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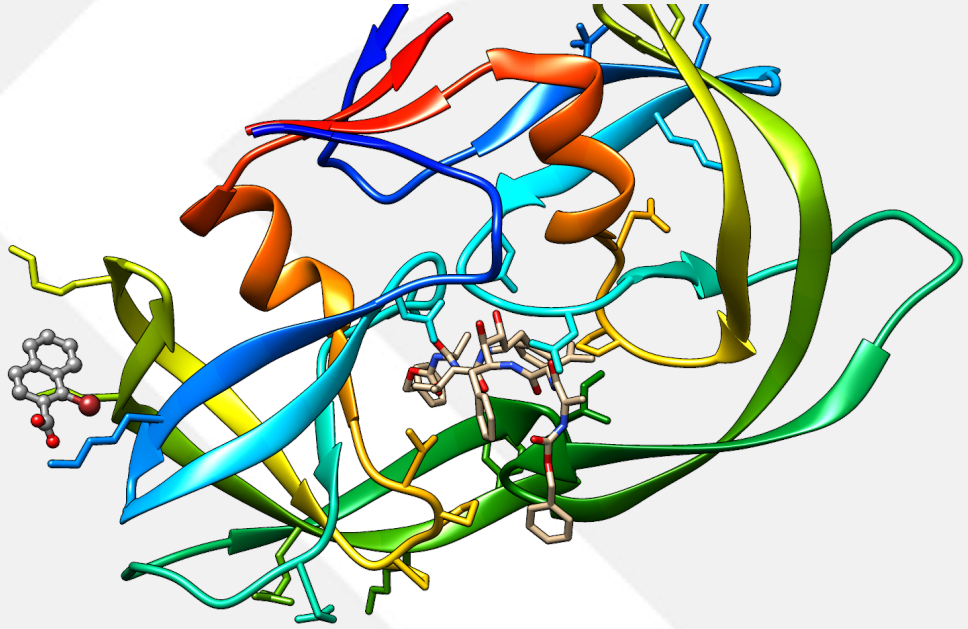
Библиотеки соединений, содержащие фрагменты 19F- и Br-

Crystallographic and ^{19}F NMR fragment-libraries

Fluorine Fragments (1480 compounds)



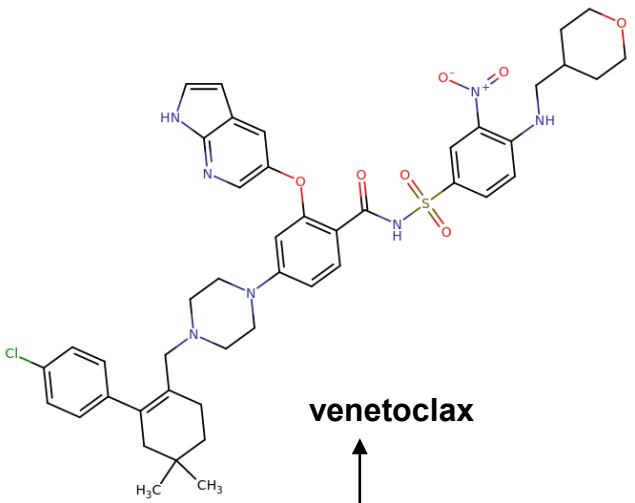
Bromine Fragments (629 compounds)

Growing interest in fragment-based drug discovery (FBDD)

The interest in FBDD from biotechnology, pharmaceutical companies and academia is constantly growing. FBDD is applied to a wide range of drug targets and has been used in the development of four marketed drugs: vemurafenib, venetoclax, erdafitinib, pexidartinib [1, 2]

Main Fragment Based Screen Methods:

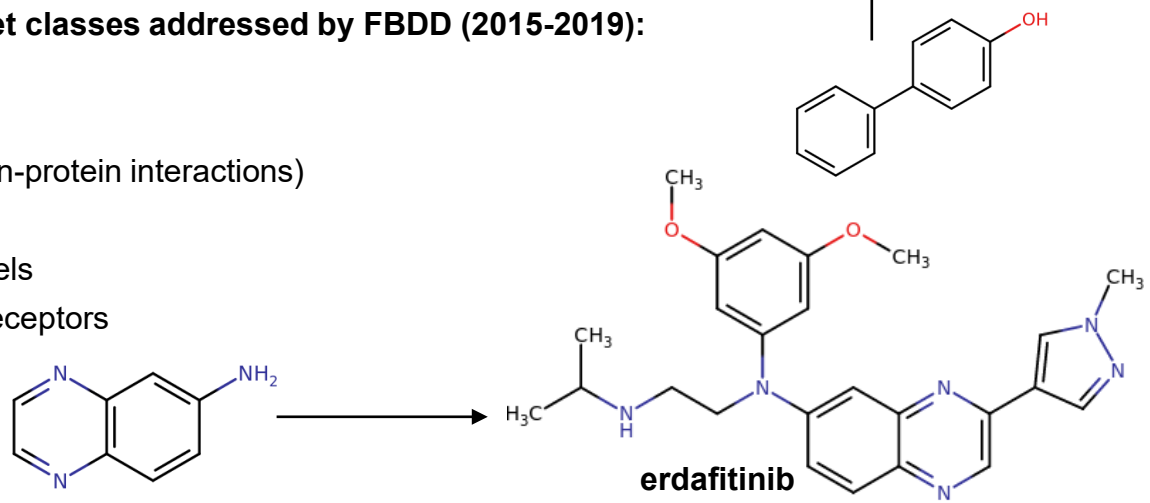
- X-ray
- NMR (ligand-observed,
- thernal shift, protein observed)
- Biochemical Assays
- SPR (surface plasmon resonance)
- MST (Microscale Thermophoresis)
- Literature search
- Virtual screening



