Dobexilate as a Lead Compound in Angiogenesis Inhibition Search

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Fibroblast growth factors (FGFs) are powerful angiogenic polypeptides, whose mitogenic activity requires the presence of heparin-like compounds. Inhibition of angiogenesis-promoting factors such as fibroblast growth factor is considered to be a potential procedure for inhibiting solid tumor growth. Although several peptide-based inhibitors are currently under study, the development of antiangiogenic compounds of small molecular size is a pharmacological goal of considerable interest. We have study the effect of dobexilate *in vitro* and *in vivo* in order to find a minimum compound capable of inhibiting angiogenesis and tumor growth. Cell cultures as well as animal model experiments have shown clearly an angiogenesis suppressing effect event at low concentration as 50 μM. To provide structural information of this process we have solve the three-dimensional structure of a dobexilate-FGF complex. The structure gave us a clear image of the antiangiogesis mechanism of the dobexilate molecule which consists in the steric hindrance of interaction between the FGF molecule and the low affinity membrane receptor of this molecule in the plasma membrane, hampering in this way the beginning of the signalling cascade. Further studies of different groups in the minimal dobexilate structure could give us a more powerful and less toxic antiangiogenic compound using the disruption of the interaction of FGFs with heparin and heparan sulphates as its principal mechanism.

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