

Welcome to the 17<sup>th</sup> edition of the BioSolveIT newsletter!

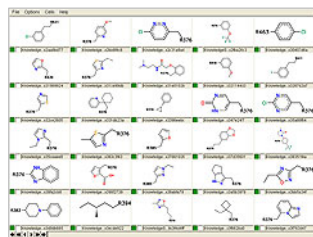
In our newsletter we publish information about new developments, events, milestones, and scientific facts on a quarterly basis.

## combinatorial chemistry in a can do *KnowledgeSpace*

The *KnowledgeSpace*, provided by BioSolveIT on a completely free complimentary basis, is a fragment space derived from 82 different published combinatorial synthetic protocols from the *Journal of Combinatorial Chemistry*. The protocols selected to create the fragment space consisted of GPCR, Protease, Kinase and Chemistry Driven synthetic protocols.



The *KnowledgeSpace* consists of **10,879 unique fragments** derived from the combinatorial chemistry protocols. These fragments were approved by a medicinal chemist by eye and deemed to be of significant drug like nature. The properties of the fragments are mainly respect the *Fragment Rule of 3* proposed originally by Astex, with filters applied for the properties of *logP*, donors and acceptors and molecular weight. Thus 90% of fragments have a molecular weight between 100-250 Daltons. Half of the molecules in the space contain at least 1 ring structure with approximately the remaining two quarters equally split between having no ring structure or 2 rings.



These ~11k fragments in the *KnowledgeSpace* can be combined in synthetically restricted ways using **488 unique linker types**, with these linker type constraints for compatibility and joining fragments in different ways there is the capability of potentially producing **11,725,417,388 virtual products** that can actually be made! These searchable virtual products permit a vast improved coverage of chemical space in comparison to other screening solutions due to the potential diversity in the *de novo* compounds that can be screened. The *KnowledgeSpace* has been validated to retrieve known drugs and drug like molecules. See the details of some work in recent presentations where 1376 molecules from *Drugbank* were used as queries to create drug like molecules with *FTrees-FS* and how known CDK2 inhibitors were created *de novo* containing different CDK2 synthetic protocols with *FlexNovo*. The *KnowledgeSpace* is easily searched with our tools and has also been integrated into *Pipeline Pilot*<sup>®</sup> and *KNIME*<sup>®</sup> to enhance your existing pipelines and workflows. If you have any questions or would like access to the *KnowledgeSpace* please do [write to us](#).

## drag, drop, dock! – free BioSolveIT KNIME<sup>®</sup> extensions

Ever envied people who can create workflows and discovery pipelines by just dragging and dropping with a mouse? Now you can too without paying any overwhelming costs, drag and drop at no additional cost!

BioSolveIT have developed *KNIME*<sup>®</sup> extensions for their most prominent virtual screening tools. *KNIME*<sup>®</sup>, an Information Miner developed at Konstanz university is an open source project. *KNIME*<sup>®</sup> is a free, modular and extendable data exploration platform to visually create data pipelines.

What does this mean for me you may be asking yourself?

Imagine, you wanted to filter a molecular database, screen it using docking then compare your best hits to your corporate compound database. This is a very easy workflow which can be 'plugged together' within minutes by **dragging/dropping** and connecting the so-called *KNIME*<sup>®</sup> extensions in your work space area within *KNIME*<sup>®</sup>.



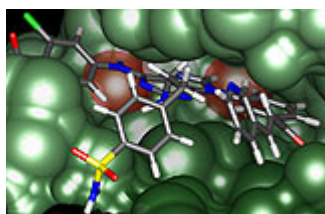
The open source *KNIME*<sup>®</sup> project contains some of the most advanced machine learning, clustering and cheminformatics algorithms available, they have been created by multiple sources but can be

all accessed and linked together **under one roof** - this powerful platform is shared throughout the community and can be potentially utilized by you!

Setting up our extensions is child's play: once the KNIME® installer has finished its work, the installation of our BioSolveIT KNIME® extensions is quick and straightforward. On examining the BioSolveIT extensions, Professor Michael Berthold, KNIME®-creator and founder commented "Very impressive!". Also, as has been previously mentioned to our customers, for licensees of the respective tools, our KNIME® extensions are **free of charge**. Following our mantra of one license = interface access galore for our customers ease of use! The BioSolveIT KNIME® Extensions for *FlexX*/*SIS* and *FTrees* can be [downloaded now](#).

## structure-based fragment design piecing it all together with *FlexNovo* \_\_\_\_\_

BioSolveIT recently released *FlexNovo 1.6*, a structure based design method inherently working in a **fragment based design** way! *FlexNovo* pieces together fragments to generate **novel molecular entities** within a protein active site. *FlexNovo* input consists of a combinatorial chemistry or fragment space. Using such a chemistry space permits the synthetic tractability of compounds from a virtual screen. Resulting compounds can be traced back to the original chemical library or synthetic protocol underlying the generation of the compound and thus the **synthesizability problem of virtual molecules** is alleviated.



Within *FlexNovo* the user may either start from a known fragment binder or from alternative sources. For fragment growing one potential starting point is the results of a fragment crystallographic screen. Or alternatively compatible sub-structures can be matched and compatible molecules can be mapped to similar positions in the binding pocket of existing ligand binders. This provides a starting point to further explore the chemical environment of the binding pocket. If such information is lacking then the software can suggest a viable starting structure and design a novel compound in several molecular connecting steps following the initial placement.

Some preliminary results from *FlexNovo* were [presented at the last Spring ACS Meeting](#) in Salt Lake City, where the software was applied to the problem of finding novel molecular entities as starting structures in the quest for CDK2 inhibitors.

