Antiproliferative effects of new N-alkylamino carbazole derivatives on breast cancer cell lines

D. Iacopetta[1], A. Chimento[1], R. Mazzotta[1], A. Capasso[2], R.A. Mordocco[1], F. Grande[1], M.S. Sinicropi[1], A. Caporale[2], F. Di Cristo[2], A. Foglia[2], P. Longo[3], V. Pezzi[1], C. Saturnino[2]

[1]Dept. of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Arcavacata di Rende, (CS), Italy
[2]Dept. of Pharmacy, University of Salerno, 84084 Fisciano (SA), Italy
[3]Dept. of Chemistry and Biology, University of Salerno, via Giovanni Paolo II, 132, 84084 Fisciano (SA), Italy

Chemotherapics used in cancer treatment elicit pleiotropic effects interfering, for instance, directly on DNA metabolism or endoplasmic organelles functions. DNA has been a remarkable bioreceptor for a large number of molecules still remaining one of the major biological target for the design of anticancer agents. Amongst them, carbazole derivatives represent an important and heterogeneous class of anticancer agents, which have been reported not only to intercalate DNA but also to inhibit telomerase and topoisomerase activity and regulate protein phosphorylation. These compounds drew a growing interest over the last two decades and a few representatives as, for instance, ellipticine [5,11-dimethyl-6H-pyrido(4,3-b)carbazole] and rebeccamycin [1,11-dichloro-12-(4-O-methyl-β-D-glucopyranosyl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione], two naturally occurring carbazole alkaloids displaying DNA intercalative antitumor activity, have been effective for the treatment of cancer. Starting from ellipticine, many analogues have been synthesized and tested for their antitumor activity, showing satisfactory results in several cancer type and, most importantly, in metastatic breast cancer. Ellipticine and its derivatives are able to trigger a variety of biological responses caused by the interaction with specific cellular compartments, as nucleus, mitochondrion and endoplasmic reticulum. Because of their polycyclic, planar and aromatic structure, carbazoles activity is strictly related to their ability to intercalate DNA, which remains one of the main targets for cytotoxic carbazoles. However, carbazole derivatives showed also the ability to interfere with DNA-dependent enzymes, as topoisomerases I/II and telomerase, or against other targets such as cyclin-dependent kinases and estrogen receptors. Out of all the carbazole derivatives tested for their cytotoxic activity, only some have entered clinical trials and only very few have been approved for the treatment of cancer so far, because of the occurrence of severe side effects or multidrug resistance. Herein we report the design and the synthesis of new series of N-alkylamino carbazole derivatives. These compounds have been prepared following a procedure recently optimized in our laboratories. We also examined the effects of these compounds on cell proliferation against estrogen receptor positive (ER+) MCF-7 and estrogen receptor negative (ER-) MDA-MB-231 human breast cancer cell line at different concentration using the MTT assay. We found that one of them significantly reduced cell proliferation in both breast cancer cells line, whereas others compounds did not show considerable negative effects. The inhibitory effect elicited by this compound on triple negative breast cancer cell line (MDA-MB-231), unresponsive to anti-estrogens, could open new perspectives for novel pharmacological approaches in breast cancer therapy.