137. Small molecule inhibitors against Cancer-associated P.

(University of Florida)

Asset Overview

Product Type	Small Molecule
Disease Area	Oncology
Indication	Cancer
Current Stage	Lead Optimization
Target	Protein arginine methyltransferase 5
MoA	inhibit protein arginine methyltransferase 5 activity in cellular processes
Brief Description	• These small molecules are inhibitors against protein arginine methyltransferase 5, which plays a role in tumor development and is overexpressed in several cancers, including lymphoma, glioblastoma, colorectal cancer, and prostate cancer. • Inhibiting protein arginine methyltransferase 5 may be an effective treatment for inflammation and auto-immune disorders. Previously reported small molecule inhibitors of this protein have low potency or lack in vivo activity, limiting clinical applications. • Researchers at the University of Florida have developed competitive compounds that inhibit protein arginine methyltransferase 5 activity in cellular processes. • These small molecules have a 25-fold greater binding affinity and 40-fold greater efficacy than previous inhibitors of protein arginine methyltransferase 5. • These small molecules are effective in vivo and have a high potency, making them strong therapeutic candidates for the treatments of cancer and autoimmune disorders.
Intellectual Property	US20220185792A1
Publication	Cryo-EM structure-based selection of computed ligand poses enables design of MTA-synergic PRMT5 inhibitors of better potency. Communications Biology, (2022)
Inventors	Chenglong Li, Xiaozhi Yang, Wei Zhou

Highlights

- Can be incorporated in pharmaceutically acceptable salts, solvates, hydrates, or drugs, facilitating the development of new therapeutics
- Active in vivo, making clinical applications feasible
- Have high binding affinity and efficacy, resulting in a higher potency than other inhibitors

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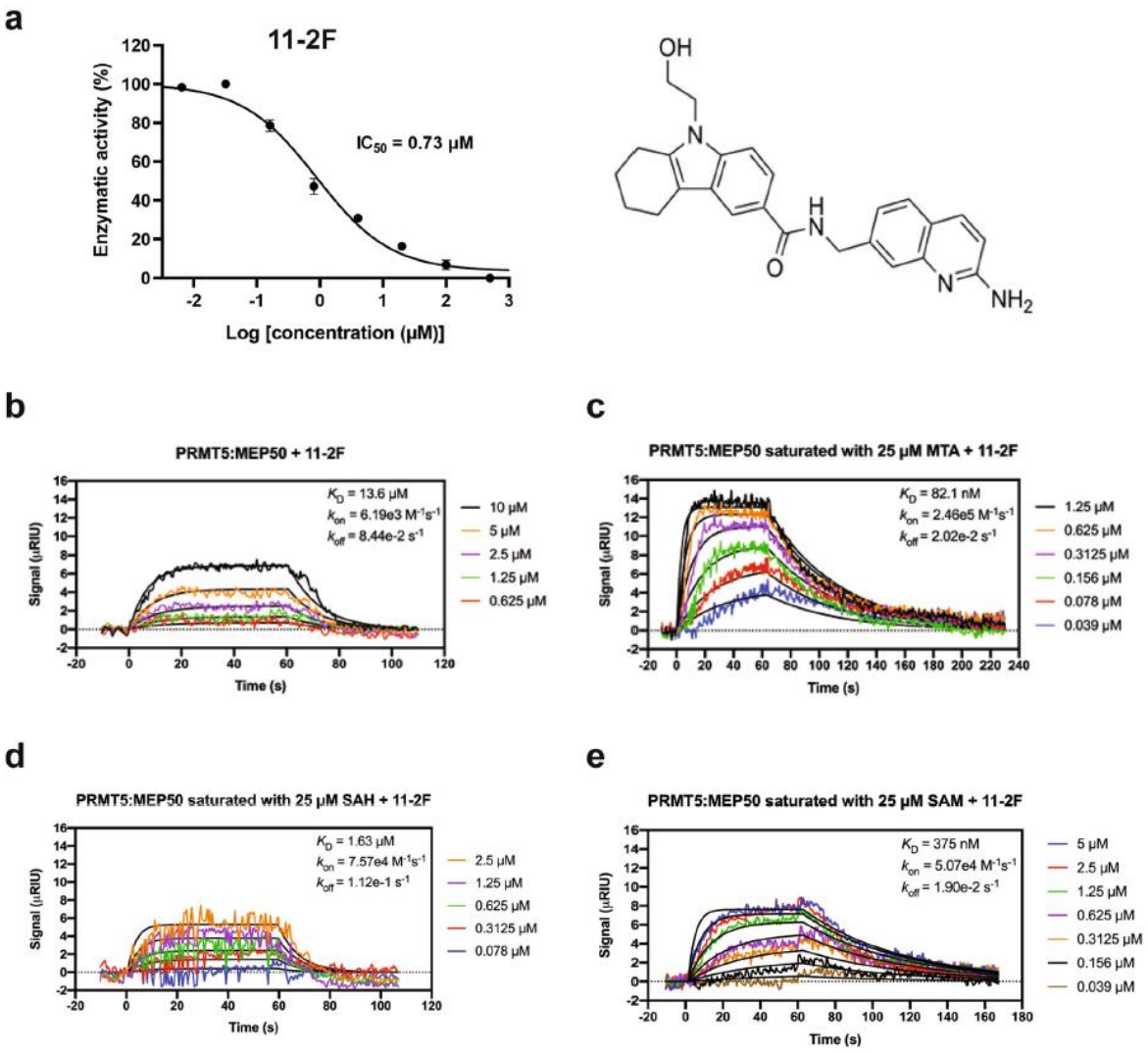
Key Data

An inhibitor 11-2F of PRMT5 exhibits positive cooperativity with MTA



a Dose-dependent inhibition of enzyme activity by 11-2F. IC50 ~730 nM. The chemical structure of 11-2F is showed on the right. Errors: s.d., n = 3. b SPR of 11-2F binding and unbinding to PRMT5:MEP50 in the absence of MTA, leading to a calculated KD ~13.6 μM. c SPR of 11-2F interaction with the enzyme in the presence of MTA. KD ~82 nM. The apparent positive coupling coefficient between 11-2F and MTA is ~166. d, e SPR of 11-2F binding to PRMT5:MEP50 complex in the presence of SAH (d) and SAM (e), showing much weaker affinity, 1.6 and 0.38 μM, respectively, and thus much weaker synergy than MTA.

