**Reference annotations**

**Ref #5.** Skok Ž, Zidar N, Kikelj D, Ilaš J. Dual Inhibitors of Human DNA Topoisomerase II and Other Cancer-Related Targets. J. Med. Chem. [Internet]. 63(3), 884–904 (2020). Available from: <https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b00726>

This article describes the benefits of using medications of dual targets to manage Chemotherapeutics cancer resistant drugs.

**Ref #27**. Zhang X, Bao B, Yu X, et al. The discovery and optimization of novel dual inhibitors of topoisomerase ii and histone deacetylase. Bioorg. Med. Chem. [Internet]. 21(22), 6981–6995 (2013). Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0968089613008031>

This paper shows the the utilization of 5- FU as a key pharmacophore in the structures of structure with reported HDAC and Topo inhibitors

**Ref #28.** Cincinelli R, Musso L, Artali R, et al. Hybrid topoisomerase I and HDAC inhibitors as dual action anticancer agents. PLoS One [Internet]. 13(10), e0205018 (2018).

**Ref #36.** Yu C-C, Pan S-L, Chao S-W, et al. A novel small molecule hybrid of vorinostat and DACA displays anticancer activity against human hormone-refractory metastatic prostate cancer through dual inhibition of histone deacetylase and topoisomerase I. Biochem. Pharmacol. [Internet]. 90(3), 320–330 (2014). <https://linkinghub.elsevier.com/retrieve/pii/S0006295214003311>

This couple of articles report the synergistic anticancer effect upon a concurrent treatment with Topo I/ HDAC II dual inhibitor medications.

**Ref #**51. El‐Sabbagh OI, El‐Sadek ME, El‐Kalyoubi S, Ismail I. Synthesis, DNA binding and antiviral activity of new uracil, xanthine, and pteridine derivatives. Arch. der Pharm. An Int. J. Pharm. Med. Chem. 340(1), 26–31 (2007).

**Ref #**52. Mousa BA, Bayoumi AH, Korraaa MM, Assy MG, El-Kalyoubi SA. One pot Synthesis, DNA binding and fragmentation in vitro of new fused uracil derivatives for anticancer properties. Afinidad. 69(559) (2012).

This couple of articles report the synthetic procedure of 5, 6‑Diamino-1,3-dimethyluracil hydrochloride (17a)