Interested researchers can request their evaluation copy [here](#).

## BioSolveIT sun rises through the clouds in the east \_\_\_\_\_

BioSolveIT is proud to announce **CloudScientific** as their **new distributor for China**, they are based in Shanghai and specialize in serving the life sciences community by providing integrated scientific software solutions. CloudScientific is a spin out of **InforSense**, a market leader for intelligence informatics solutions for life sciences research and business. "We have a broad range of skills from biomarker discovery, drug discovery and development up to the pre- and clinical stage", says Jiancheng Lin, CEO of CloudScientific. "Our software solutions range from Chem- and Bioinformatics, Molecular Modeling and Computational Chemistry to Toxicology, pre- and clinical PK/PD modeling to analysis and data management, and our tools now comprise the BioSolveIT suite of software for rapid and straightforward drug discovery."

"I am very pleased with this new collaboration. This will further strengthen our market representation in Asia", says Dr. Christian Lemmen, CEO of BioSolveIT. CloudScientific has set the same goals as BioSolveIT has, serving the customer better by delivering unique and,



when necessary, customized software that accelerates research due to its high level of scientific innovation and thus puts the user one or two steps ahead of its competitors.

As commented by Jiancheng Lin, "CloudScientific has developed rapidly since it was established, and by cooperating with BioSolveIT, we are able to significantly expand our portfolio with the best of breed technologies from BioSolveIT in drug discovery research to the benefit of our customers." All interested parties in evaluating or obtaining information about BioSolveIT software for China should [contact Tao Huang](#) at CloudScientific.

## tips & tricks: ReCore – fragment growing

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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 of tips & tricks we will demonstrate how our scaffold replacement tool *ReCore* can be used for **fragment-growing** type of applications. The scenario we describe here is quite typical in the lead optimization phase of a project. [Read more!](#)

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

## BioSolveIT news in brief

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- BioSolveIT has been busy this year with workshop and training people in their successful fragment based ligand design tools. Workshops were already held this year at the 27<sup>th</sup> Noordwijkerhout-Camerino-Cyprus Conference "Trends in Drug Research" in Noordwijkerhout, the Netherlands and at the eCheminfo Drug Discovery Design Methods & Applications in Oxford, UK. There will be further workshops at the [Vienna Drug Design Summer School](#) and the [FBLD 2009 conference](#) at York University, UK in September.
- Recently released BioSolveIT software: *KNIME*<sup>®</sup> components, *ReCore 1.8.15* with quick and easy installation and *FTrees 2.1* which reads SMILES and SD Fragment Spaces.
- Dates for your diary:** BioSolveIT will be present at the following events:

Aug 16 <sup>th</sup> - 20 <sup>th</sup>	<a href="#">238<sup>th</sup> ACS National Meeting &amp; Exposition</a> , Washington, DC, USA <ul style="list-style-type: none"><li>– <a href="#">COMP 95: A Fresh Look on 3D Database Searching: Towards a Unified Description of Pharmacophoric Features and Shape</a> (M. Rarey, J. Schlosser, and C. Schärfer)</li><li>– <a href="#">COMP 147: PoseView - 2D visualization of protein-ligand complexes</a> (K. Stierand)</li><li>– <a href="#">CINF 87: Operating in Chemical Spaces: Novel Methods for Lead Identification and Library Design</a> (M. Rarey and R. Fischer)</li><li>– <a href="#">COMP 338: Synthetically accessible compounds from giant virtual chemistry spaces</a> (C. Lemmen, C. Detering, M. Gastreich, and H. Claußen)</li><li>– <a href="#">CINF 86: Merging and growing fragments interactively</a> (M. Gastreich and C. Lemmen)</li></ul>
Sep 21 <sup>st</sup> - 23 <sup>rd</sup>	<a href="#">Fragment-Based Lead Discovery Conference</a> , York, UK <ul style="list-style-type: none"><li>– <a href="#">Interactive Fragment Growing, Linking, and Merging</a> (M. Gastreich)</li></ul>
Sep 29 <sup>th</sup> - 30 <sup>th</sup>	<a href="#">Chemical Computing Group European User Group Meeting 2009</a> , Basel, Switzerland <ul style="list-style-type: none"><li>– <a href="#">Access to the Chemical Universe</a> (C. Lemmen)</li></ul>

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](mailto:Contact@BioSolveIT.de).

## literature corner

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- Fragment Shuffling: An Automated Workflow for Three-Dimensional Fragment-Based Ligand Design*  
Britta Nisius and Ulrich Rester  
J. Chem. Inf. Model., 2009, 49 (5), pp 1211-1222  
[details here](#)
- A Structure-Based Approach to Ligand Discovery for 2C-Methyl-d-erythritol-2,4-cyclodiphosphate Synthase: A Target for Antimicrobial Therapy*  
Nicola L. Ramsden, Lori Buetow, Alice Dawson, Lauris A. Kemp, Venkatsubramanian Ulaganathan, Ruth Brenk, Gerhard Klebe, and William N. Hunter  
J. Med. Chem., 2009, 52 (8), pp 2531-2542  
[details here](#)

- Bioisosteric Similarity of Molecules Based on Structural Alignment and Observed Chemical Replacements in Drugs*  
Markus Krier and Michael C. Hutter  
J. Chem. Inf. Model., 2009, 49 (5), pp 1280-1297  
[details here](#)

## upcoming articles

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- Seminal DrugScoring is back
- LeadIT* leading the future

## contact

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