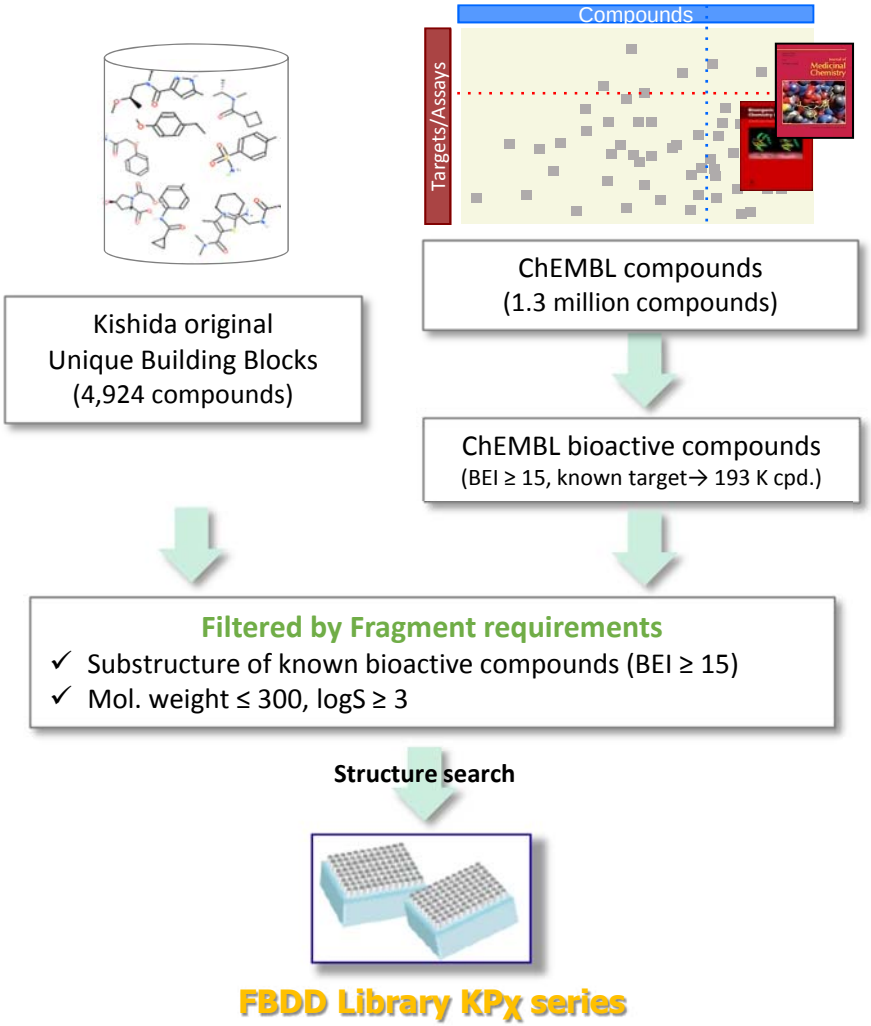
PharmaDesign Original Fragment Library Series

FBDD Library KPχ vol.1&2

Fragment screening is becoming the method of choice for drug discovery. PharmaDesign designed and developed two types of fragment-based drug discovery (FBDD) libraries with and without containing fluorine compounds. Both libraries complies on "Rule of 3 (Ro3)" with having high aqueous solubility, uniqueness, diversity and bio-activity to be druggable target. KPχ vol-2 is designed with having fluorine content, which can be detected using ^{19}F-NMR for weak-affinity signals. During the stage of fragment selection or filtration, both ChEMBL (having 1.3M compounds) and the original Kishida building-block, which contains latest trends such as sp^3 enriched compounds, are considered as starting material to compose KPχ libraries.

How to create the Library



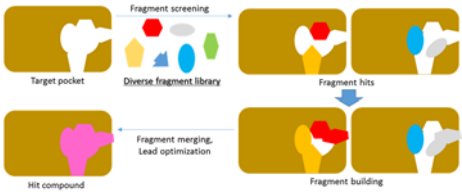
Key features

- "Hybrid" resources from ChEMBL and original Kishida building block
- Meets fragment requirement with considering Ro3 and bio-activity
- Considering aqueous solubility, uniqueness, diversity for the better draggability
- KPx vol-1 is enriched with sp^3 compounds as well as aromatic
- KPx vol-2 is fluorine-containing FBDD library good for ^{19}F-NMR analysis
- All compounds are synthesizable and deliverable to global market

Why FBDD??