venetoclax

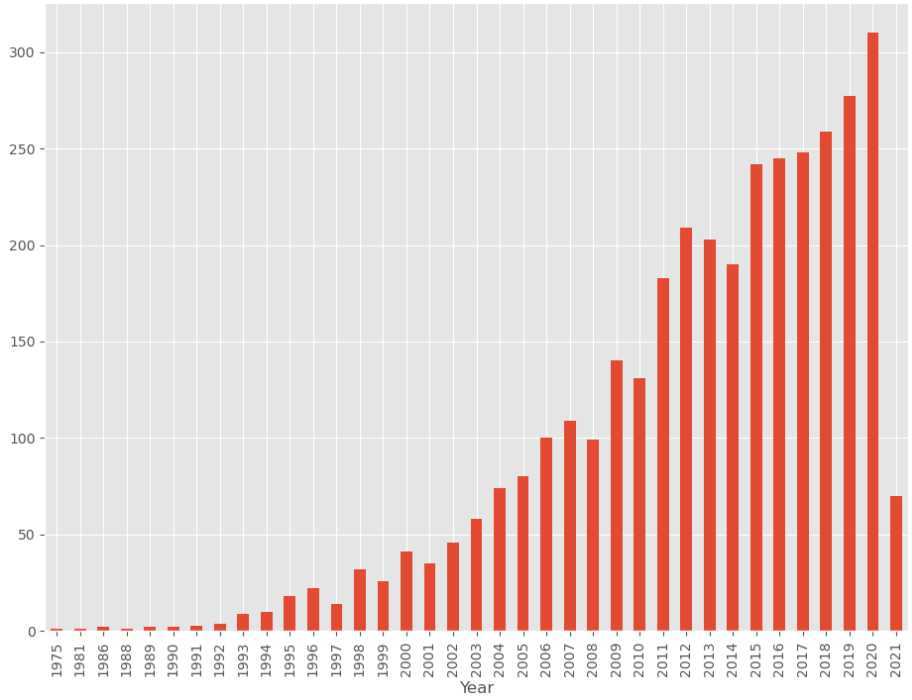
Popular target classes addressed by FBDD (2015-2019):

- Kinases
- Proteases
- PPI (protein-protein interactions)
- GPCRs
- Ion Channels
- Nuclear Receptors



erdafitinib

Pubmed search results by years (by “fragment based drug design”)



1. Jahnke W, Erlanson DA, de Esch IJP, Johnson CN, Mortenson PN, Ochi Y, Urushima T. Fragment-to-Lead Medicinal Chemistry Publications in 2019. J Med Chem. 2020 Dec 24;63(24):15494-15507. doi: 10.1021/acs.jmedchem.0c01608. Epub 2020 Nov 23. PMID: 33226222.
2. Li Q. Application of Fragment-Based Drug Discovery to Versatile Targets. Front Mol Biosci. 2020 Aug 5;7:180. doi: 10.3389/fmolb.2020.00180. PMID: 32850968; PMCID: PMC7419598.

Fluorine Fragments: benefits and usage

High sensitivity to protein binding makes ligand-based fluorine NMR screening a valuable tool for fragment screening [1]. Fluorine chemical shifts are monitored to detect binding. The method could be broadly classified to:

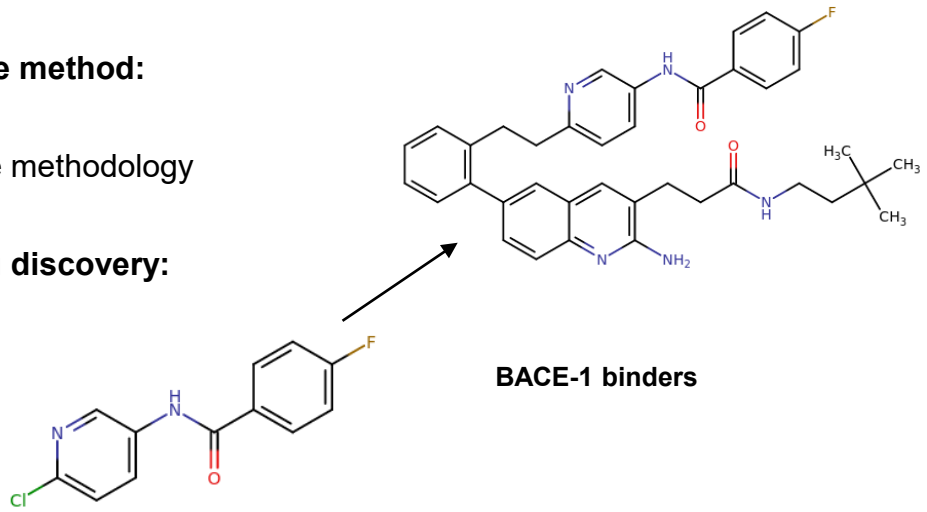
- PrOF (protein-observed fluorine NMR) – protein observed technique
- N-FABS (n-fluorine atoms for biochemicalscreening) – substrate/cofactor observed technique
- FAXS (fluorine chemical shift anisotropy and exchange for screening) – ligand observed technique

Main benefits of the method:

