



Welcome to the 16th edition of the BioSolveIT newsletter!

In our newsletter we publish information about new developments, events, milestones, and scientific facts on a quarterly basis.

fragment growing and merging: ReCore – software that belongs on your desk!_____

[ReCore](#) is a 3D ligand-based tool that permits a user to generate new ligand cores from fragments in the blink of an eye. ReCore was [recently reviewed](#) in the Computer Software Review of JACS by [John H. Van Drie](#) of [Van Drie Research LLC](#). The tool was originally co-developed between our academic partner the Center for Bioinformatics (ZBH) at the University of Hamburg and the drug design group of F. Hoffmann-La Roche AG (Basel). The JACS article states the origins of ReCore ensure that **"the quality of the science underlying ReCore is first-rate"**. The method is an ideal solution for evading patent issues whilst working with competitor molecules, generating novel ligand chemistries and broadening your molecular diversity in your design projects. In addition, it can also be used for **fragment growing and fragment merging** (take a look at [this month's tips'n'tricks](#)). The JACS article also comments that **"the way this software leads the user to think about the design of bioactive molecules is very appealing"**.

In order to assess the ability of ReCore to design molecules of interest, it was 'test driven' on 3 different systems. The first was a problem encountered by the reviewer, John Van Drie, many years ago when attempting to discover novel D1-dopamine antagonist scaffolds using competitor compounds. **ReCore produced the specific scaffold which led to Abbott's A-68930**, an inhibitor which was designed in a pharma project. Other systems investigated were a peptide bound to a HIV protease and a pre-clinical candidate, in these experiments very interesting chemical suggestions were produced and the reviewer comments "ReCore did suggest some scaffolds that I had never thought of, which stimulated new thinking".

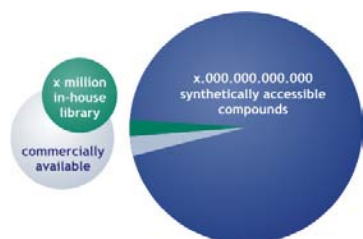
The JACS article concludes that **'software of this sort belongs on the desk of any chemist designing bioactive molecules'**. If you require any more information or would like to evaluate ReCore for free for 2 weeks please [follow this link](#).

leadin' the fragment discovery space way_____

Computer-aided drug design has been used within the pharmaceutical and biotech industries for decades now with virtual screening becoming a routine methodology employed to help in the design process. Molecular docking as a method for virtual screening has been viewed upon with varying degrees of skepticism. [FlexX](#) uses a fragment-based methodology with incremental construction to grow molecules within an active site; the FlexX methodology has had over 12 years of development for docking and growing fragments in virtual screening. A recent FlexX success story against a potential tuberculosis target is [reviewed in this issue's literature corner](#). This success was even mentioned on the emerging fragment-based ligand design blog called 'Practical Fragments', where the editor in chief Teddy Zartler commented **"It is interesting to see docking actually working with fragments. It has always been my impression that you can get a lot of poses out of a dock with a fragment. With this paper I am proven wrong."**

Fragment-based ligand design (FBLD) as a field has been gaining momentum over the last few years and has recently become one of the hottest discussed topics and applied methods in the drug discovery industry. Fragment libraries or fragment spaces offer a way to cover large areas of chemical space, and combinations of these fragments **relate much better to what a synthetic chemist is capable of and cover a much larger diversity than any in-house or commercially available molecular library**. Combined with (retro)synthetic rules, innumerable large numbers of virtual compounds covering a highly diverse chemical space can be screened in a time efficient manner to facilitate the discovery of sensible molecules within minutes. Over the past couple of years BioSolveIT have accelerated their development of fragment-based virtual screening technologies to become the world's leading provider of FBLD software solutions. BioSolveIT is

leading the way with its diverse and highly efficient FBLD suite of software. The underlying algorithms have been specifically designed for FBLD to optimally design compounds from fragments.



Hence, why our FBLD tools come with various flavours of [publicly available fragment spaces](#), which have been sensibly shredded with retrosynthetic rules and filtered by a medicinal chemist's eye for immediate virtual fragment design success. The most recent addition to our range of fragment spaces is the 'KnowledgeSpace' which encompasses **17,794 unique fragments** and comprises about **23,000,000,000 virtual products**. The 'KnowledgeSpace' is easily searched with our tools and has also been integrated into Pipeline Pilot to potentially enhance your existing workflows.

