OC-4

Citotoxic effects against drug-resistant tumor cells of novel 12*h*-chromeno[2,3-*c*]isoquinolin-5-amine derivatives targeting g-quadruplex dna and monoamine oxidases

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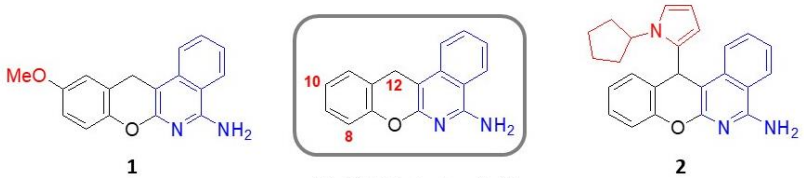
About forty 4*H*-chromene derivatives fused with imidazo[1,2-*a*]pyridine and isoquinolin-1-amine, synthesized through sequential three-component domino reactions [1,2], were assayed for the affinity to G-rich oligonucleotides with known tumorigenic properties (c-KIT, c-MYC, HTS), through the thiazole orange (TO) displacement assay. Only the 12*H*-chromeno[2,3-*c*]isoquinolin-5-amine scaffold proved to bind G-quadruplex DNA (G4-DNA) sequences, and the derivatives **1** and **2** proved to diplace TO from G4-DNA with a potency similar to berberine (positive control).

Recent evidence highlighted the role of monoamine oxidases (MAOs) in sustaining tumor resistance and proliferation [3]. Interestingly, among analogs diversely decorated at C8, C10 and C12, cmpds **1** and **2** achieved MAO A and B inhibition with single digit micromolar IC_{50}s. In addition, they proved to inhibit P-glycoprotein (P-gp), which is associated with multidrug resistance (MDR) in cancer cells.



1
MAO B, IC_{50} = 1.28 μM
P-gp, IC_{50} = 12.3 μM

G4-DNA binders' scaffold

2
MAO B, IC_{50} = 1.96 μM
P-gp, IC_{50} = 6.71 μM

The most potent G4-DNA binders and MAO inhibitors, tested in some tumor cell lines, namely MCF-7 (breast carcinoma), HCT116 (colon cancer), SK-OV-3 (ovarian carcinoma with intrinsic resistance to cisplatin), A2780 (ovarian carcinoma cell) and A2780cp8 (ovarian carcinoma with acquired resistance to cisplatin), showed promi promising anticancer activity in the low μM range (IC_{50}s < 10 μM in most cases).

[1] O.A. Storozhenko, A.A. Festa, D.R. Bella Ndoutoume, A.V. Aksenov, A.V. Varlamov, L.G. Voskressensky, *Beilstein J. Org. Chem.* **2018**, 14, 3078-3087.
[2] X. Yue, A.A. Festa, O.A. Storozhenko, A.V. Varlamov, K. Subramani, A. Boccarelli, R. Purgatorio, C.D. Altomare, L.G. Voskressensky, *Bioorg. Chem.* **2020**, 104, 169.
[3] J.C. Shih, *J. Neural Transm.* **2018**, 125, 1553-1566.