Case Study: EPHA2

Hit discovery
Date: 12.27. 2022

Hit identification for targeting Tyrosine Kinase EphA2

We used a well-established AI program, DeepMatcher-Hit v1.8, to discover the best pose for targeting EPHA2. Through 2D/3D virtual screening and filtering of one billion chemicals library pool, we identified 200 AI Hits of best poses, including some FDA-approved drugs such as Dasatinib, Osimertinib, and Bosutinib (Table 1). Using binding energy-based association analysis and clustering, we categorized these compounds into 9 distinct groups (Fig. 1 and 2). AI Hit compounds with the highest binding energy values were arranged and ranked in each cluster. Based on these results, our platform is capable of screening novel drug-like compounds at the first-in-class level from highly diverse chemical libraries.

Table 1. AI-Hits with B.E. (kcal/mol) lower than the reference threshold

No	CHEM	PDB	PLI	B.E.	MMGBSA	MW	HBA	HBD	LogP
1	Hit1	[illegible]	-2	-46	-79.612	1345.59	15	8	4.0..
2	Hit2	[illegible]	48	-34	-36.138	496.484	7	2	4.8..
3	Hit3	[illegible]	64	-33	-41.739	518.584	8	2	4.8..
4	Hit4	[illegible]	18	-33	-37.942	572.584	8	2	4.2..
5	Hit5	[illegible]	59	-32	-39.08	519.632	9	2	5.0..
6	Hit6	[illegible]	19	-31	-54.927	461.536	7	2	4.6..
7	Hit7	[illegible]	45	-31	-52.241	486.562	7	2	5.09..
8	Hit8	[illegible]	73	-31	-47.689	539.579	11	2	4.1..
9	Hit9	[illegible]	69	-31	-52.134	535.613	9	3	4.9..
10	Hit10	[illegible]	66	-31	-51.205	527.614	8	2	5.1..
11	Hit11	[illegible]	64	-31	-37.513	513.584	7	2	5.5..
12	Hit12	[illegible]	29	-31	-55.565	431.447	9	2	3.7..
13	Hit13	[illegible]	42	-31	-57.142	491.554	7	1	3.2..
14	Hit14	[illegible]	60	-31	-30.529	510.541	9	3	4.7..
15	hit15	[illegible]	50	-31	-53.743	497.588	7	1	3.6..
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20	hit20	[illegible]	31	-30	-43.624	431.487	7	1	3.7..

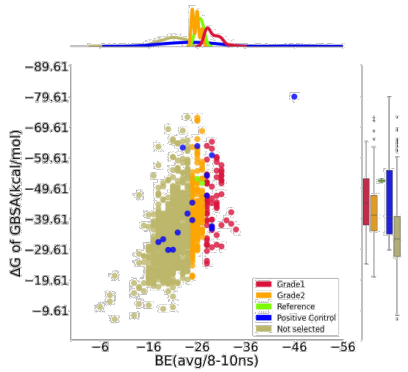


Fig. 1 Ranking evaluation of AI Hits. Correlation between B.E. vs. mm-GBSA free energy. To show the agreement in trends with generally accepted tools, the scores (B.E.) were compared with MMGBSA (Mikko & Olli), and the result shows a moderate correlation.

Association of AI Hit compounds based on B.E

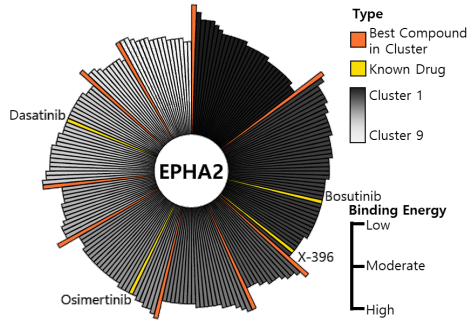


Fig.2 Association analysis of AI identified candidates based on B.E AI-detected compounds grouped by cluster with binding energy bars. Dark colors show clusters, orange/yellow indicate high binding energy for cluster/drug

Distribution of each AI-Hits and their binding energy

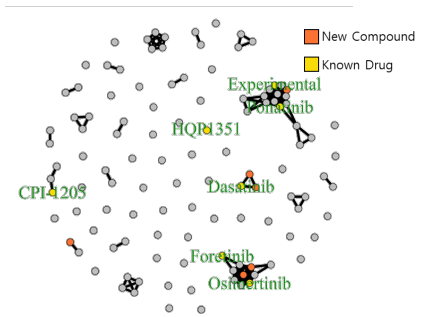
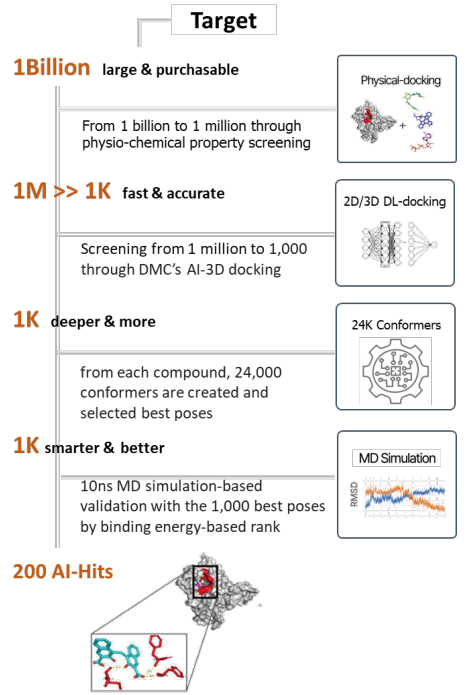


Fig.3 Association network between AI-detected compounds including known drug annotation. Each point represents an AI-Hit, and connected lines indicate the association between compounds. The top hit compounds in each cluster are colored orange, and known drug compounds are colored yellow.

AI program with DeepMatcher-Hit v1.8



- AI-based drug discovery platform "DeepMatcher®-Hit" conducts a comprehensive screening to find appropriate hit compounds using up to 1 billion compound library. The platform is fully automated and modulated into three parts for AI based 2D chemical screening, AI based 3D docking and Molecular docking simulation. Additionally, with our own high-performance computing infrastructure,
- EphA2 receptor tyrosine kinase: Ephrin receptors (Eph) represent the most important class of receptor tyrosine kinases (RTKs). EphA2 is a tyrosine kinase belonging to the Eph receptor family and is known to be produced in large quantities in tumor tissues(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8035212/).
- Further validation and testing are necessary to confirm the efficacy of these compounds in-vitro & in-vivo.