Subject: Lilly Medchem Rules
Posted by mvamos on Thu, 16 Apr 2020 18:50:08 GMT
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Possible new feature idea: whether structures in a set conform to the Lilly Medchem Rules.

Original paper: https://pubs.acs.org/doi/10.1021/jm301008n
GitHub: https://github.com/IanAWatson/Lilly-Medchem-Rules

Subject: Re: Lilly Medchem Rules
Posted by nbehrnd on Thu, 23 Apr 2020 17:29:06 GMT
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The publication you cite (ACS' Author Choice, thus open access) was published in 2012, J. Med. Chem. currently is aware of 141 publications citing this work; some you might know. The history of commits in the repository notes for Dec 14, 2017 «First working version for version 2», too.

Are there additions / modifications to the set of 275 MedChem rules of the 2012 publication which you would like to suggest to consider today? The approach suggested indeed is complementary to the approach of druglikeness in DW,[1] in turn borrowed from the earlierr OSIRIS Property Explorer.

[1] http://www.openmolecules.org/properties/properties.html#drug score

Subject: Re: Lilly Medchem Rules
Posted by mvamos on Mon, 27 Apr 2020 22:25:13 GMT
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I do wonder what the druglikeness (pi) in the "drug score" actually measures, or how it's measured. My feeling is this Lilly calc might be less about solubility/polarity like the "drug score" and more related to functional groups.

The authors of the 2012 paper do have a paper from 2018 (https://doi.org/10.1021/acsmedchemlett.8b00097 on a related topic, but it seems to be a distinct set of PAINS rules. So perhaps the 2012 paper is the best guide.

Subject: Re: Lilly Medchem Rules
Posted by IanWatson on Sun, 03 May 2020 19:21:33 GMT
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I am one of the authors of the Lilly papers. Indeed the Medchem Rules paper was all about

undesirable functional groups. There were other tools for property calculations.
The rules seem to have stood the test of time well, and are in widespread use. I have fielded lots of questions from people about building and using the software. I do not have a good feel for whether or not people have made substantial modifications to the rule set.

One of the important innovations was the concept of a demerit. Most rule sets are either 'in' or 'out'. We introduced the idea of a demerit. This arose because the team of medicinal chemists could not agree on Nitro groups. Some did not mind them, some did not like them at all. When we suggested the demerit idea, that was something they could all embrace, because while having one might be OK, most chemists were united in considering two such groups undesirable. From there, we ended up with lots of demerited, rather than rejected, functional groups.

The rules were developed at a time when there were a great many molecules available for purchase, so they tend to be fairly strict. I am open to ideas about rules that might be overly harsh, or other motifs that should be flagged.

The work we did with PAINS was to investigate how they worked - well for the assay formats for which they were developed, less so elsewhere. A byproduct of that was an implementation in our own query file format - rather than SLN. We did extensive checking of these results compared to Sibyl, but some things about SLN, and the results their software produced, never made sense to me.

Both these projects required sophisticated substructure search concepts, many of which would be hard to express in standard smarts notation. We made some interesting extensions to both smarts and matching concepts in order to express the ideas or chemists were describing.

So, back to the original question, would it be a useful annotation for molecules, I would say yes. The software is widely used, over 100 citations, and many people wold be familiar with the results. I would be happy to help with any tooling needed.

Ian

Subject: Re: Lilly Medchem Rules
Posted by thomas on Fri, 08 May 2020 16:02:07 GMT
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I checked the 2012 paper and believe that adding these rules to DataWarrior would be a valuable extension. There have been quite some requests for unwanted feature flagging and it seems Ian Watson and colleagues made an excellent job. However, the effort to add the rules list to DataWarrior would be significant. Like the conversion from SLN to SMARTS, one would have to convert the 2012 rules into idcodes (the openchemlib structure encodings used by DataWarrior) and to write additional code for the more general rules and their combinations with SMARTS. openchemlib query features are not 1:1 compatible with SMARTS, thus in some cases one would have to guess what the intention was and replace with the appropriate query feature.

If the large majority of rules can be expressed with a substructure alone and somebody could translate these rules into idcode using an openchemlib structure editor, that would help a lot...

Thomas

Subject: Re: Lilly Medchem Rules
Posted by evehom on Tue, 15 Sep 2020 14:29:59 GMT
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Hi Thomas

I think the REOS rules by Pat Walters & colleagues from Vertex (https://www.sciencedirect.com/science/article/abs/pii/S13596 4469701163X?via%3Dihub are substantially easier to implement (but also well-established) since they were written as SMARTS and there are 'only' 117. I can provide you with the list if you are interested.

Cheers/Evert