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Novel quinuclidinone derivatives induced apoptosis in human breast cancer via targeting p53

Malki, A.[a], Elbayaa, R.Y.[b,c], Ali, O.[d], Sultan, A.[d], Youssef, A.M.[b,e]

[a] Department of Biomedical Science, College of Health Sciences, Qatar University, Doha, Qatar

[b] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt

[c] Department of Analytical & Pharmaceutical Chemistry, Faculty of Pharmacy & Drug Manufacturing, Pharos University in Alexandria, 21311, Egypt

[d] Department of Biochemistry, Faculty of Science, Alexandria University, Alexandria, Egypt

[e] College of Pharmacy, Al Ain University of Science and Technology, Al Ain, United Arab Emirates

Abstract:

Small molecules that can target human cancers have been highly sought to increase the anticancer efficacy, the present work describes the design and synthesis of novel series of five quinuclidinone derivatives (2a-2e). Their anticancer activities were investigated against breast cancer cells MCF-7, MDA-MB-231 breast cancer cells harboring mutant p53 and normal breast counterpart MCF-12a. Derivative 2e reduced proliferation of MCF-7 and MCF-12a while it has no effect on MDA-MB-231. Derivative 2e induced apoptosis in MCF-7 cells which is further confirmed by TUNEL assay and it reduced the percentage of cell in G2/M phase as confirmed by increased expression of cyclin B and reduced expression of cyclin D1. Derivative 2e reduced expression levels of Mdm2, Akt and ERK1/2 by and increased expression level of p53. Moreover, the apoptosis induction by 2e was also inhibited by PFT-α as evidenced by non-significant induction of apoptosis after treatment of MCF-7 cells with both derivative 2e and PFT-α. In addition, docking study reveals that derivative 2e has a binding pattern close to the pattern observed in the structure of the lead fragment 5,6-dimethoxy-2-methylbenzothiazole bound to T-p53C-Y220C. The above findings demonstrate that derivative 2e induces apoptosis in MCF-7 cells via targeting p53 which merits further development. © 2017 Elsevier Inc.

Reference: