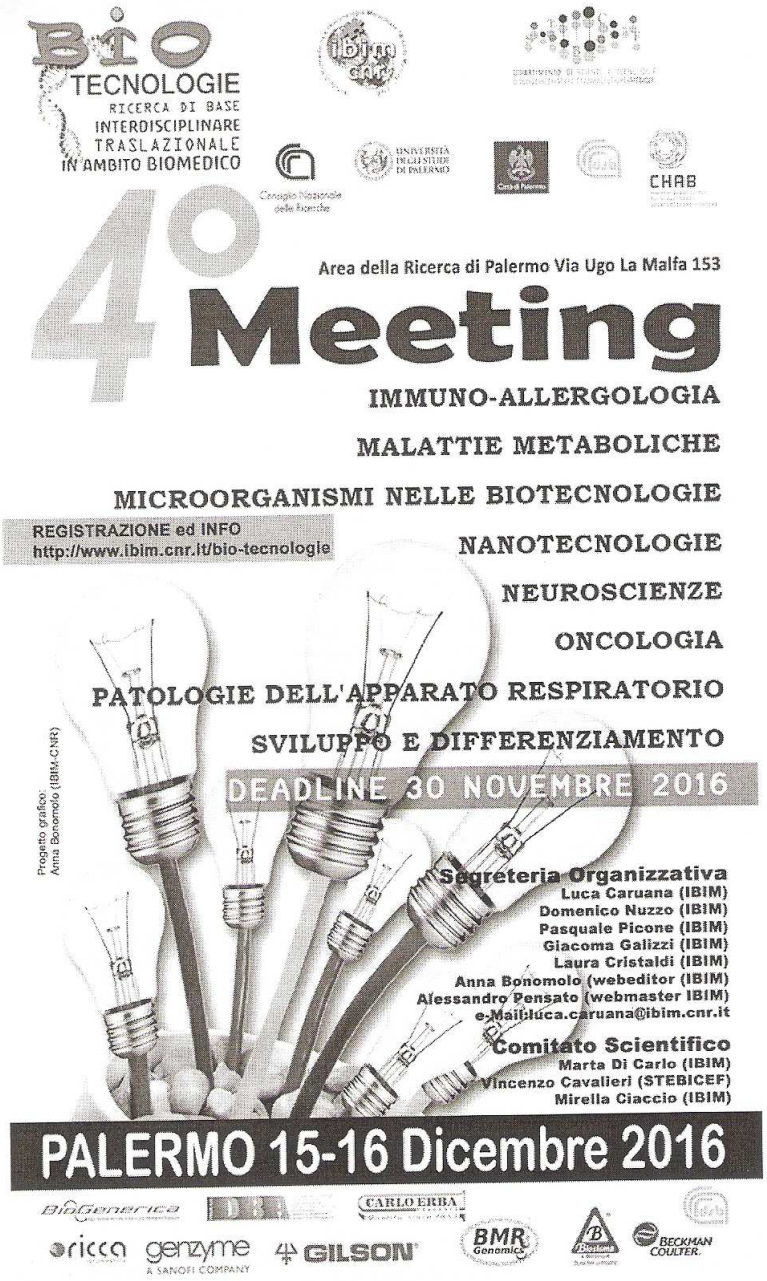
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Synthesis and antiproliferative activities of two new analogs of tetrazepinones

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Drug resistance in cancer treatment calls for the availability of new chemotherapeutic agents able to overcome this phenomenon. In the literature is reported the synthesis of some benzo-1,2,3,5-tetrazepin-4(3H)-ones which, like temozolomide, contain the N=N-N(CH_3)CO-N atomic sequence. Tetrazepinones were shown to be much more active than temozolomide when tested against a variety of alkylating agent resistant cell lines such as SF-188 (human brain cancer), WiDR (human colon cancer), OVCAR-3 (epithelial ovarian cancer) and MCF-7 (human breast cancer). All the experimental results so far obtained suggest that tetrazepinones follow a mechanism of action different from that of temozolomide, but still it is not well established. Based on the encouraging results, we report the multistep synthesis and the biological results of two new analogs of tetrazepinones: the 3,5-dimethyl-6-phenyl-8-(trifluoromethyl)-5,6-dihydropyrazolo[3,4-*f*][1,2,3,5]tetrazepin-4(3H)-one and the 3-(2-chloroethyl)-5-methyl-6-phenyl-8-(trifluoromethyl)-5,6-dihydro pyrazolo[3,4-*f*][1,2,3,5]tetrazepin-4(3H)-one. Both compounds showed a pro-apoptotic activity against HL60 and K562 resistant cell lines. Flow cytometry studies carried out on K562 cells allowed to establish that the methyl derivative induces G_0-G_1 phase arrest followed by apoptosis, whereas the chloroethyl derivative is a not phase-specific agent.

1. Maggio, B et al. (2008) Eur J Med Chem 43: 2386-2394.

2. Maggio, B et al. (2015) Eur J Med Chem 96: 98-104.