Design, Synthesis and Cytotoxicity Evaluation of New 3, 5-Disubstituted-2- Thioxoimidazolidinones

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Abstract: ***Background:*** Some 2-thioxoimidazolidinones have been reported as anti-prostate and anti-breast cancer agents through their inhibitory activity on topoisomerase I that is considered as a potential chemotherapeutic target.

Objective: A new series of 3,5-disubstituted-2-thioxoimidazolidinone derivatives **10a-f** and their S-methyl analogs **11a-f** were designed, synthesized and evaluated for cytotoxicity against human prostate cancer cell line (PC-3), human breast cancer cell line (MCF-7) and non-cancerous human lung fibroblast cell line (WI-38).

Results and Method: While compounds 10a-f showed a broad range of activities against PC-3 and MCF-7 cell lines IC50 = 34.0 – 186.9 and 24.6 – 147.5 µM respectively), the S-methyl analogs 11a-f showed (IC50 = 22.7 – 198.5 and

188.2 – 16.9µM respectively) in comparison with 5-fluorouracil (IC50 = 60.7 and 40.7 µM respectively). 11c (IC50 22.7 and 29.2 µM) and 11f (IC50 = 28.7 and 16.9 µM) were the most potent among all compounds against both PC-3 and MCF-7 respectively with no cytotoxicity against WI-38.

Conclusion: The newly synthesized compounds showed good activity against PC-3 and MCF-7 cell lines in comparison with 5-fluorouracil. Compounds **11c** and **11f** bound with human topoisomerase I similar to its known inhibitors and significantly inhibited its DNA relaxation activity in a dose dependent manner which may rationalize their molecular mechanism as cytotoxic agents.