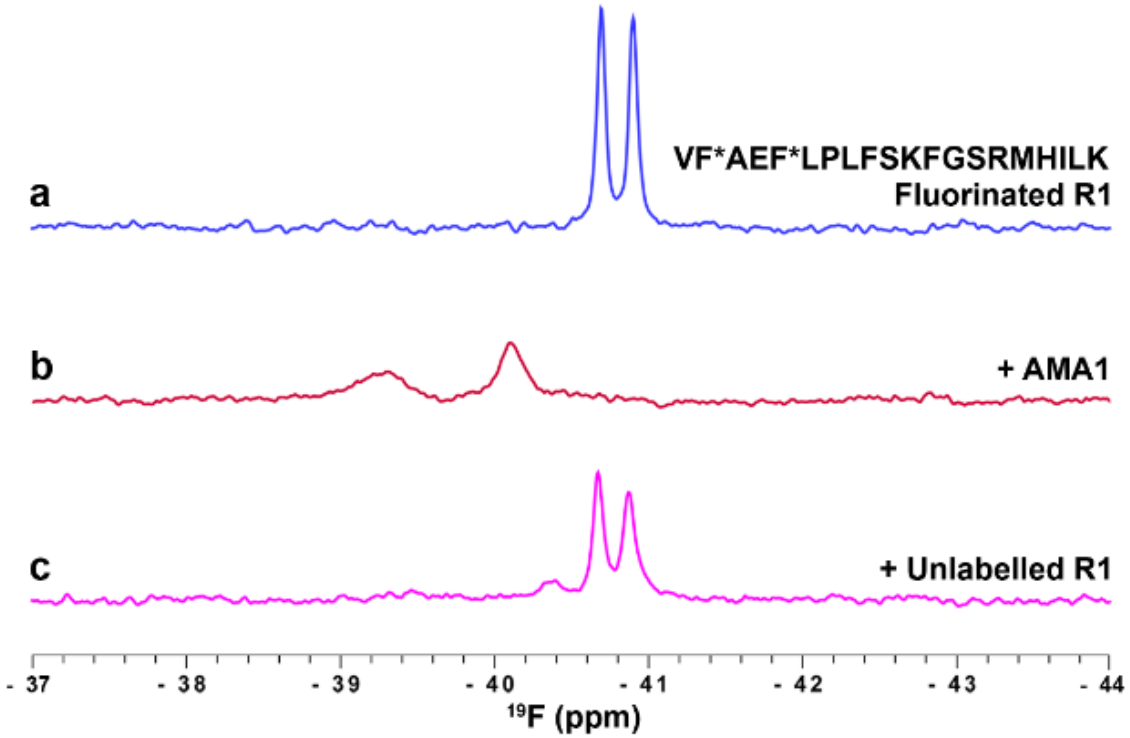
- High sensitivity
- Easy setup of the methodology

Application in drug discovery:

- BACE-1 [2]
- HSP90 [3]
- Factor D [4]
- Trypsin [5]



BACE-1 binders



Fluorinated peptide ligand binding to SPSB2. ^{9}F NMR signal becomes broad in the presence of the receptor. Adopted from [6]

1. Dalvit C, Vulpetti A. Ligand-Based Fluorine NMR Screening: Principles and Applications in Drug Discovery Projects. J Med Chem. 2019 Mar 14;62(5):2218-2244. doi: 10.1021/acs.jmedchem.8b01210. Epub 2018 Oct 29. PMID: 30295487.
2. Jordan JB, Poppe L, Xia X, Cheng AC, Sun Y, Michelsen K, Eastwood H, Schnier PD, Nixey T, Zhong W. Fragment based drug discovery: practical implementation based on ¹⁹F NMR spectroscopy. J Med Chem. 2012 Jan 26;55(2):678-87. doi: 10.1021/jm201441k. Epub 2012 Jan 11. PMID: 22165820.
3. Casale E, Amboldi N, Brasca MG, Caronni D, Colombo N, Dalvit C, Felder ER, Fogliatto G, Galvani A, Isacchi A, Polucci P, Riceputi L, Sola F, Visco C, Zuccotto F, Casuscelli F. Fragment-based hit discovery and structure-based optimization of aminotriazoloquinazolines as novel Hsp90 inhibitors. Bioorg Med Chem. 2014 Aug 1;22(15):4135-50. doi: 10.1016/j.bmc.2014.05.056. Epub 2014 Jun 14. PMID: 24980703.
4. Vulpetti A, Randl S, Rüdisser S, Ostermann N, Erbel P, Mac Sweeney A, Zoller T, Salem B, Gerhartz B, Cumin F, Hommel U, Dalvit C, Lorthiois E, Maibaum J. Structure-Based Library Design and Fragment Screening for the Identification of Reversible Complement Factor D Protease Inhibitors. J Med Chem. 2017 Mar 9;60(5):1946-1958. doi: 10.1021/acs.jmedchem.6b01684. Epub 2017 Feb 20. PMID: 28157311.
5. Vulpetti A, Schiering N, Dalvit C. Combined use of computational chemistry, NMR screening, and X-ray crystallography for identification and characterization of fluorophilic protein environments. Proteins. 2010 Dec;78(16):3281-91. doi: 10.1002/prot.22836. PMID: 20886466.
6. Norton RS, Leung EW, Chandrashekaran IR, MacRaild CA. Applications of (19)F-NMR in Fragment-Based Drug Discovery. Molecules. 2016 Jul 16;21(7):860. doi: 10.3390/molecules21070860. PMID: 27438818; PMCID: PMC6273323.

