Thalidomide repositioning: derivatives with promising anti-breast cancer effects.

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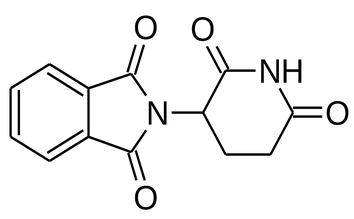
Introduction

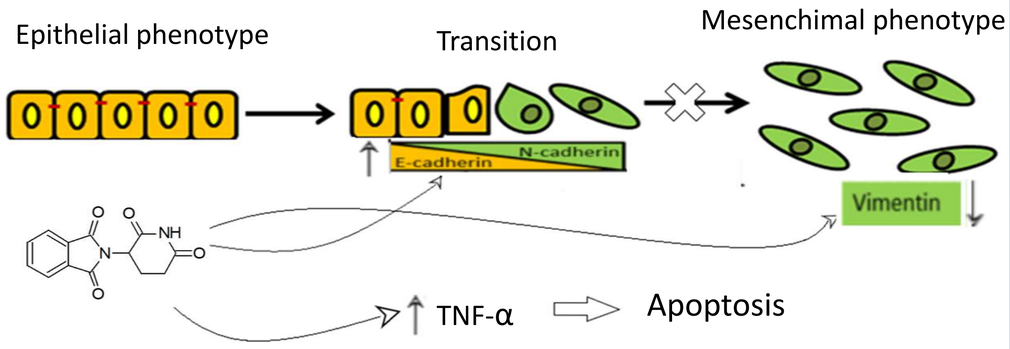
Thalidomide is an old well-known drug firstly used as morning sickness relief in pregnant women and then withdrawn from market due to its severe side effects on fetal normal development. More recently, however, further surveys renewed the interest on this drug. The reason lies in its efficacy in many important disorders including multiple myeloma, breast cancer, and HIV-related diseases. It became clearer that thalidomide exerts multifaceted properties, directing the efforts of many research groups toward the synthesis of several derivatives and the study of their effects, mostly as new anti-cancer agents [1,2].



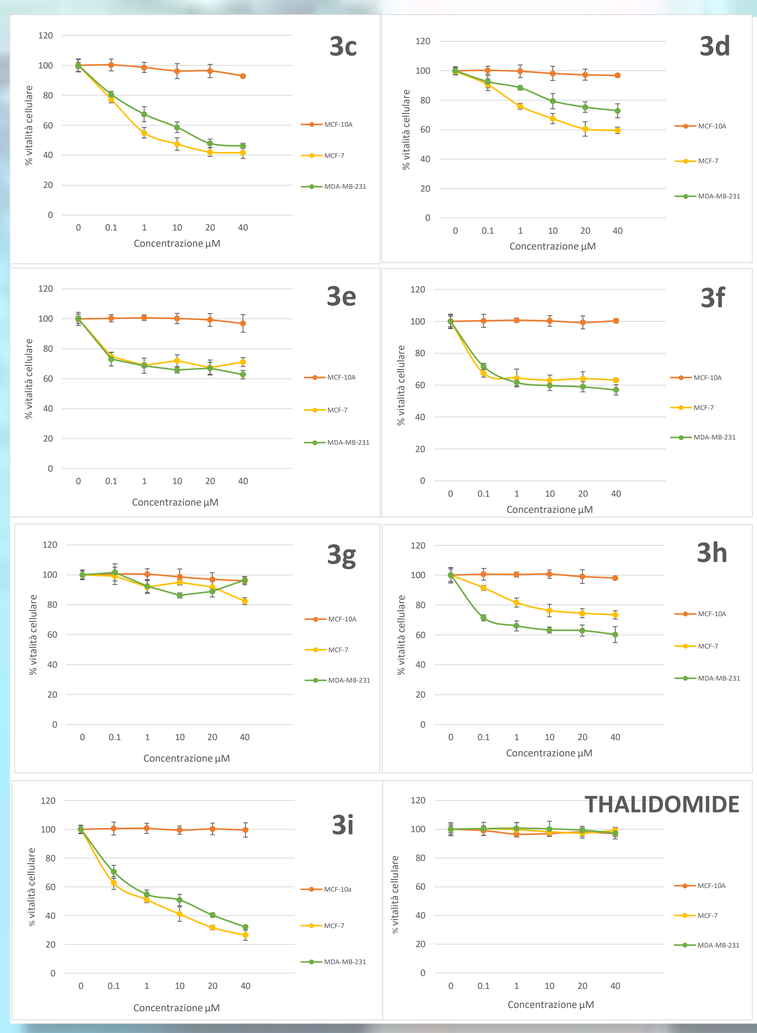
Aim of the work

A recent work on thalidomide correlated compounds [3] demonstrated that they are very effective in inducing cancer cells death by triggering TNFα-mediated apoptosis. The most active compounds, bearing a phthalimido moiety in their structure, were able, as well, to reduce drastically the migration of breast cancer cells, through the regulation of two proteins involved in epithelial-mesenchymal transition (EMT), vimentin and E-cadherin.

