CERTARA

Man vs. Machine

Muse Invent identifies and optimizes lead candidates with plausible virtual synthetic chemistry routes

Drug discovery teams often face roadblocks in their projects due to gaps between computer-aided drug design (CADD) and the medicinal chemistry lab. Thus, CADD scientists frequently identify promising ideas only to find that the medicinal chemists are unable to synthesize them.

Muse Invent, only from Certara, is the first commercial software that marries synthetic chemistry with computational drug design for out-of-the-box chemistry thinking. It enables researchers to create drug candidates with novel structures, scaffolds or side-chains that are not only synthesizable, but it also shows how to produce them in the lab.

Muse Invent uses a molecular evolution process to create generations of ideas. These design ideas evolve to optimize the score and satisfy the design criteria, and virtual synthetic reactions are performed in Muse Invent's Synthesis Mode. As a result, all ideas generated have a virtual synthetic pathway to allow assessment of synthetic feasibility.

Chemists take the "Man vs. Machine" challenge

Can chemists distinguish "real" vs. "virtual" synthetic chemistry schemes? Muse Invent was recently showcased at the 2014 American Chemical Society Meeting. At this meeting, 13 chemists were presented with four reaction schemes that showed the synthesis pathways to potential drug candidates. For each reaction scheme, the chemists were asked whether the scheme was from the literature or from Muse Invent. The results were as follows:

- 38% of the chemists surveyed correctly identified the "REAL" reaction scheme from the literature as being real. This is worse than random.
- Chemists correctly identified "virtual reaction schemes" from Muse Invent 59% of the time; slightly better than random guessing.
- Only 1 of 13 chemists surveyed correctly identified the origin of all four reaction schemes.

In short, the chemists were unable to distinguish virtual synthetic chemistry from Muse Invent from a real synthesis from the literature.

Highlights

- Muse Invent is a molecular design workflow designed to accelerate the identification and optimization of lead candidates
- Muse Invent provides a "virtual" synthetic pathway to design ideas that are generated
- Chemists rated the synthetic schemes proposed by Muse Invent as "highly plausible"; they felt the chemistry was realistic and likely to succeed in the lab
- Chemists surveyed were unable to distinguish virtual synthetic chemistry from Muse Invent from a literature synthesis

Muse Invent's virtual synthesis pathways rated highly plausible

Certara scientists demonstrated Muse Invent to a group of chemists at a large chemical company. The chemists were fascinated with this powerful and easy-to-use molecular modeling solution. Some of their comments about Muse Invent included:

- "I like that Muse [Invent] performed reactions that joined two reactants and formed a ring in one operation. That builds a lot of complexity quickly."
- "It's kind of nice to have those synthetic routes there, so even if [they] are not the ones I would have thought of, it's nice to see the reaction scheme and have options to go with."
- "I have a high degree of confidence the reaction schemes would work."

Professional chemists deemed the virtual synthesis pathways proposed by Muse Invent to be highly plausible and indicated that its chemical syntheses could likely be successfully performed in the lab. To quantify the feasibility of Muse Invent's virtual synthetic pathways compared to "real chemistry," the chemists were asked to rate a set of 18 synthesis pathways where:

- Ten of the synthesis pathways were selected from a set generated by Muse Invent
- Eight were taken from literature synthesis of known drugs
- The rating scale was from 1 to 10
  1 = I don't see any way to modify this scheme to work in the lab.
  10 = I believe this would work with little/no modification.

The results? The virtual chemistry reactions received an average score of 7.5 whereas the literature chemistry reactions received an average score of 8.2 with an average standard deviation of 1.6.

Let Muse Invent be your source of inspiration

With Certara's Muse Invent, you can leverage the CADD software solutions your organization is currently using, build more effective predictive models, and generate more new ideas. By identifying and optimizing lead candidates that are also synthetically accessible, Muse Invent bridges the gap between *in silico* drug design and the real world constraints of what can be produced in a lab.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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