TACKLE | Cross-European Collaboration for Targeted Degradation of AKR1B10 to Address Anthracycline Resistance

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Geneva Health Forum 2026

1. Introduction

AKR1B10 can metabolize anthracyclines and contribute to chemotherapy resistance.[1]

PROTACs recruit an E3 ligase for protein degradation, with precedent in AKR1C3.[2]

Objective

Design and synthesize AKR1B10-directed candidates for biological validation.

2. Design Strategy

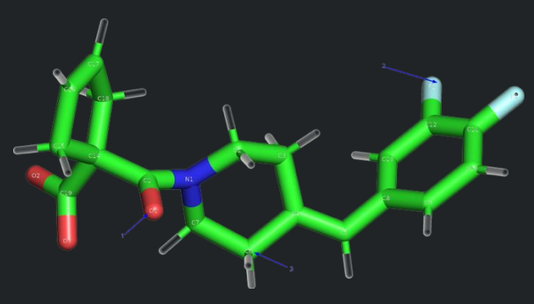
Warhead selection

13
scaffolds assessed

3 known inhibitors
10 virtual-screening hits

IN1 and B06 selected

Exit-vector analysis



B06: F2 attachment

PROTAC design

	P1	P2	P3
IN1	IN1_P1	IN1_P2	IN1_P3
B06	B06_P1	B06_P2	B06_P3

6 candidate structures

2 warheads × 3 PEG-like linker lengths, each with a lenalidomide-derived CRBN recruiter.

Scaffold selection guided by docking, MD, MM/GBSA and solvent-exposure analysis.

3. Results & Discussion

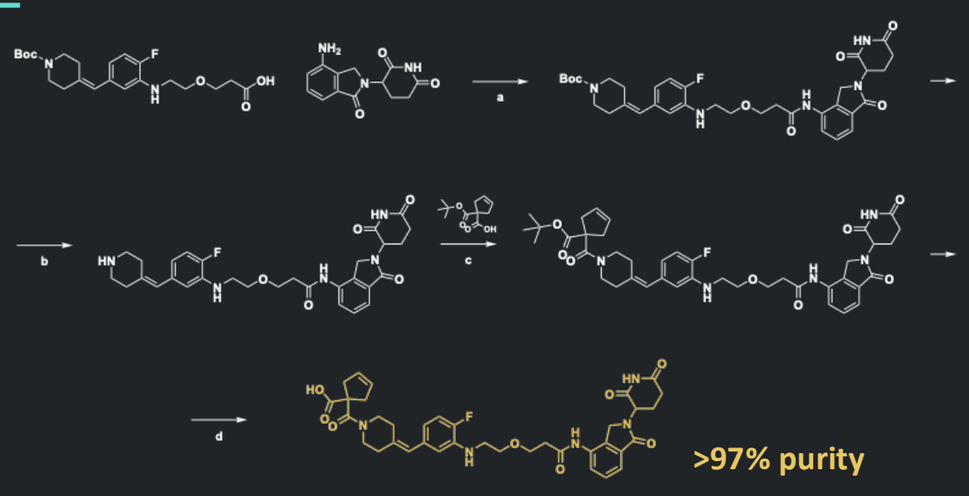
3.1 Computational prioritization

6 designs × 2 starting models × 3 replicas
36 trajectories; ~31.5 µs aggregate sampling

Metric	B06_P1	Other designs
Complex motion	Clearest plateaus	Broader motion or persistent drift
Protein separation	M1/M2 overlap ~43–45 Å	Shifted or broader distributions
Interface contacts	Most reproducible across replicas	More heterogeneous interfaces

Qualitative priority: B06_P1 > B06_P2 > B06_P3 > IN1 series

3.2 Modular synthesis

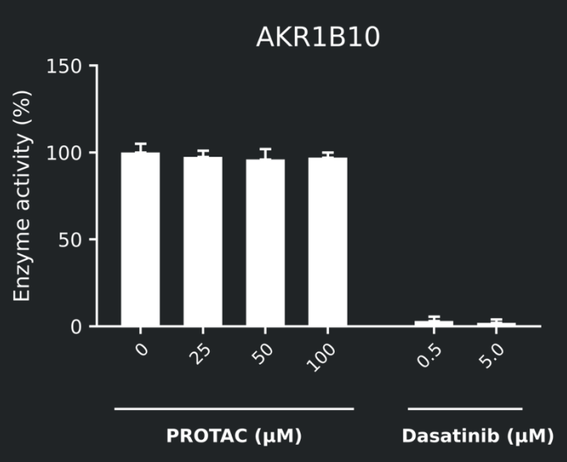


>97% purity

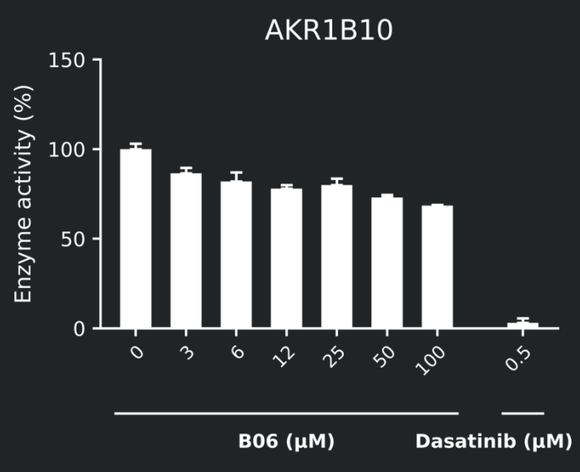
(a) propylphosphonic anhydride, TEA, THF, 90 °C, 3 h, 42%; (b) 4 M HCl in dioxane, DCM, rt, 1 h, quantitative; (c) 1-(tert-butoxycarbonyl)cyclopent-3-ene-1-carboxylic acid, EDC·HCl, HOBt, DIPEA, DMF, rt, 2 h, 59%; (d) TFA, DCM, rt, 2 h, 29%