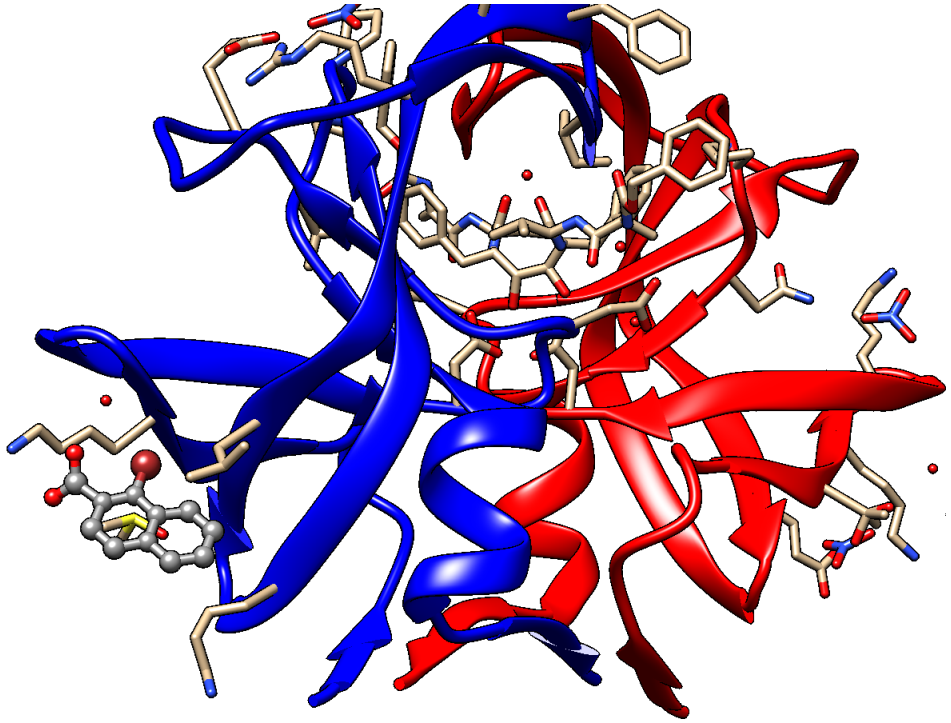
Brominated fragment library : benefits and usage

Recent advances in X-ray crystallography have improved the throughput of X-ray fragment based screening [1]. Electron density if bromine can be easily located via anomalous scattering [2, 3]

Main benefits of the method:

- Three-dimensional perspective of the binding landscape
- Broad range of detected ligand affinities from sub-nanomolar to millimolar

Number of application in drug discovery has been reported HIV protease [2]



Interactions of brominated fragment in the exosite of HIV protease

1. Tiefenbrunn T, Forli S, Happer M, Gonzalez A, Tsai Y, Soltis M, Elder JH, Olson AJ, Stout CD. Crystallographic fragment-based drug discovery: use of a brominated fragment library targeting HIV protease. Chem Biol Drug Des. 2014 Feb;83(2):141-8. doi: 10.1111/cbdd.12227. Epub 2013 Oct 30. PMID: 23998903; PMCID: PMC3898673.
2. Tiefenbrunn T, Forli S, Happer M, Gonzalez A, Tsai Y, Soltis M, Elder JH, Olson AJ, Stout CD. Crystallographic fragment-based drug discovery: use of a brominated fragment library targeting HIV protease. Chem Biol Drug Des. 2014 Feb;83(2):141-8. doi: 10.1111/cbdd.12227. Epub 2013 Oct 30. PMID: 23998903; PMCID: PMC3898673.
3. Liu Q, Hendrickson WA. Contemporary Use of Anomalous Diffraction in Biomolecular Structure Analysis. Methods Mol Biol. 2017;1607:377-399. doi: 10.1007/978-1-4939-7000-1_16. PMID: 28573582; PMCID: PMC5541782.

Selection criteria

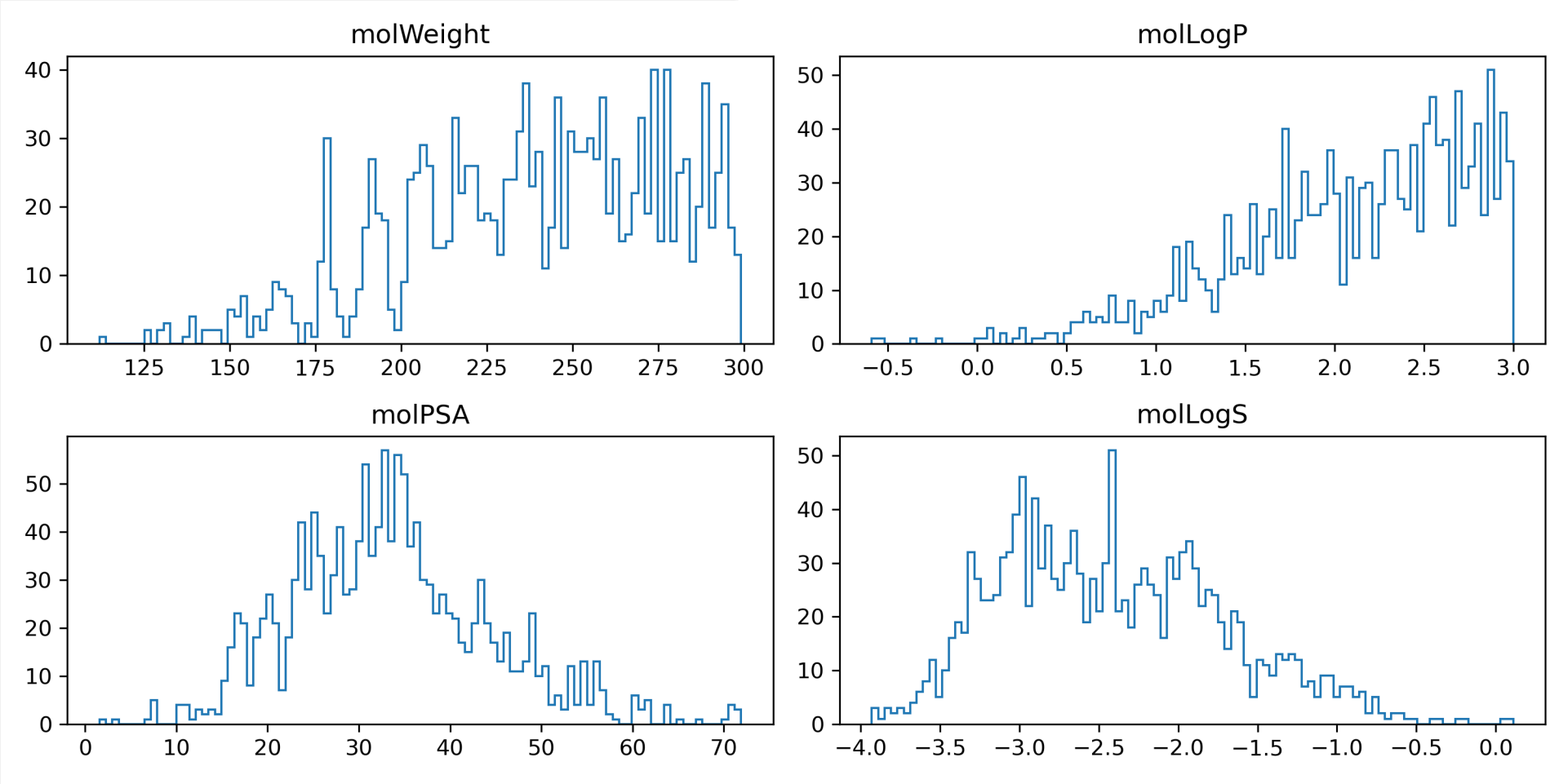
Fluorine Fragments (1480 compounds):

