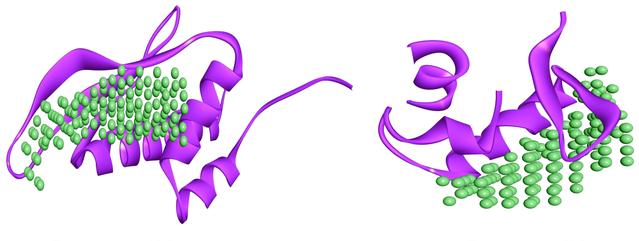
CASE STUDY: **TARGETING RNA-BINDING PROTEIN ADAR1**

RECEPTOR.AI

BACKGROUND:

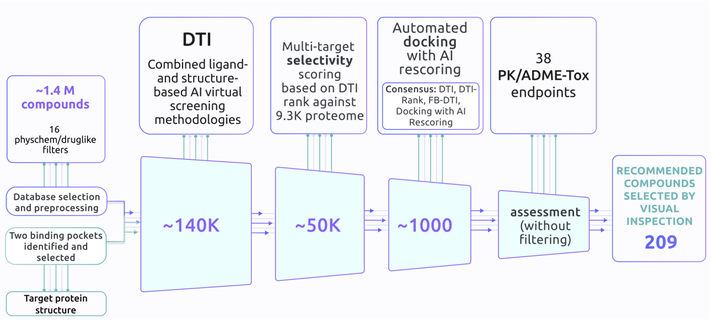
Challenging target: RNA-binding protein which should be targeted by allosteric mechanism only to avoid unspecific off-target effects. Only a few known allosteric inhibitors exist. Two previously unknown allosteric binding pockets were identified by Receptor.AI's proprietary pocket detection AI model.



Pocket #2 Pocket #1

METHODOLOGY:

Virtual Screening result: Enamine common stock collection of 1.4 million compounds was screened. 1000 ranked candidate compounds were prioritized. 209 of them were selected for experimental validation.



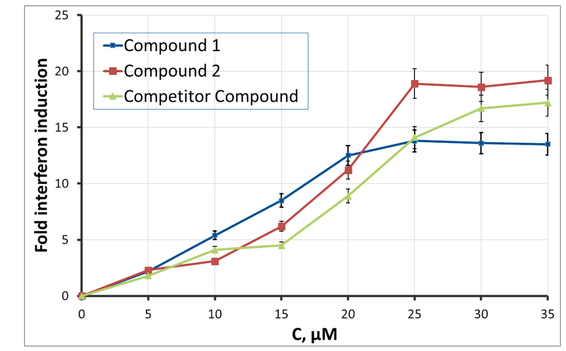
1.4 M	209	4	18x
compounds screened	hit candidates selected	potent compounds identified	interferon induction by lead-like compound

RESULTS:

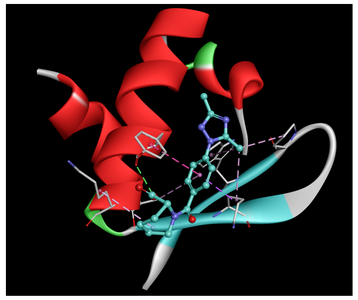
Biological validation: The experimental validation was performed using a high throughput p110 knockout cell-based assay. The criteria for a hit compound was established as a 5-fold increase in interferon induction compared to the control, with the desirable outcome being a 10-fold increase in interferon induction to surpass the efficacy of siRNA alternatives. In this assay, 4 hit compounds were identified, and their ability to induce interferons was confirmed across various cell lines, including A549 p110 KO, HCT116, and B16F10.

Compound	Fold interferon induction, 25 uM	EC 50, uM
#1	13.8	13.2
#2	18.9	16.4
#3	10.7	22.1
#4	8.6	38.0
Competitor #1	14.1	17.5

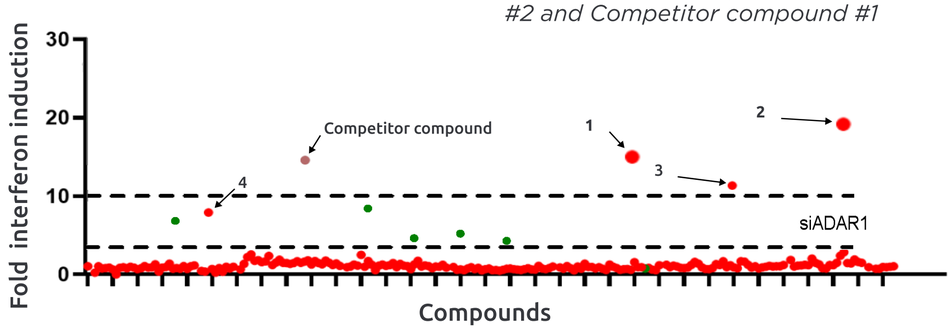
Hit compounds: Hit compounds were validated by the dose-response analysis. Two of them exhibit comparable or superior maximal interferon induction with lower EC_{50} in comparison to a competing compound. This was achieved on a much 2.5 times smaller screening library (209 against 500 for competitors). Active scaffolds have been selected for further series expansion and optimization.



Dose-Response relationship for Compound #1, #2 and Competitor compound #1



The binding pose for the compound #2 mentioned above



Interferon induction observed at 25 uM for Receptor.AI hit compounds #(1-4) obtained through virtual screening, a competitor small molecule, and ADAR1 siRNA