Fragment-based drug discovery (FBDD) became a popular method since its first concept was discovered in 1980s. It helps to get "partial hit" into target pockets, however, also requiring subsequent "fragment-building" processes to be a hit compound. Bio-activity, best range of molecular weight, numbers of protein donor/acceptor, solubility are needed to be considered to compose ideal fragment library.

- Typical FBDD requirement (Ro3)
- Molecular weight < 300
- ClogP < 3
- # Hydrogen bond donors < 3
- # Hydrogen bond acceptor < 3
- # Rotatable bonds < 3



Schematic image of fragment-based drug discovery (FBDD)

Worldwide distribution network

United States / Canada
Oakwood Products, Inc.
730 Columbia Hwy. N, Estill, SC 29918
U.S.A.
TEL +1 800 467 3386
FAX +1 803 739 6957
www.oakwoodchemical.com
Email: requests@oakwoodchemical.com

United Kingdom / Europe
Fluorochem Ltd.
Unit 14
Graphite Way, Hadfield, Derbyshire
SK13 1QH United Kingdom
TEL +44 1457 860 111
FAX +44 1457 892 799
www.fluorochem.co.uk

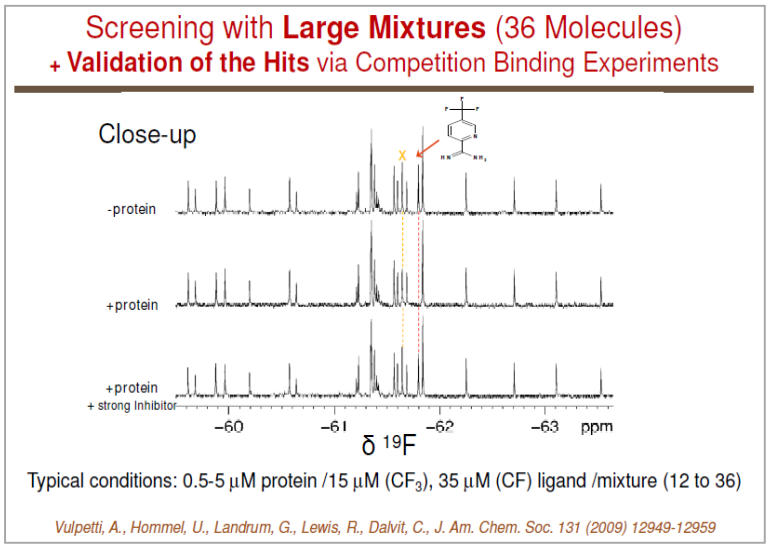
Apollo Scientific Limited
Whitefield Rd, Bredbury, Stockport, Cheshire,
SK6 2QR United Kingdom
TEL +44 161 406 0505
FAX +44 161 406 0506
www.apolloscientific.co.uk

Singapore
Scientific Hub Services (SHS) Pte Ltd.
3 Science Park Drive, #02-12/25 The Franklin,
Office Suite 2 Singapore Science Park I,
118223 Singapore
TEL +65 9850 2655
FAX +65 6640 1351
www.sci-hub.com

China
Seiko Trading Shanghai Co.,Ltd.
3C, 315 Guangyuan Road, Shanghai
200030 China
TEL +86 21 6090 5268
FAX +86 21 6090 5269
www.seikonet.cn

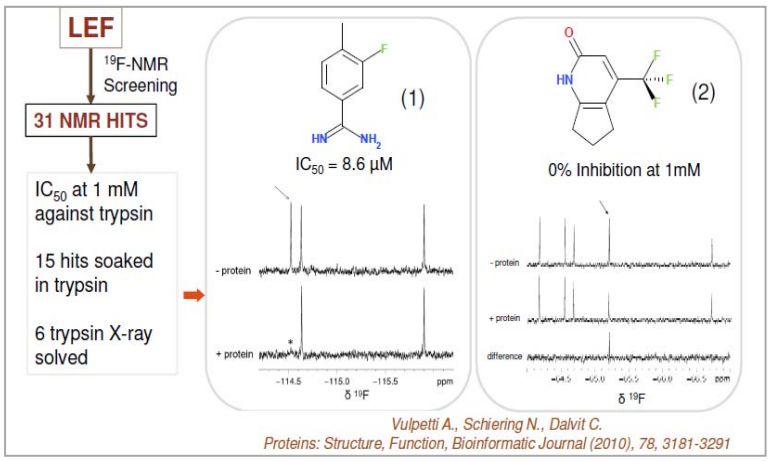
KISHIDA
KISHIDA CHEMICAL Co.,Ltd. | E shiyaku@kishida.co.jp | W soyaku.kishida.co.jp
11-8, 2-chome Shin-ohashi, Koto-ku 135-0007 Tokyo Japan | TEL +81-3-5625-5595 FAX +81-3-5625-5596

