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A G-quadruplex/i-motif switch in the HRAS promoter as target for anthrathiophenediones that show a strong anti-proliferative activity in urinary bladder cancer cells

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Evidence that guanine repeats of genomic DNA are able to adopt non-canonical G-quadruplex structures is rapidly growing, in particular since it was demonstrated that these unusual DNA structures occur in the cell. Recently, we have discovered that a G-quadruplex/I-motif switch in the *HRAS* promoter controls gene expression (a) and we thus designed small molecules that efficiently target the molecular switch. These quadruplex-binding ligands will open up a new approach in cancer therapy (a). In the present work we tested a number of antrathiophenediones with two alkyl side arms each bearing a terminal methylamino (2) or delocalized cationic guanidino (1) or chloroacetamidino (3-7) group. We discovered that the chloroacetamidines penetrate cancer cells more efficiently than non-cancer cells, and that they locate in the cytoplasm and nucleus. Among the analogs tested, compound 3, with two ethyl side chains, was found particularly bioactive in urinary bladder cancer cells, as it extinct the expression of oncogenic *HRAS*. We found that 3 stabilizes the G-quadruplex/I-motif switch and inhibits MAZ, a transcription factor that unfolds the switch and activates transcription. The extinction of *HRAS* results in the blockade of the cell cycle in the G2/M phase and in suppression of cyclin D1. This brings the cells to apoptosis (PARP-1 cleavage, caspases 3/9 activation). The impact of compound 3 on pathways downstream of RAS was also analyzed.

Biography

Luigi E Xodo had his degree in chemistry at the University of Trieste (Italy). He worked for a couple of years at the Universities of Reading and Surrey (UK) before being appointed Associate Professor at the University of Trieste. At present, he is full Professor of Biochemistry at the University of Udine (Italy). He published more than 90 papers in reputed journals.

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