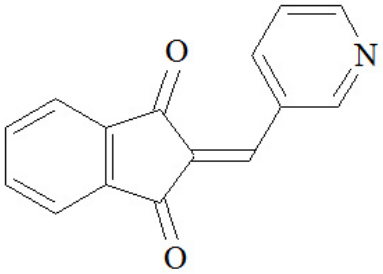


Compound PRT4165 (ST024375) inhibits both Bmi1 (a known oncogene)/Ring1A self-ubiquitination and Top2α ubiquitination in-vitro. Identified inhibitor could be used to directly target the oncogenic properties of Bmi1. Top2α is an important molecular targets for antitumor drugs.

IDNUMBER **ST024375**

Contact us to order . Prices are **0.1mg/$35.00, 0.25mg/$42.00, 0.5mg/$55.00, 1mg/$62.00, 2mg/$92.00, 5mg/$125.00, 10mg/$178.00** plus shipping

Published Identifier: **PRT4165**

CAS 31083-55-3 Formula: C15H9NO2 IUPAC NAME: 2-(3-pyridylmethylene)cyclopenta[1,2-a]benzene-1,3-dione

SMILES: C1(/C(c2ccccc2C1=O)=O)=C/c1cnccc1

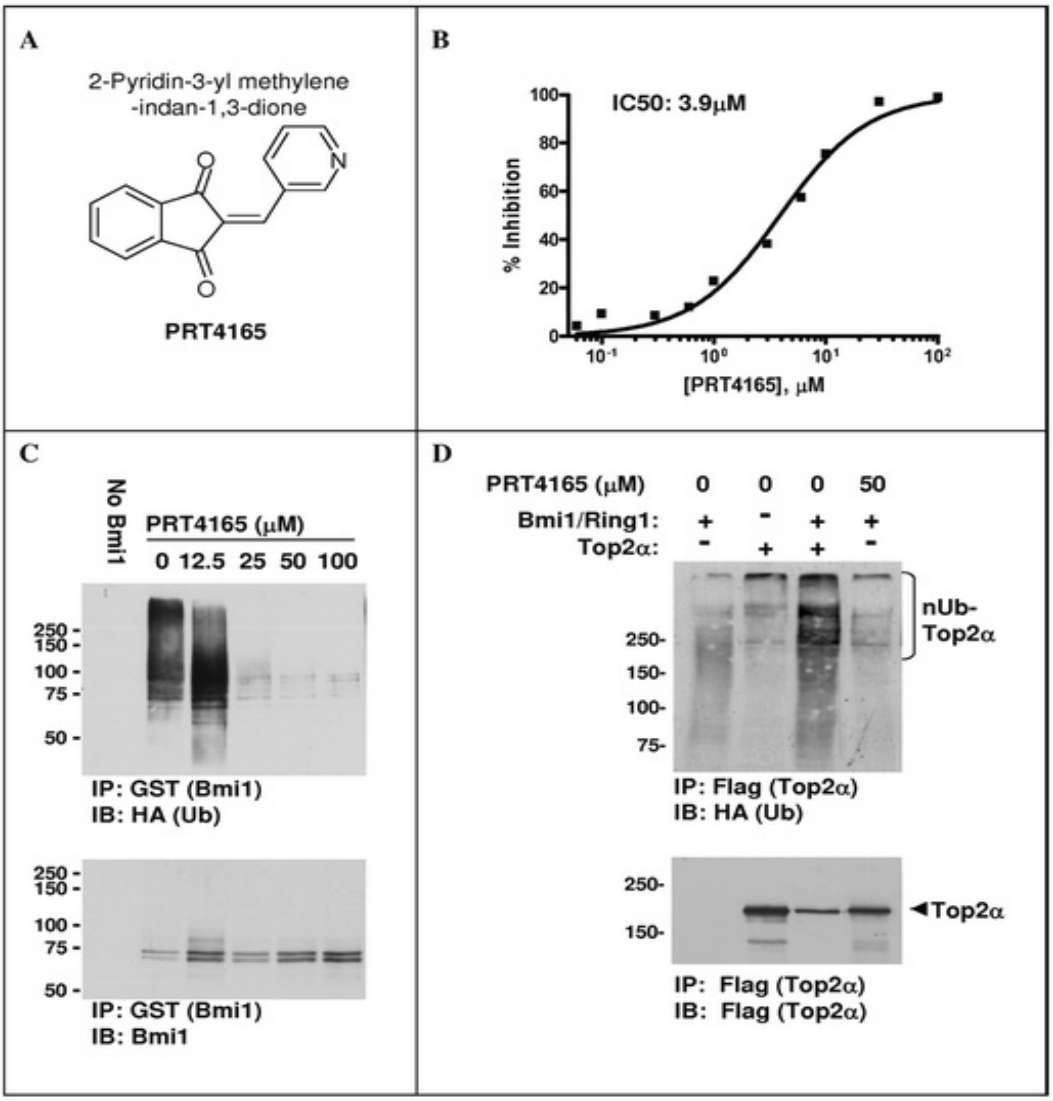
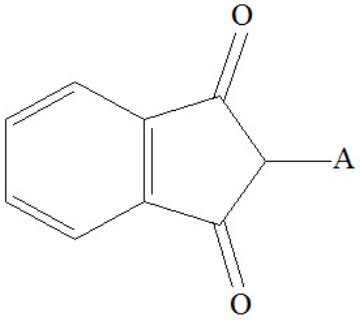