Examples of ^{19}F-NMR screening



Typical conditions: 0.5-5 µM protein /15 µM (CF_3), 35 µM (CF) ligand /mixture (12 to 36)

Vulpetti, A., Hommel, U., Landrum, G., Lewis, R., Dalvit, C., J. Am. Chem. Soc. 131 (2009) 12949-12959



Vulpetti A., Schiering N., Dalvit C.
Proteins: Structure, Function, Bioinformatic Journal (2010), 78, 3181-3291

SPECIFICATION / PACKAGING INFORMATION

	Vol-1	Vol-2
Product name	FBDD Library KPχ Vol-1	FBDD Library KPχ Vol-2
Type	General (non-fluorine)	Fluorine-contained
Number of fragment	500	500* as of Aug 2015, number increasing
Amount of compounds	5 to 50 mg (flexible on demand)	
Format	Solid (some contains oily form)	
Purity	> 95 % (generally >98 % in actual)	
Packaging	96 tube well plate (maximum 80 compounds in one plate)	
Storage condition	Cold and dark place	
Database supply	Compound structure and properties (e.g. BEI value, logS[simulated]): with sdf format in CD-ROM media	
General notice	➢ Please be careful when opening the vial cap. Compounds might be stuck to the reverse side of the vial cap due to vibration during delivery. ➢ This product is for research use only. ➢ For further technical details and sales pricing, lead time, please contact your local distributor or Kishida Chemical (shiyaku@kishida.co.jp).	

Key features of fluorine-contained library

- Designed for high resolution ^{19}F-NMR
- LogS[simulated]*1 ≥ 3, as an indication for high aqueous solubility
- BEI*2 ≥ 15, as an index for high bio-activity*3
- searched from novel Kishida K building blocks (K-BBs), which both contains aromatic ring and sp^3 enriched compounds, for the better hit for druggable target
- Dissociation constant (K_D) determination by differential chemical shift perturbation and line broadening in ^{19}F-NMR*4
- Simultaneous binding fragments can be identified and oriented based upon ^{19}F-^{19}F NOEs.*5
- 100% abundant ^{19}F enables fragment mixture screening to perform high through put hit detection.

*1: *1: Using StarDrop (http://www.optibrium.com/stardrop/) for the simulation. To verify the simulated value, 51 compounds selected by structural diversity clustering analysis were subjected of actual solubility measurements in PBS buffer.

*2: BEI (Binding Efficiency Index) is a calculated value divided compound activities (Ki, Kd or log IC50) by its molecular weight. In case of compound with MW 400 and 0.9µM IC50, BEI = 15. We assume that BEI value more than 15 agree with "high bio-activity".

*3: having more than 15 BEI our of 193 K compounds registered in ChEMBL (https://www.ebi.ac.uk/chembl/).

*4: *J. Med. Chem.*, **2012**, *55* (2), pp 678–687

*5: In case of the hit detection of multiple ligands present within the same tested mixture.

PharmaDesign Inc.

PharmaDesign Inc. is a selective Genomic Drug Discovery venture company founded by professionals on bioinformatics and rational drug design. PharmaDesign contributes to the health and welfare of people by devoting its latest genomic drug discovery technique to develop innovative and specialized medicines. PharmaDesign Inc. has developed the Pharma ShapeSim Library with disclosing an agreement with Kishida Chemical for global sales and marketing distribution.

W | www.pharmadesign.co.jp

KISHIDA

KISHIDA CHEMICAL Co.,Ltd. | E shiyaku@kishida.co.jp | W soyaku.kishida.co.jp
11-8, 2-chome Shin-ohashi, Koto-ku 135-0007 Tokyo Japan | TEL +81-3-5625-5595 FAX +81-3-5625-5596