3.3 Enzyme assays

B06_P1 (PROTAC)

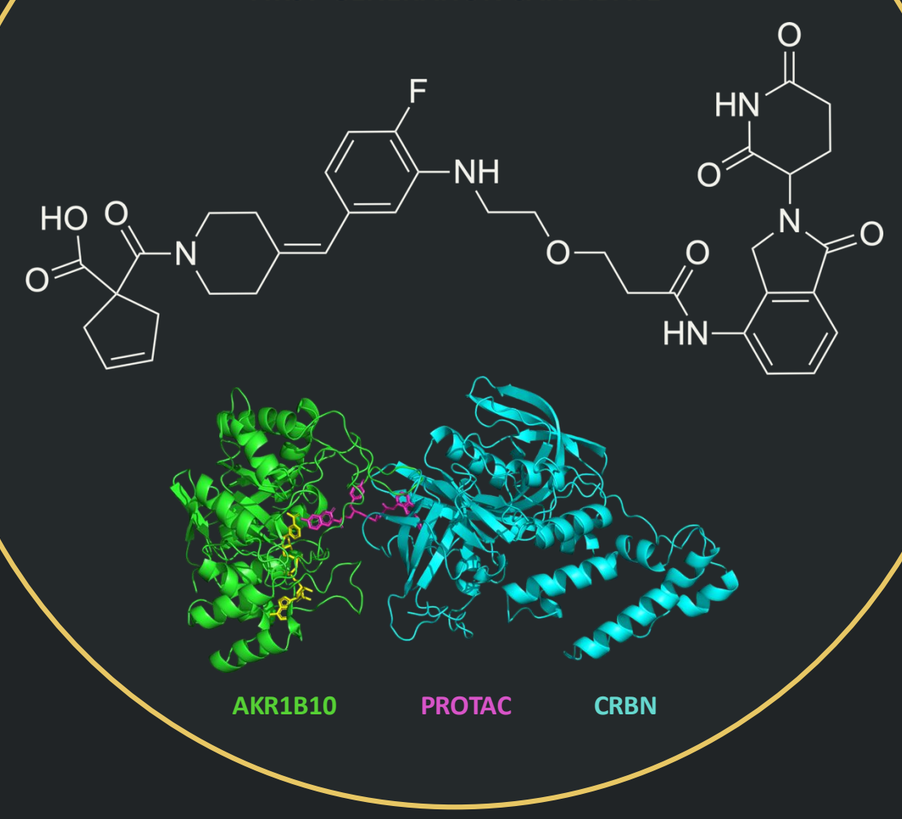


B06 warhead



B06_P1

FIRST-GENERATION CANDIDATE



Predicted assembly.
Experimental degradation testing is the next step.

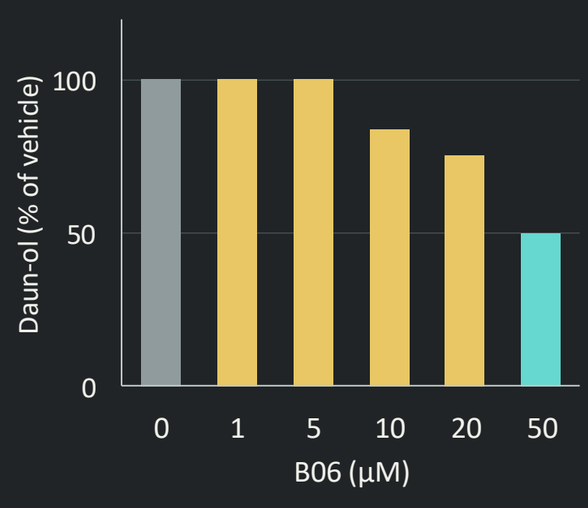
B06: modest inhibition.
B06_P1: no AKR1B10 catalytic inhibition up to 100 µM.

3.4 Cellular readouts

HCT116–AKR1B10

B06 (1–50 µM) did not reduce daunorubicin metabolism.

A549 cells



Values from the preliminary report; vehicle = 100%.

Cellular B06_P1 degradation and anthracycline resensitization remain to be tested.

Enzyme assay: daunorubicin 500 µM, 30 min; UHPLC daunorubicinol readout. Activity relative to DMSO.

4. Conclusions & Next Steps

TACKLE has delivered a first candidate and an integrated workflow. Preliminary biology will guide the next cycle of degrader development.

- Target engagement and cellular degradation assays
- Warhead optimization, including dasatinib[1]
- Anthracycline resensitization studies

5. References

1. Büküm N et al. Biochem Pharmacol. 2021;192:114710. doi:10.1016/j.bcp.2021.114710.
2. Carmona AV et al. Commun Chem. 2024;7:95. doi:10.1038/s42004-024-01177-4.

6. Acknowledgements

1CORE Grant agreement 1010898226 Erasmus+ European Universities Project

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Co-funded by the European Union

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