"I want to follow my own synthetic rules" - you got it! Designing your own fragment space from your known in-house combinatorial chemistries provides the best possibility of designing molecules with the highest potential synthesizability and IP content (see table).

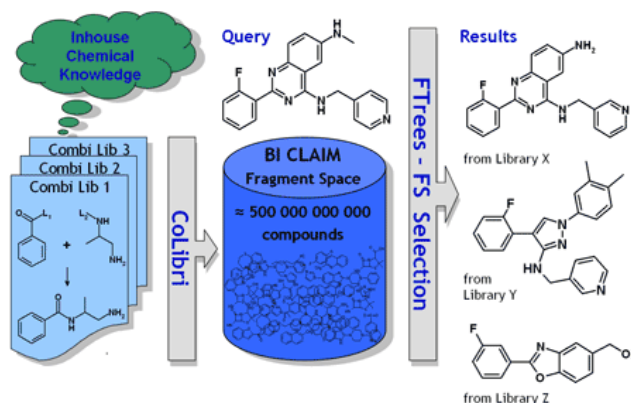
	origin of		P(Synth'y)	Content of IP
	fragments	connection rules		
shredding	public compounds shredded	public shredder rules	good	low
	<u>corporate</u> compounds shredded	public shredder rules	better	mid
	<u>corporate</u> compounds shredded	<u>corporate</u> shredder rules	better	high
combichem	combichem reagents	public combichem rxns	best	low
	<u>corporate</u> combichem reagents	<u>corporate</u> combichem rxns	best	high

So create and design your own proprietary fragment space and virtually empower and complement your in-house combinatorial chemistry efforts. That's what Pfizer and Boehringer Ingelheim did: by searching trillions and billions of molecules respectively, they have harvested rewarding hits from the fragment seeds they sowed and successfully published their work (see above). [Contact us](#) today if you wish to use these new powerful approaches to help your chemists discover leads from virtual hits that won't give your medicinal chemists the synthetic blues.

Boehringer paper lays CLAIM to FBLD success

Boehringer Ingelheim GmbH (BI) have published a **prospective success story** using BioSolveIT's market leading fragment-based ligand design technology. The technology was initially developed with Pfizer Inc. who retrieved hits from 3 trillion products in minutes. Two prospective applications, a GPCR design project and a protease inhibitor project **yielding nano molar compounds** are now also reported by BI.

BI has consulted with BioSolveIT to achieve a highly unique and tailored solution to fragment based drug discovery. BioSolveIT utilized its expertise and facilitated the design of a proprietary fragment space termed BI-CLAIM ("Boehringer Ingelheim Comprehensive Library of Accessible Innovative Molecules"). The BI-CLAIM fragment space contains about 1,600 scaffolds and 30,000 reagents, which encode roughly **500 billion possible virtual compounds**. This vast fragment space was successfully searched with BioSolveIT's [FTrees](#) technology in only a matter of a couple of minutes!



Currently, most large pharmaceutical companies are exploring the diverse, novel, and rewarding discovery opportunities available with BioSolveIT fragment-based virtual screening. In addition, **ArQule** are one of the latest companies who have constructed a fragment space from available reagents and more than 30 ArQule Platform Chemistries. The application of their fragment space with regards to identifying kinase inhibitors with a type IV mechanism of action will be [presented at the forthcoming Spring ACS](#). If you would also like to join with BioSolveIT in piecing together

fragments for discovery success please do [contact us](#) and read our [current whitepaper](#) on this valuable piece of novel technology!

emerging India – piecing together Asian support

BiosolveIT GmbH is pleased and proud to announce that it has recently joined forces with [Apsara Innovations Pvt Ltd](#) in India to add another piece of Asian support to complement our existing Asian partner in Japan, [Ryoka Systems](#).

Apsara Innovations is a rapidly expanding and emerging Indian company based in Bangalore. It has been a successful distributor of scientific software **solutions in India for around 10 years** and their large **customer base of over 250 companies** stretches from North to South India. They offer a range of products from material sciences to life sciences software and are an experienced re-seller of scientific software solutions, with extremely attractive offerings for educational institutions. They are a results oriented organization with a very clear goal to work closely with customers and help them to reach their goals and objectives, which aligns very well with BioSolveIT's working philosophy!

