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Profile of novel reversible & first-in-class covalent small molecule inhibitors of PARG

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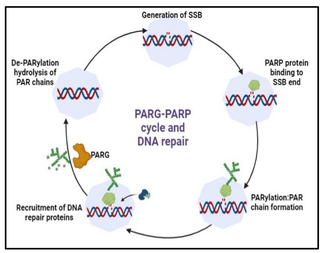
Background

Poly(ADP-ribose) glycohydrolase (PARG) is the primary enzyme involved in the dePARylation process of single strand break repairs (SSBRs). It interacts with various Poly (ADP-ribose) polymerase (PARP) proteins to facilitate error-free and timely DNA repair. The balance between PARP and PARG activity is essential for efficient DDR. Inhibition of PARG leads to altered DNA repair in cancer cells. We have identified highly potent reversible and first-in-class covalent inhibitors with picomolar IC_{50} in the biochemical PARG enzyme assay. The direct pharmacodynamic measurement of PARG inhibition in cells leads to a dose dependent increase in PARylation signature, as seen with both our reversible and covalent inhibitors. Notably, the covalent inhibitors have sustained PARylation even upon washout. Both reversible and covalent compounds show significant anti-proliferative activity in ovarian and breast cancer cell lines.



Inhibition of PARG hydrolase (Biochemical) activity

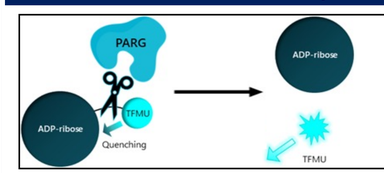


Figure 1: Principle of PARG enzymatic assay
Compounds from different scaffolds were evaluated for inhibition of PARG enzymatic activity using a Fluorescence based assay

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Compound	% inhibition			IC_{50} nM
	1000 nM	100 nM	10 nM	
Ideaya Ref	-	91	84	1.2 nM
Compound A	-	89	85	< 10 nM
Compound B	-	96	91	< 10 nM
Compound C	-	87	90	< 1 nM
Compound D	95	84	31	< 20 nM
Compound E	92	91	78	< 20 nM
Compound F	90	86	53	< 20 nM

Table 1: Biochemical screening results of representative NCEs from reversible and covalent inhibitors

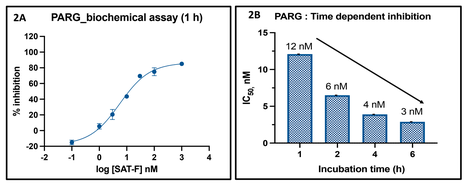

Figure 2: Biochemical potency of covalent molecule SAT-F increases over time
2A : Dose response curve for SAT-F ; **2B** : Time dependent inhibition of PARG activity by SAT-F

- Multiple compounds demonstrate IC_{50} in low nM range
- ***Satya's covalent PARG inhibitor SAT-F shows time dependent increase in potency in biochemical assay (Figure. 2B)***

Pharmacodynamic readout : Increase in PARylation

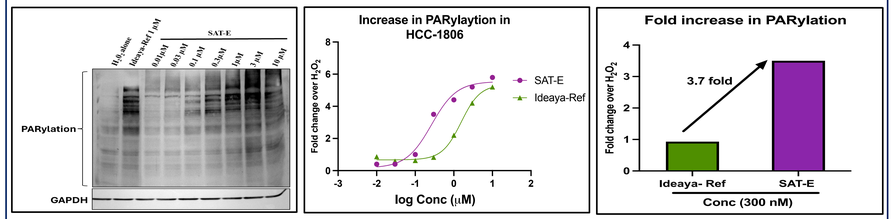

Figure 3A: Effect of SAT-E (reversible inhibitor) and Ideaya-Ref on increase in PARylation upon induction of DNA damage by H_2O_2. SAT-E demonstrates a **3.7-fold** higher PARylation compared to the Ideaya-Ref molecule

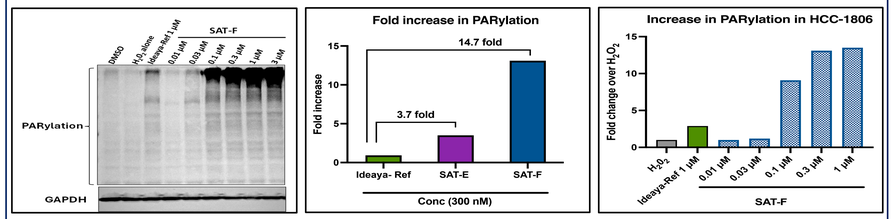

Figure 3B: Covalent inhibitor SAT-F demonstrates a **14.7-fold** higher PARylation compared to Ideaya-Ref molecule

