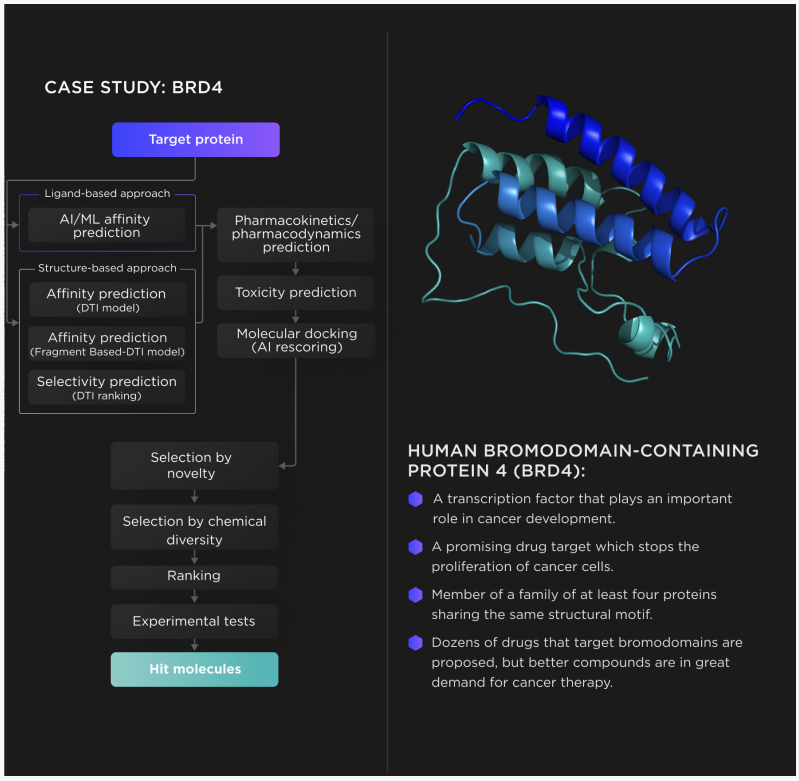
Developing novel inhibitors of BRD4 to fight leukaemia with RECEPTOR.AI SaaS Platform

LONDON, UNITED KINGDOM, August 28, 2022 /EINPresswire.com/ -- RECEPTOR.AI SaaS platform for drug discovery

Our AI-based drug discovery platform allows virtual screening of billions of chemical compounds in just a few hours against the protein target of interest to find the molecules with the best binding propensity, which are called hits.

The platform is fully automated and combines 40+ integrated AI models with in silico approaches, such as AI-assisted molecular docking. Our technique ensures the identification of high-quality hits, which are favourable candidates for further lead discovery and optimisation. Our partnership with top biotech companies allows us to synthesise and experimentally evaluate hit compounds alongside in silico predictions to provide precise and reliable results.



The BRD-4: workflow and features of the target

Application of RECEPTOR.AI SaaS platform

The Receptor.AI SaaS platform allows the user to automate small molecule drug discovery workflow. The platform is modular and fully configurable, allowing the construction of a drug discovery R&D pipeline, which meets any specific needs of the client (integration of the custom-tuned AI models, incorporation of chemical databases and custom datasets, etc.).

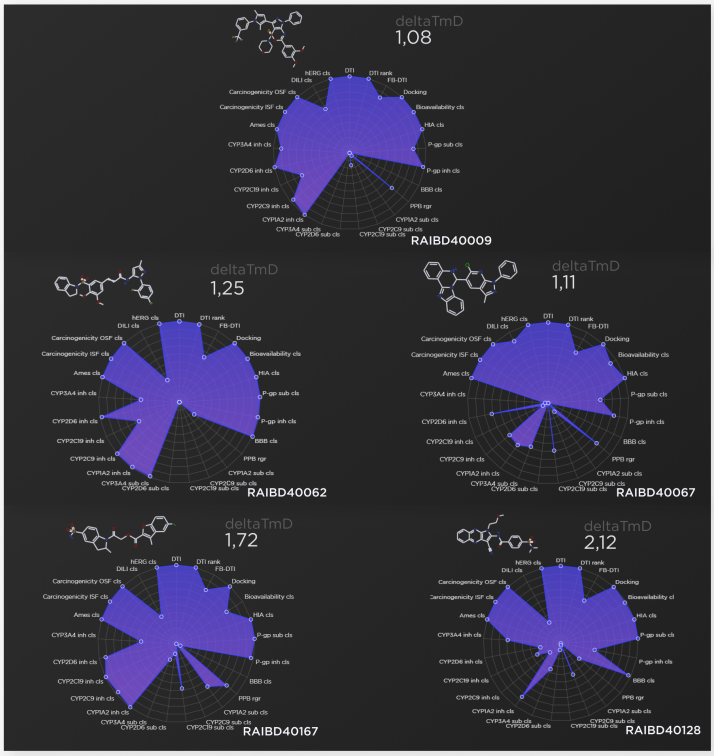
Receptor.AI SaaS platform currently implements the phase of hit discovery and performs two-stage virtual screening: initial screening of the large chemical spaces followed by the precise secondary screening within a preselected pool of compounds. The platform assesses the compounds based on their predicted affinities and pharmacokinetic profiles. The next version of the platform will include lead discovery and lead optimisation modules as well.