- Molecular Weight < 300 Da
- Lipophilicity – cLogP < 3
- Polar Surface Area ($Å^2$) – PSA < 80
- Number of freely rotatable bonds < 3
- Number of hydrogen bonds acceptors < 3
- Number of hydrogen bonds donors < 3

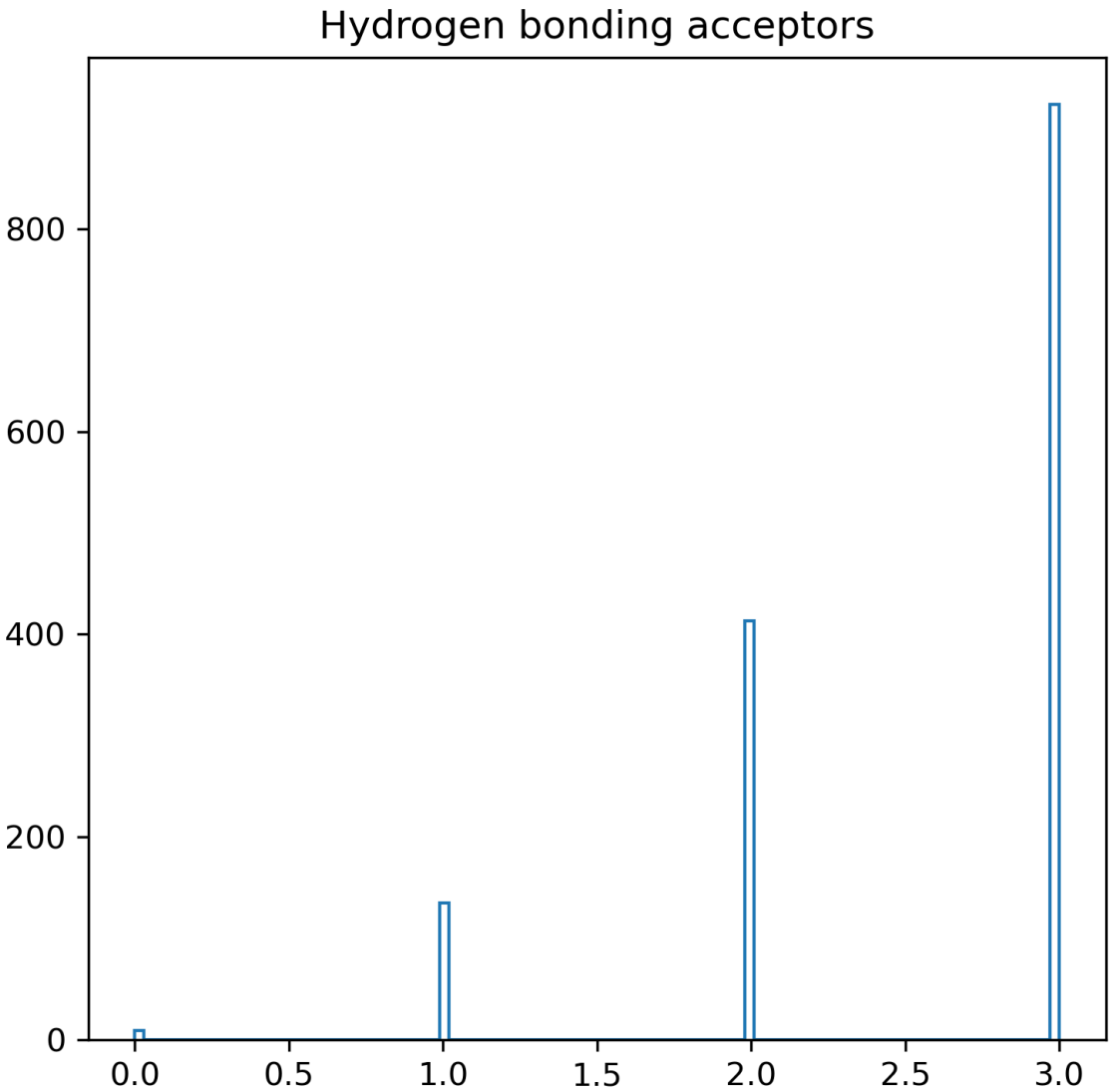
Bromine Fragments (629 compounds):

