**Highlights**

* A novel set of uracil-linked Schiff’s bases has been designed and synthesized.
* Their cytotoxicity was assessed against three cancer cell lines.
* Lung cancer cells A549 were the most sensitive.
* Compounds **22, 25,** and **30** displayed the most potent activity.
* Compound **22** was further evaluated for its inhibition effect on both HDAC II & Top I targets.
* Apoptosis induction, BAX, Bcl2, and cell cycle analysis were performed as well.