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