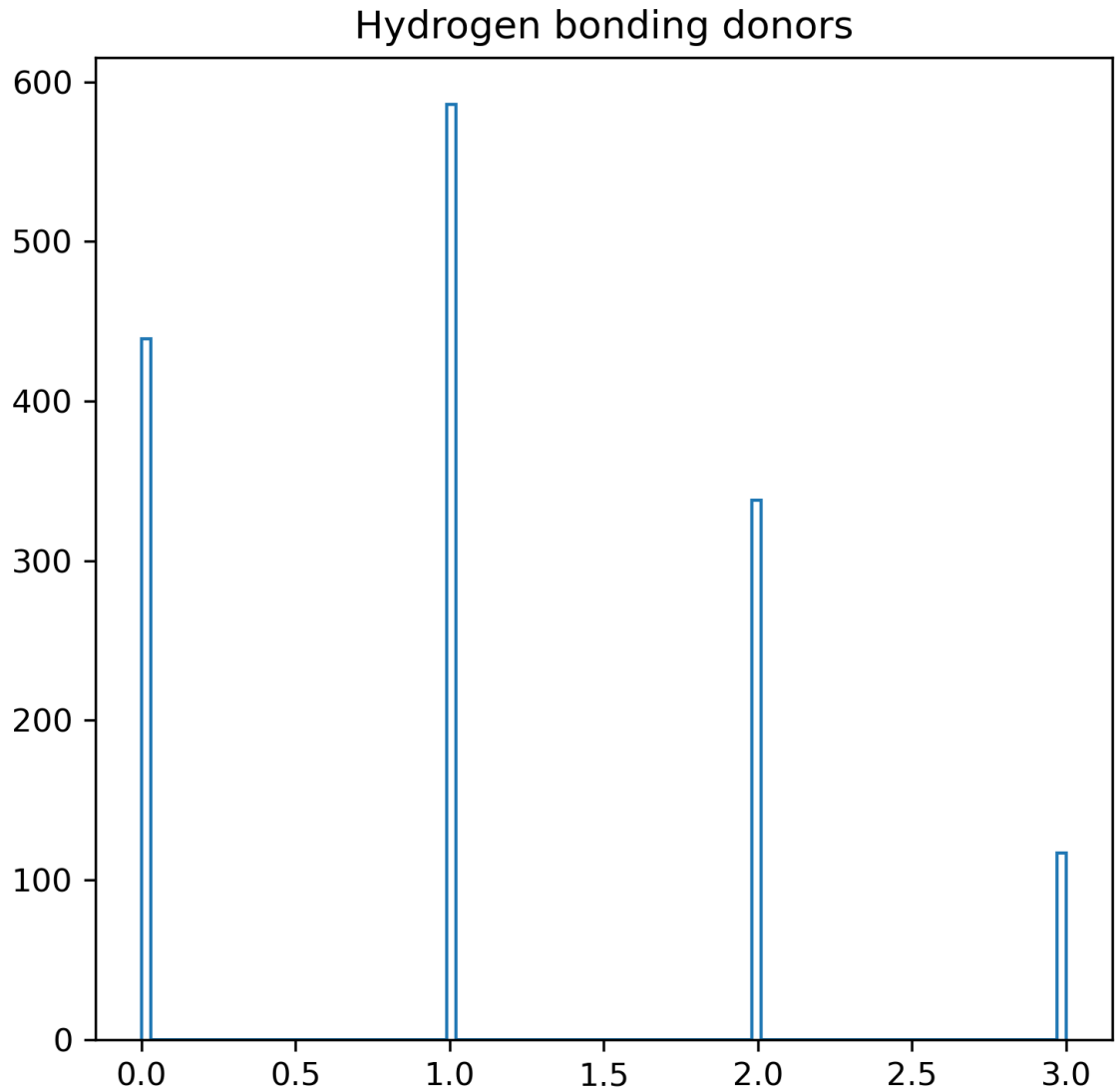
- Molecular Weight < 380 Da (increased from the
- commonly used 300 Da to account for the bromine atom)
- Lipophilicity – cLogP < 3
- Polar Surface Area ($Å^2$) – PSA < 80
- Number of freely rotatable bonds < 3
- Number of hydrogen bonds acceptors < 3
- Number of hydrogen bonds donors < 3

