F_2-DABOs ANTAGONIZE CELL PROLIFERATION AND INDUCE CELL DIFFERENTIATION BY INHIBITING A NON-TELOMERIC ENDOGENOUS REVERSE TRANSCRIPTASE

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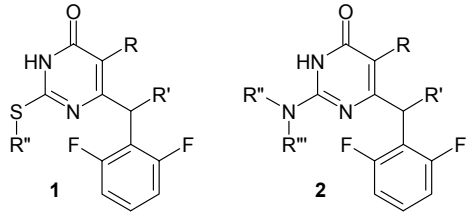
Endogenous, non-telomeric reverse transcriptase (RT) is encoded by two classes of repeated genomic elements, retrotransposons and endogenous retroviruses [1], and is an essential component of the retrotransposition machinery of both types of elements. Expression of RT-coding genes is generally repressed in non-pathological, terminally differentiated cells, but is active in early embryos, germ cells, embryo and tumour tissues, all of which have a high proliferative potential. To clarify whether reverse transcription is functionally implicated in control of cell growth, differentiation and in embryogenesis, recent experiments [2] have been undertaken to inactivate the endogenous RT activity. Indeed, we found that RT inhibition by nevirapine and efavirenz, non-nucleoside RT inhibitors (NNRTIs) widely used in the treatment of AIDS, has a great impact on a variety of cell lines, of both murine and human origin, and can cause a significant decrease of cell growth concomitant with the stimulation of differentiation [2].
2,6-Difluorobenzyl-*S*-DABOs and -*N*-DABOs (F_2-DABOs, **1** and **2**) are the latest generations of a class of NNRTIs developed by our group in the past decade [3]. They are active at low nanomolar concentrations in cell-based and enzymatic assays. With the aim to further investigate the antiproliferative and cytodifferentiating activity of NNRTIs we chose MC1047 and MC1220, respectively, as representatives of the F_2-DABO classes and tested them against endoRT. In experiments with human differentiating cell systems, the two compounds significantly reduced cell proliferation and facilitated the morphological differentiation of cells. These results propose F_2-DABOs as useful tools in preventive and/or curative therapy to counteract the loss of differentiation in de-differentiating pathologies and as antiproliferative drugs in tumour therapy.



R,R'= H, Me, Et, *i*-Pr
R",R'"= alkyl, cycloalkyl

References:
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