Even now, in the early stages of our partnership, our involvement with Apsara Innovations is very fruitful with them having already successfully supplied and supported 7 different customers with BioSolveIT products. Including NIPER, Chandigarh, St. Antony's College, Shillong and Sir MVIT, Bangalore. Ashok Betraj, CEO of Apsara Innovations, commented that "we are very satisfied with the impact of FlexX in India and other BioSolveIT products". Apsara Innovations have 3 dedicated people headed by a Solutions Manager to handle the technical support, demonstrations, training and sales of BioSolveIT software. They have been fully trained in BioSolveIT products and are very enthusiastic to help and extremely supportive.

All interested parties in evaluating or obtaining information about BioSolveIT software for India should [contact Girinath G. Pillai](#) at Apsara Innovations.

tips & tricks: ReCore - fragment merging

This section today focuses on troubleshooting and aspects of ReCore that are either not very well known or are sometimes misunderstood, so we see them as important points to bring to your attention. In this issue we present a **fragment merging exercise** in our tips'n'tricks which will help you learn how to connect all those small fragment hits found in your crystallographic screens! [Read more!](#)

You can view previous topics of tips'n'tricks [here](#). If you have any questions or know of any tips'n'tricks yourself that you would like to share with the BioSolveIT user community, we would appreciate your input at ReCore@BioSolveIT.de.

BioSolveIT news in brief

- The original 1996 FlexX paper ranks 83rd in the Top 100 most cited articles from the Journal of Molecular Biology!
- Webinars - BioSolveIT recently successfully hosted 2 webinars on ReCore. If you are interested in participating in future webinars and interactively being informed regarding BioSolveIT software please do [contact us](#).
- Recently released BioSolveIT Software: new [Pipeline Pilot Components](#), [FTreesXL 1.1.5](#), [FlexX 3.1.3](#), [ReCore 1.8.14](#), and [FlexS 1.30.1](#) (windows version)
- Dates for your diary:** BioSolveIT will be present at the following events:

Mar 22nd - Mar 26th

[237th ACS National Meeting & Exposition](#), Salt Lake City, UT, USA. BioSolveIT will be attending this meeting and presenting 2 talks in the CINF session: "[A fragment based de novo application in the context of the active site](#)" and "[Avoiding pitfalls in molecular docking](#)". Our academic partners from the University of Hamburg will also be presenting a talk titled "[LoFT - Focused library design using feature tree similarity](#)".

Apr 22 nd - Apr 24 th	EuroCUP III , Toledo, Spain. BioSolveIT will be presenting: " Synthetic Accessibility and IP Protection in Fragment Based Design ".
May 3 rd - May 8 th	Trends in Drug Research , Noordwijkerhout, Netherlands BioSolveIT will be hosting a "Free Interactive Workshop on Virtual Screening and Fragment Based Ligand Design" and registration is now open. BioSolveIT will also be presenting: "Searching the impossible - Designing libraries from large virtual chemistry spaces"
May 14 th	Spring UK-QSAR , Sandwich, UK.

If you would like to meet one of our representatives to discuss any questions or have any kind of feedback please email us at Contact@BioSolveIT.de.

literature corner

- Discovery of Novel Nitrobenzothiazole Inhibitors for Mycobacterium tuberculosis ATP Phosphoribosyl Transferase (HisG) through Virtual Screening*
Yoonsang Cho, Thomas R. Ioerger, and James C. Sacchettini
J. Med. Chem. 51(19):5984-92. (2008)
[details here](#)
- In Silico Screening for PTPN22 Inhibitors: Active Hits from an Inactive Phosphatase Conformation*
Shuangding Wu, Massimo Bottini, Robert C. Rickert, Tomas Mustelin, and Lutz Tautz
ChemMedChem. 2009 Jan 28. [Epub ahead of print]
[details here](#)
- Identification of Novel HCV RNA-dependent RNA polymerase Inhibitors Using Pharmacophore-Guided Virtual Screening*
Jinyoung Kim, Ki-sun Kim, Dong-Eun Kim and Youhoon Chong
Chem. Biol. Drug. Des. 2008; 72: 585 - 591
[details here](#)

upcoming articles

- KNIME Components
- KnowledgeSpace

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