Based on these interesting results, a small library of phthalimide derivatives were synthesized and studied for their antitumor activity on breast cancer cells.



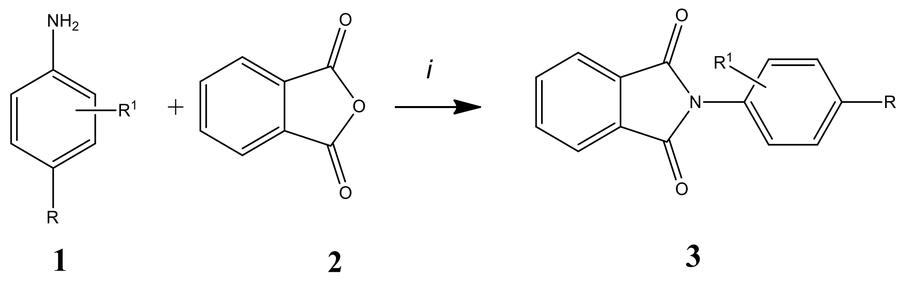
Results and discussion



Compounds 3i and 3c displayed an interesting activity towards MCF-7 cells at the highest concentration tested, 40 µM (cell viability percentage of 26% and 42%, respectively). 3d and 3f exhibited a lower antiproliferative activity towards MCF-7 cell lines (cell viability at 40 µM: 60%, 63% e 63%, respectively). Compounds 3e, 3g and 3h were almost inactive (cell viability > 70% at 40 µM). Compounds 3i and 3c were also the most active towards MDA-MB-231, that is a highly methastatic cell line (cell viability percentage of 32% and 46%, respectively). Compounds 3e, 3f, 3h and 3z were less active. Thalidomide, instead, possessed a poor anticancer activity against both cell lines. All the compounds showed no cytoxicity towards MCF-10A.

Methodology

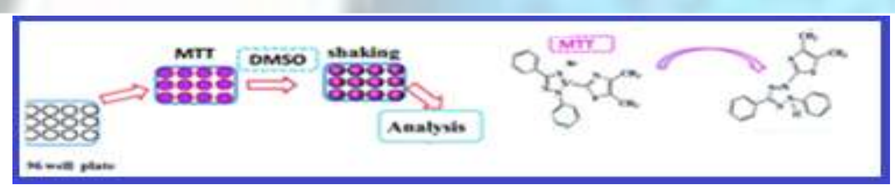
Synthesis



a: R = R[1]= H
b: R = H; R[1] = 2-F
c: R = 4-MeOPh; R[1] = H
d: R = 4-OPh; R[1] = H
e: R = Cl; R[1] = 2-F
f: R = Cl; R[1] = 2-Br
g: R = F; R[1] = 2-Cl
h: R = F; R[1] = 3-F
i: R = 2-Cl-OPh; R[1] = H

Reagents and conditions: (i) Et_3N, toluene, Δ, 5h.

Biological evaluation



The effect on cells viability of thalidomide analogues 3c-i has been measured towards two human breast cancer cell lines, namely estrogen receptor positive (ER+) MCF-7 and triple negative (ER-, PR-, and HER-2/Neu not amplified) MDA-MB-231 cells and against a non-tumoral cell line (MCF-10A) by using 3-(4,5-dimethylthiazol-2-y1)-2,5-diphenyltetrazolium (MTT) test.

Cells were treated with increasing concentrations (0,1, 1, 10, 20 and 40 µM) of each compound for 72 h. Untreated cells were supplemented with the DMSO (final concentration 0.1%) and used as a control. Thalidomide has been used as reference molecule in this assay.

Conclusions and perspectives

Compounds 3c–i were prepared and tested for their effects on cell viability via the MTT test. 3i and 3c, bearing a substituted phenoxy group, exhibited the best activity towards both MCF-7 and MDA-MB-231 cell lines, while thalidomide was inactive at the highest concentration used. All MCF-10A. Other studies will be carried out to assess the capability of ththe compounds showed no cytotoxicity towards the non-cancerous breast cell line e most active compounds to induce apoptosis via TNF-α and inhibit EMT.

References

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