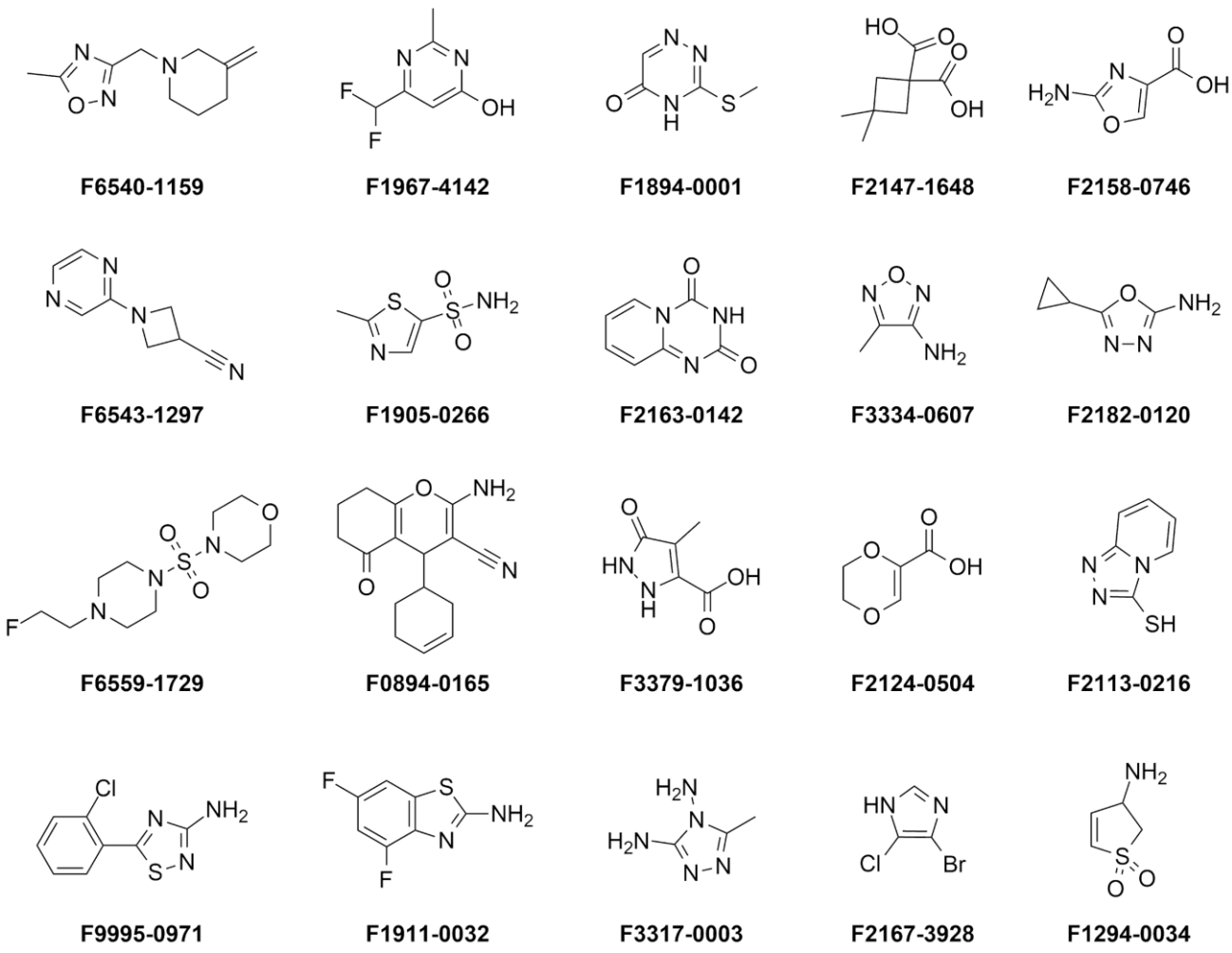

Figure 1. Representative compounds from Fragment Library with Experimental Solubility Data

References

1. Avdeef, A., C.M. Berger, and C. Brownell, *pH-metric solubility. 2: correlation between the acid-base titration and the saturation shake-flask solubility-pH methods.* Pharmaceutical research, 2000. 17(1): p. 85-89.
2. Avdeef, A., *Solubility*, in *Absorption and Drug Development*2012, John Wiley & Sons, Inc. p. 251-318.
3. Alsenz, J. and M. Kansy, *High throughput solubility measurement in drug discovery and development.* Advanced drug delivery reviews, 2007. 59(7): p. 546-567.
4. Hoelke, B., et al., *Comparison of nephelometric, UV-spectroscopic, and HPLC methods for high- throughput determination of aqueous drug solubility in microtiter plates.* Analytical chemistry, 2009. 81(8): p. 3165-3172.
5. Tihanyi, K. and M. Vastag, *Solubility, delivery and ADME problems of drugs and drug- candidates*2011: Bentham Science Publishers.
6. Valko, K., *Physicochemical and biomimetic properties in drug discovery: chromatographic techniques for lead optimization* 2013: John Wiley & Sons.
7. Pitt, A., *High-throughput screening to determine aqueous drug solubility: the author describes an aqueous solubility screening assay methodology that uses 96-well plates and compares performance to the conventional shake-flask method.* Pharmaceutical Discovery, 2005. 5(1): p. 46-50.