Property space of the selected fluorine compounds



Property space of the selected fluorine compounds





Examples of fluorine compounds

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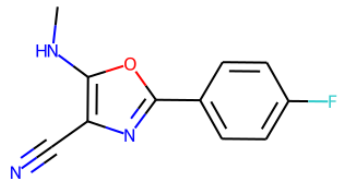
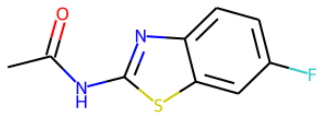
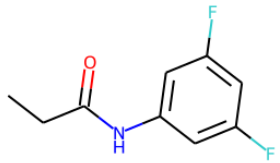
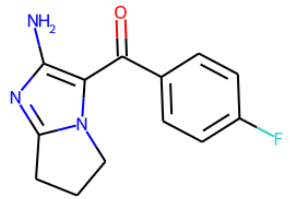
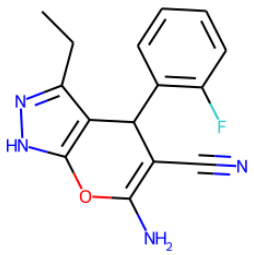
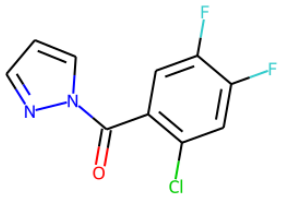
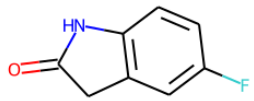
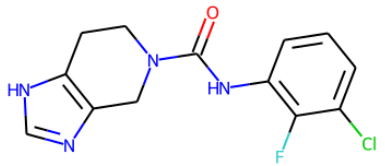
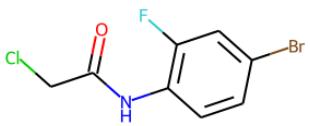
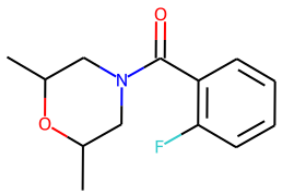
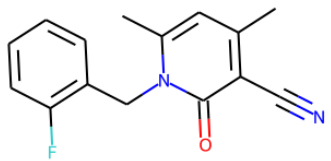
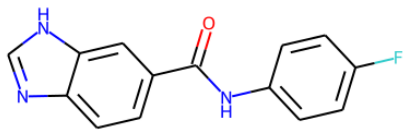
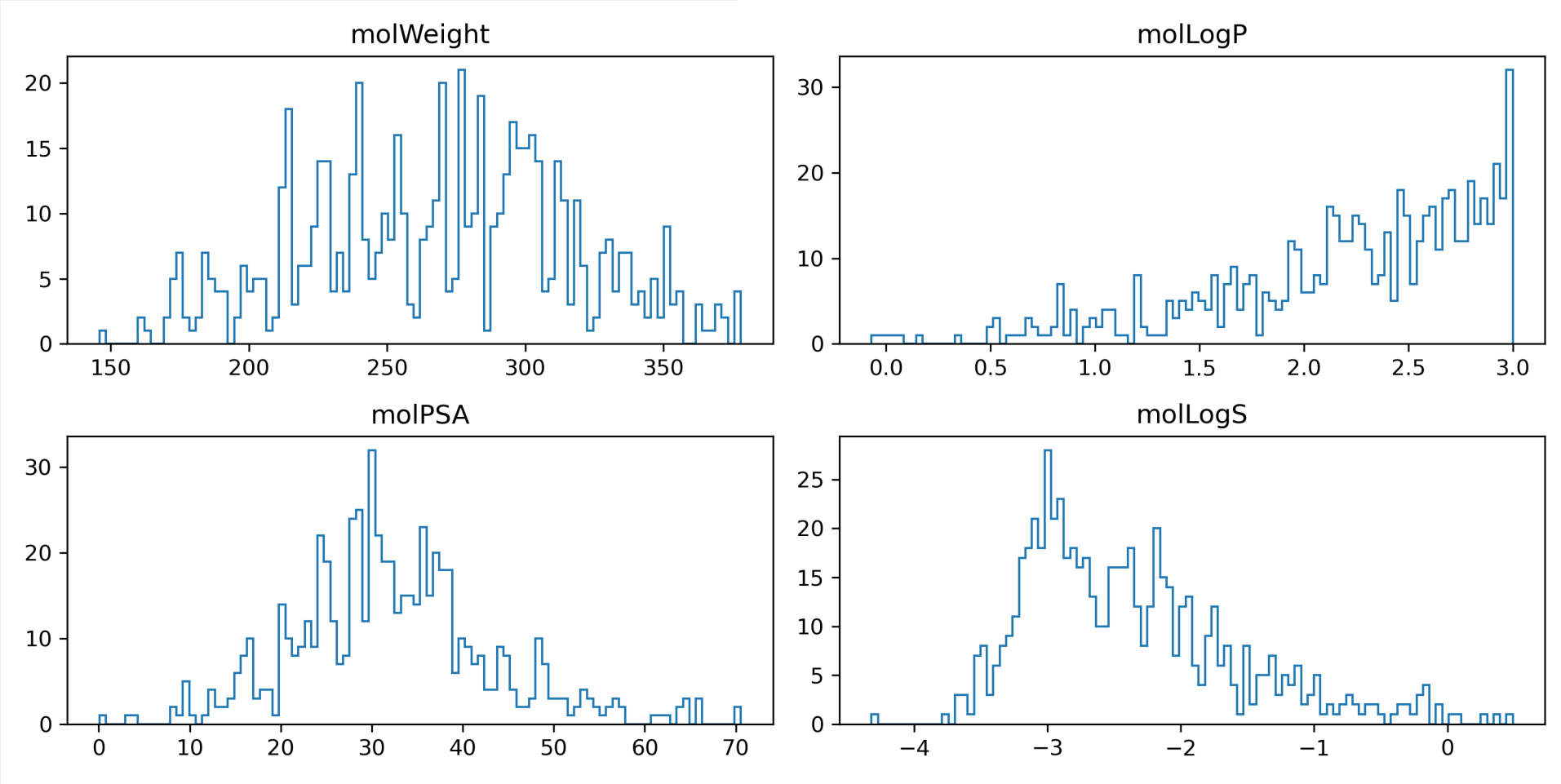













