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Design and Synthesis of Novel Non CYP 2D6 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 (GI50) that was 1000 times more potent than that of TAM (GI50 <0.005μM 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

Nehal has got her Master's degree in Pharmaceutical Chemistry from the German University in Cairo in 2015. She is currently working as a Research Assistant in Zewail City of Science and Technology. Moreover, Nehal is a Drug Design Ph.D. student in Zewail City. She has 2 publications in reputable international journals as well as an accepted Poster in another international conference.

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