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Design and synthesis of novel non CYP2D6 mediated Tamoxifen analogues

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Tamoxifen (TAM) is a widely used drug in the prophylaxis and treatment of breast cancer. TAM is metabolized to the more active 4-hydroxytamoxifen (4-OH-TAM) and endoxifen by cytochrome P450 (CYP) mainly CYP2D6 and CYP3A4 enzymes. Due to the genetic polymorphisms in CYP2D6 genes, high variation in the clinical outcomes of TAM treatment is observed among women of different populations. To address this issue, novel TAM analogues with possible altered activation pathways were synthesized. These analogues were tested for their antiproliferative action on MCF-7 breast cancer cell lines as well as their binding affinity for estrogen receptor (ER) ER-α and ER-β receptors. These entire novel compounds showed better antiproliferative activity than did TAM on the MCF-7 cells. Moreover, compound 1 exhibited a half maximal growth inhibition (GI_{50}) that was 1000 times more potent than that of TAM (GI50<0.005 μM vs. 1.58 μM, respectively). Along with a broad spectrum activity on various cancer cell lines, all the TAM analogues showed considerable activity on the ER-negative breast cancer cell line. For further study, compound 2 was incubated in human liver microsomes (HLM), human hepatocytes (hHEP) and CYP2D6 supersomes. The active hydroxyl metabolite was detected after incubation in HLM only, implicating the involvement of other enzymes in its metabolism. These results prove that this novel series of TAM analogues might provide improved clinical outcomes for poor 2D6 metabolizers.

Biography

Nermin S Ahmed is currently a Lecturer in Chemistry for Engineering at the German University in Cairo. She has completed her Bachelor's degree from Ain Shams University, Cairo in May 2000. She has completed her Master's in Science in the German University in Cairo in October 2007 and her PhD from the same University in June 2010. Her research interest includes design and synthesis of novel pharmaceutical moieties and analysis using GC/MS techniques.

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