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ATTI DEL CONGRESSO

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Synthesis and antiproliferative Activity of isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one derivatives

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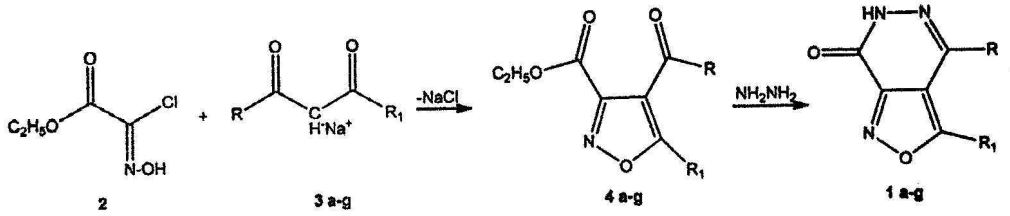
A screening conducted by NCI (USA) on compounds available in our laboratory allowed to discovery 3,4-diphenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one **1a** [1] as an hit compound with a good antiproliferative activity, with IC_{50} values often of sub-micromolar order.
We synthesized some analogs of this hit and also performed some molecular transformations with the aim to identify more potent agents and to understand which structural elements are important for the antitumor activity.



a: R= C_6H_5 R_1= C_6H_5; b: R= CH_3 R_1= CH_3; c: R= C_6H_5 R_1= CH_3; d: R= C_6H_4-CH_3 R_1= C_6H_4-CH_3;
e: R= C_6H_4-CH_3 R_1= C_6H_5; f: R= C_4H_3O R_1=C_6H_5; g: R= C_4H_3O R_1= C_6H_4-CH_3;

We identified another good antiproliferative compound, the 3,4-di(*p*-tolyl)isoxazolo[3,4-*d*]pyridazin-7(6*H*)-one **1d**, and ascertained the importance of the presence of aril, and not alkyl, groups on the isoxazolo-pyridazionone moiety for the antitumor activity. Studies on the cell cycle alteration and on some cellular target (ATM, procaspase-2 proteins and H2AX histone) demonstrated that **1d** is able to produce an increase of the cell population in S fase and to induce cellular death by apoptosis, probably damaging the DNA with double strand breaks. UV-vis titration, viscosity and circular dichroism measurements showed that the compound is able to give an interaction with the DNA double strand.

[1] G. Renzi, V. Dal Piaz, *Gazz. Chim. It.*, 1965, **95**, 1478–1491.