Novel isoxazole derivatives: Synthesis and biological properties evaluation

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Excessive or insufficient angiogenesis (new blood vessels formation) is connected with many human diseases, including cancer, retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis and haemangioma. Thus, the development of specific anti-angiogenesis agents constitutes an attractive therapeutic approach for the treatment of these diseases, emerging the development of new highly active small organic molecules as potent inhibitors of angiogenesis. During the last decade several molecules containing diverse azaheterocyclic rings in their structural framework have been considered, designed, synthesized and investigated as potent inhibitors of angiogenesis [1].

In this respect, we envisioned and implemented the synthesis of several novel molecules containing the fused isoxazole skeleton and evaluate their angiogenesis inhibition derived anticancer activity. The rational to design these compounds was to combine in a single molecule the pharmacophore isoxazole ring with an alkyl-phenyl substituted ring pattern. Thus, we synthesized two distinct types of isoxazoles, one derived from acetophenone (flexible) and a second (rigid) from tetralone substrate.

Results herein indicate that the novel isoxazole derivatives are potent inhibitors of the growth of different types of endothelial cells that play important role in angiogenesis. In addition, they also inhibit the tube formation in human endothelial cells (a marker of angiogenesis).

More specifically, at 100 μM doses, two novel isoxazole derivatives (L23 and L45) inhibited competently the tube formation in human endothelial cell lines, HUVEC and HMEC-1. Similar results we obtained in same cell lines when 30 μM doses were employed. In addition, compound L23 (and to a lesser extent the L45) reduced the expression levels of the major angiogenic factor, Vascular Endothelial Growth Factor (VEGF), in HeLa cancer cells. Finally, many of the compounds tested inhibited the growth of cervical (HeLa) and liver (HepG2) cancer cells. Thus, the present results indicate that these isoxazole derivatives may be used as lead compounds for the development of potent inhibitors of angiogenesis and carcinogenesis.

References