Initial screening
The system utilises ligand-based and two structure-based screening techniques in parallel to get the most reliable virtual screening consensus scores. There are more than 35 pharmacokinetic predictive endpoints to choose from, which could be used to select the molecules with desirable ADMET properties. This allows for a much stricter selection of compounds with high predicted affinity, selectivity and activity while ensuring that they are safe, non-toxic and favourable in terms of ADMET parameters.

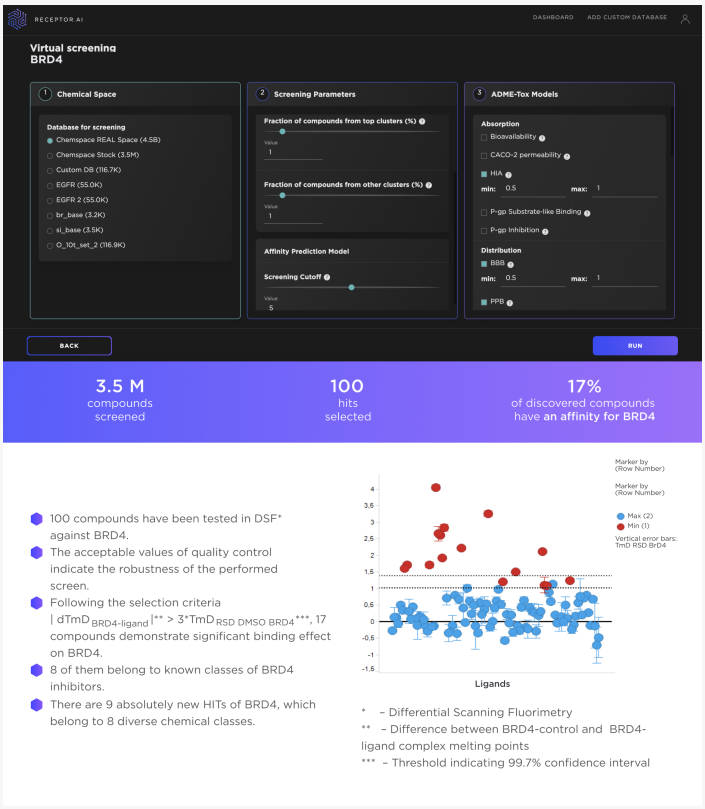
Secondary screening
The system performs fully automated AI-assisted molecular docking of the molecules selected in the initial screening phase. It prioritises the most promising candidates for further synthesis and biological validation. At this stage, the proteome-wide binding profiles are also analysed to identify possible off-target interactions and to get a reliable selectivity prediction.

Technological innovations of Receptor.AI allowed finding novel inhibitors of BRD4 in less than 6 weeks, including their synthesis and biological validation.

Enamine stock database of 3.5M high-quality drug-like molecules was screened using the Drug-Target Interactions (DTI) models integrated into the SaaS platform. After that, our proprietary ADME-Tox models were used to narrow the results with the following ADMET endpoints: Ames mutagenicity, ISF and OSF carcinogenicity, DILI, hERG toxicity, Bioavailability, HIA, BBB crossing, PPB, P-gp and cytochromes



Radar charts generated by SaaS for selected hit compounds



The results of experimental hit validation and the view of the SaaS platform interface

CYP1A2, CYP2C9, CYP3C19, CYP2D6, CYP3A4 substrate-like binding/mutagenicity. 31724 best-ranked compounds were advanced to the secondary screening phase, where they were evaluated by Molecular Docking with a custom-tuned AI-based scoring function.

Predicted ADMET profiles and activities of experimentally validated hit compounds
RAIBD40009. This compound, belonging to the previously unknown class of BRD4 inhibitors, has shown the best activity in experiments. Our multitask ADMET model predicted a low chance of hepatotoxicity and a relatively low rate of plasma protein binding, which is superior to known compounds with affinity to BRD4. The lack of cytochrome degradation may need further optimization, but it is not critical in the hit discovery stage.

RAIBD40062. This compound belongs to a previously unknown class of BRD4 inhibitors and has shown good experimental activity. It has a good distribution/bioavailability/toxicity profile and promising prospects to be biodegradable by cytochromes.

RAIBD40067. This compound belongs to a previously unknown class of BRD4 inhibitors and has shown good experimental activity. It has a high BBB crossing probability, making it a promising candidate for treating CNS-located cancers. It has a good bioavailability/toxicity profile, but its cytochrome degradation profile is questionable, and there is a probability of DILI induction.

RAIBD40167. This compound belongs to a previously unknown class of BRD4 inhibitors and has shown decent experimental activity. It has a good distribution/bioavailability profile and good cytochrome safety. But the risk of DILI is higher in comparison with the previous compounds.

RAIBD40128. This compound belongs to a previously unknown class of BRD4 inhibitors and has shown decent experimental activity. It has a good bioavailability/toxicity profile and a propensity for BBB permeation. But its PPB, DILI and cytochrome degradation profiles require further optimisation.

Details of experimental validation
100 best-ranked hit compounds were passed for experimental validation to our partners. 17 of them have shown affinity to BRD4. These compounds are currently subject to in-depth experimental validation followed by hit-to-lead and lead optimization stages.

Alan Nafiiev
Receptor.AI
+49 1517 2837276
ai@receptor.ai
Visit us on social media:
LinkedIn

try to be careful about weeding out false and misleading content. As a user, if you see something we have missed, please do bring it to our attention. Your help is welcome. EIN Presswire, Everyone's Internet News Presswire™, tries to define some of the boundaries that are reasonable in today's world. Please see our Editorial Guidelines for more information.