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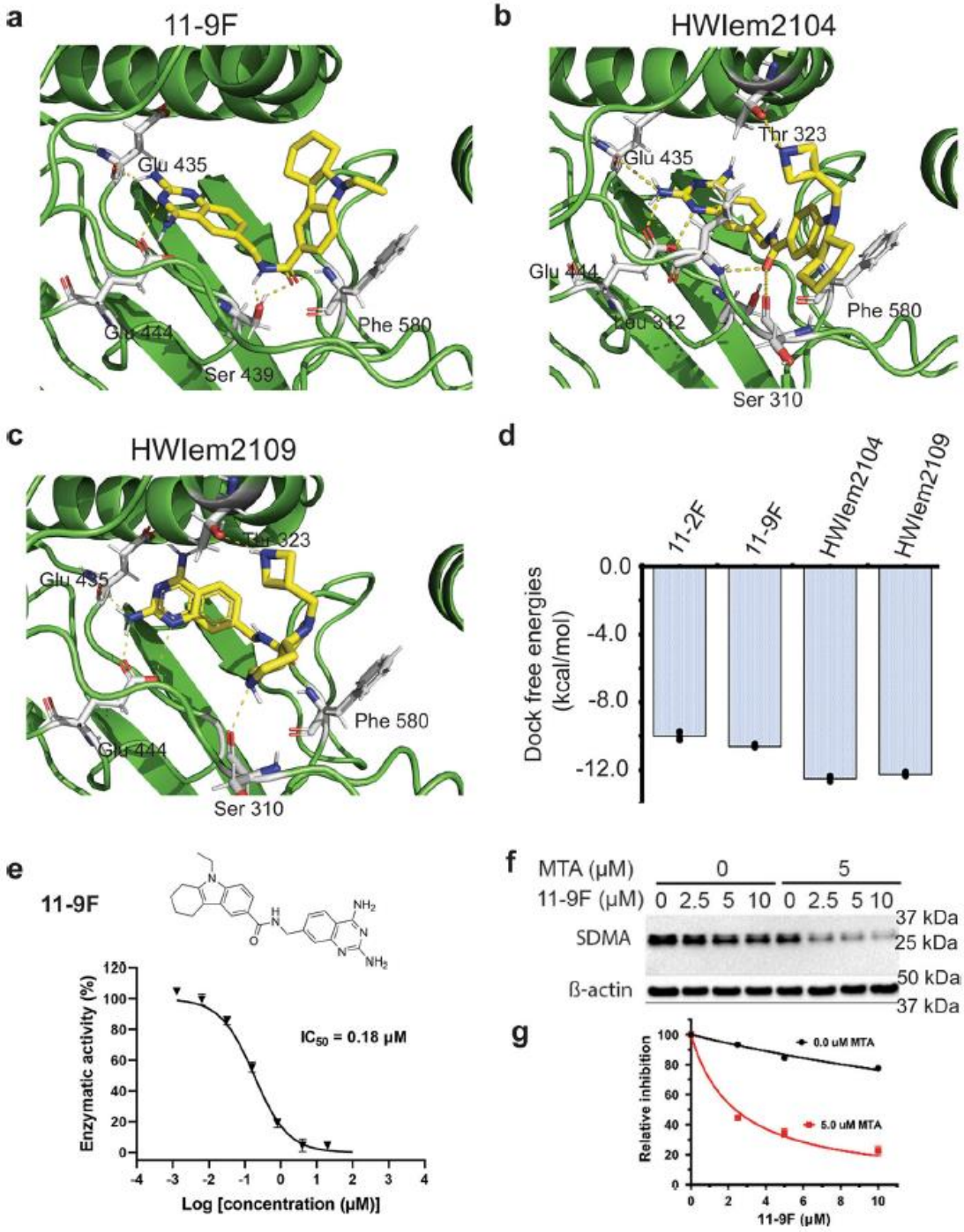
Cryo-EM SBDD yields 11-2F analogs of higher potency in PRMT5 inhibition



To be continued

Key Data

Cryo-EM SBDD yields 11-2F analogs of higher potency in PRMT5 inhibition

Three different compounds were selected based on docking analysis. 11-9 F (a), HWIem2104 (b), and HWIem2109 (c) are showed in the binding pockets with key residues contributing to their stability. d Comparison of relative docking free energy among the four compounds. e The chemical structure of 11-9F (left) and its dose-dependent inhibition of PRMT5: MEP50 enzyme activity, yielding an IC50 ~ 180 nM. Error bars: s.d. (n = 3). f Western blotting of SDMA in cells treated with 11-9 F in different concentrations with 0 and 5.0 μM MTA. g Individual bands were digitized in ImageJ, calibrated against the actin bands, and then normalized against 0 μM 11-9 F in order to generate the two plots (red vs. black). Error bars: s.d., n= 3. The relative inhibition data were fitted with an equation I = 1/(1 + [L] / IC50) to IC50 of 2.4 (red trace) and 32.4 (black trace) μM, respectively. The coupling factor between MTA and 11-9F is ~10, an indicator of strong synergy.