Covalent inhibitor shows sustained PARylation after washout

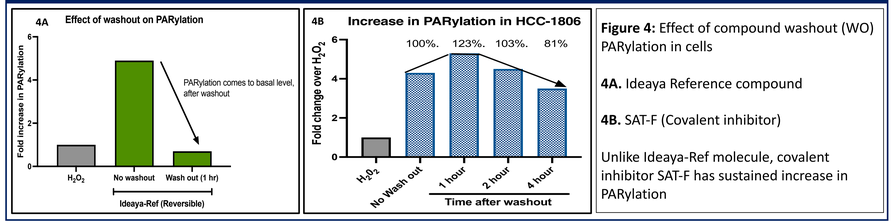

Figure 4: Effect of compound washout (WO) PARylation in cells

4A. Ideaya Reference compound

4B. SAT-F (Covalent inhibitor)

Unlike Ideaya-Ref molecule, covalent inhibitor SAT-F has sustained increase in PARylation

Docking mode of reversible and covalent PARG inhibitors

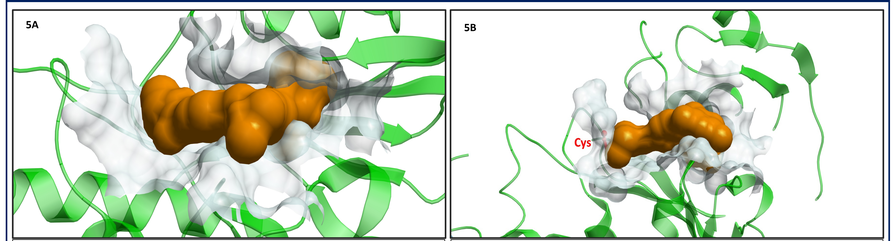

Figure. 5A Docking mode of reversible inhibitor to PARG

Figure. 5B Docking mode of covalent inhibitor to PARG

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PARG inhibitors have significant antiproliferation effect in breast cancer cells

Antiproliferative activity of reversible inhibitors

Compound	HCC-1806 IC_{50} (nM)
Ideaya ref	280
Compound A	180
Compound B	170
Compound C	190
Compound E	340

HCC-1806 is a breast cancer cell line bearing BRCA mutation

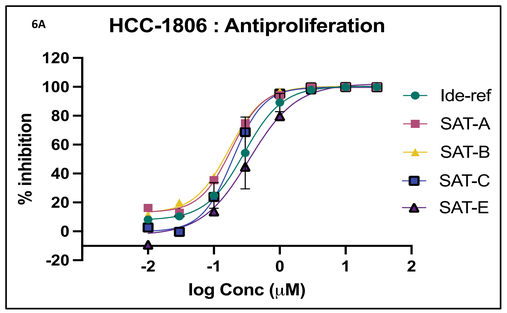
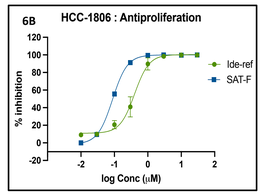


Table 2: Reversible inhibitors SAT-A, B, C and E demonstrate similar / superior antiproliferative activity as Ideaya-Ref compound in the HCC-1806 cell line
Figure 6A: Dose response curves

Compound	HCC-1806 IC_{50} (nM)
Ideaya ref	280
Compound F	90



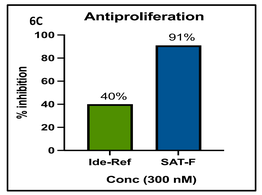


Table 3: Covalent inhibitor SAT-F is > 3-fold more potent than the reversible Ideaya-Ref molecule.
Figure 6B: Dose response curves of SAT-F and Ideaya-Ref; **Figure 6C: %** inhibition at 300 nM

Summary

- ❑ Satya has identified best-in-class reversible and first-in-class covalent PARG inhibitors from diverse chemical scaffolds
- ❑ Satya's reversible inhibitors demonstrate superior PARylation, translating to better cellular activity compared to Ideaya-Ref
- ❑ Satya's first-in-class covalent PARG inhibitors, designed for superior target engagement, result in significantly improved cellular activity
- ❑ Covalent PARG inhibition offers an excellent opportunity to improve clinical outcomes through sustained elevation of PARylation in tumors
- ❑ Combination studies including with Satya's first-in-class RAD51:BRCA2 disruptor are ongoing
- ❑ Development candidates for both reversible and covalent inhibitors expected to be identified by **Q4 2024**

American Association for Cancer Research 2024

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