Figure 8. Compound PRT4165 inhibits both Bmi1/Ring1A self-ubiquitination and Top2α ubiquitination in-vitro. A. Chemical structure of PRT4165. B. Inhibition of Bmi1/Ring1A self-ubiquitination as detected by HTRF® assay and determination of IC50 value. C. Inhibition of Bmi1-Ring1A self-ubiquitination by PRT4165 as detected by a Western-blot method. D. Inhibition of Bmi1/Ring1A-induced ubiquitination of immunopurified FLAG-Top2α. HeLa cells were transfected with FLAG-Top2α or empty vector. Twenty-four hours post transfection Top2α was immunopurified on anti-FLAG beads and used as a substrate for ubiquitination with recombinant Bmi1/Ring1A.

PRT4165, ST024375, was acquired from TimTec. Please view **PRT4165 fragmental structural analogs** available for purchase in custom amounts. The following fragment was used for the analogs search; A stands for any atom substitute.



Reference:

Alchanati I, Teicher C, Cohen G, Shemesh V, Barr HM, et al. (2009) The E3 Ubiquitin-Ligase Bmi1/Ring1A Controls the Proteasomal Degradation of Top2a Cleavage Complex – A Potentially New Drug Target. PLoS ONE 4(12): e8104. doi:10.1371/journal.pone.0008104

Abstract

Background: The topoisomerases Top1, Top2a and Top2b are important molecular targets for antitumor drugs, which specifically poison Top1 or Top2 isomers. While it was previously demonstrated that poisoned Top1 and Top2b are subject to proteasomal degradation, this phenomena was not demonstrated for Top2a.

Methodology/Principal Findings: We show here that Top2a is subject to drug induced proteasomal degradation as well, although at a lower rate than Top2b. Using an siRNA screen we identified Bmi1 and Ring1A as subunits of an E3 ubiquitin ligase involved in this process. We show that silencing of Bmi1 inhibits drug-induced Top2a degradation, increases the persistence of Top2a-DNA cleavage complex, and increases Top2 drug efficacy. The Bmi1/Ring1A ligase ubiquitinates Top2a in-vitro and cellular overexpression of Bmi1 increases drug induced Top2a ubiquitination. A small-molecular weight compound, identified in a screen for inhibitors of Bmi1/Ring1A ubiquitination activity, also prevents Top2a ubiquitination and drug-induced Top2a degradation. This ubiquitination inhibitor increases the efficacy of topoisomerase 2 poisons in a synergistic manner.

Conclusions/Significance: The discovery that poisoned Top2a is undergoing proteasomal degradation combined with the involvement of Bmi1/Ring1A, allowed us to identify a small molecule that inhibits the degradation process. The Bmi1/ Ring1A inhibitor sensitizes cells to Top2 drugs, suggesting that this type of drug combination will have a beneficial therapeutic outcome. As Bmi1 is also a known oncogene, elevated in numerous types of cancer, the identified Bmi1/Ring1A ubiquitin ligase inhibitors can also be potentially used to directly target the oncogenic properties of Bmi1.

ST024375, **Inhibitor PRT4165**, was acquired from TimTec. Please view structurally similar molecules available for purchase.

Download **Inhibitor** **PRT4165** analog structures