Property space of the selected bromine compounds



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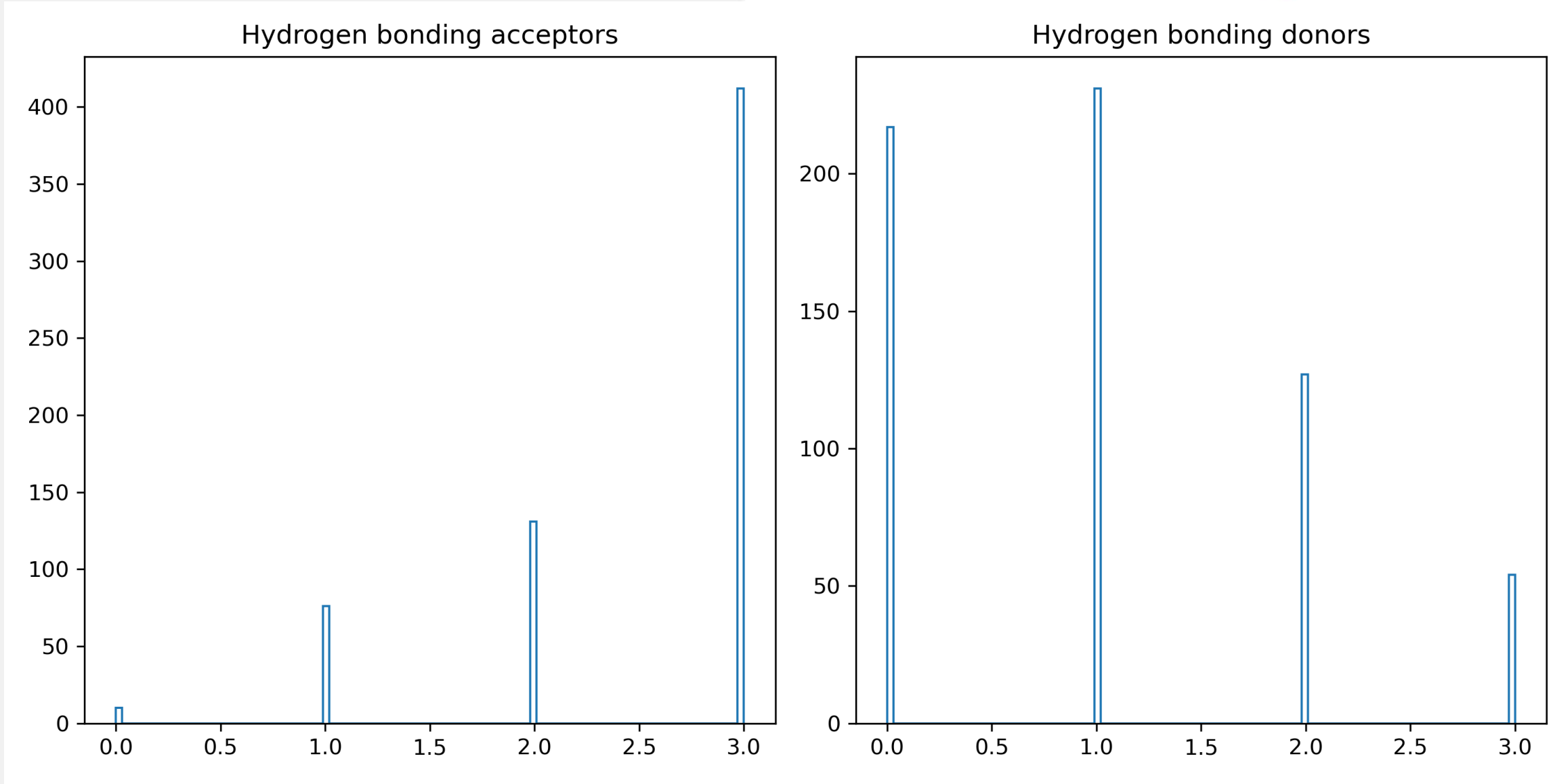

Examples of bromine compounds

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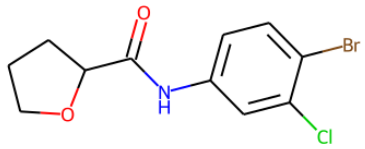

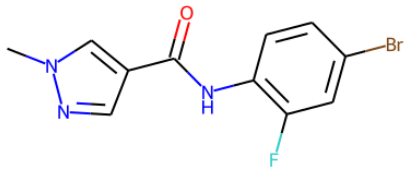

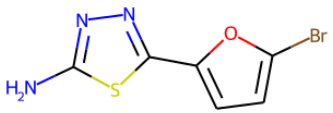

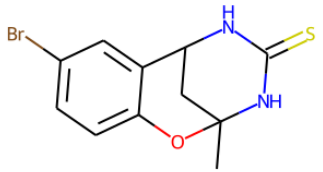

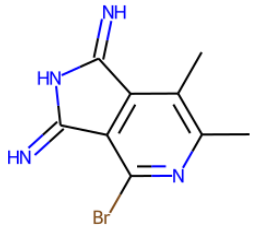

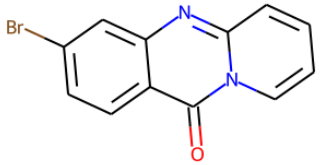

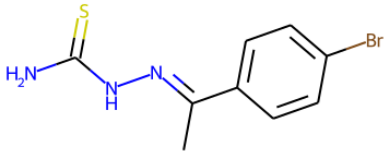

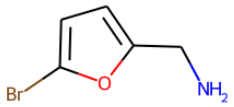

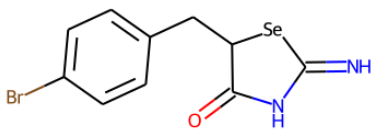

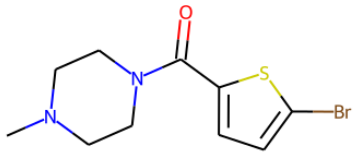

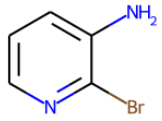

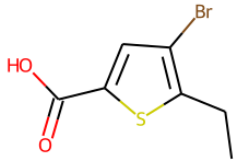

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