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Abstract

Pharmacophore modeling can provide valuable insight into ligand
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receptor interactions. It can also be used
in 3D (dimensional) database searching for potentially finding biologically active compounds and providing
new research ideas and directions for drug-discovery projects. To stimulate the structure-based drug design
against SARS (severe acute respiratory syndrome), a pharmacophore search was conducted over 3.6 millions
of compounds based on the atomic coordinates of the complex obtained by docking KZ7088 (a derivative
of AG7088) to SARS CoV M pro (coronavirus main proteinase), as reportedly recently (Chou, K. C.; Wei,
D. Q.; Zhong, W. Z. Biochem. Biophys. Res. Commun. 2003, 308, 148-151). It has been found that, of the
3.6 millions of compounds screened, 0.07% are with the score satisfying five of the six pharmacophore
points. Moreover, each of the hit compounds has been evaluated for duggability according to 13 metrics
based on physical, chemical, and structural properties. Of the 0.07% compounds thus retrieved, 17% have
a perfect score of 1.0; while 23% with one druggable rule violation, 13% two violations, and 47% more
than two violations. If the criterion for druggability is set at a maximum allowance of two rule violations,
we obtain that only about 0.03% of the compounds screened are worthy of further tests by experiments.
These findings will significantly narrow down the search scope for potential compounds, saving substantial
time and money. Finally, the featured templates derived from the current study will also be very useful for
guiding the design and synthesis of effective drugs for SARS therapy