Antitumor Active Cobalt-Alkyne Complexes Derived from Acetylsalicylic Acid: Studies on the Mode of Drug Action.

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Cobalt-alkyne complexes are drugs with remarkable cytotoxicity. From the complexes tested up to now we selected the Aspirin derivative [2-acetoxy-(2-propynyl)benzoate]hexacarbonyldicobalt (Co-ASS) as lead compound. Effects of Co-ASS on human breast cancer cell lines were superior to those of already established cytostatic agents. First structure activity studies showed that the activity depended strongly on the nature of the intact cobalt complex. In order to get more insight into the mode of action, we systematically modified the alkyne ligand and determined the cytotoxic properties of the resulting cobalt complexes. Further investigations were performed on the drug lipophilicity, the cellular uptake into MCF-7 and MDA-MB 231 breast cancer cells, the DNA-binding efficacy and the nuclear drug content. The ability to inhibit cyclooxygenase (COX) enzymes was examined for selected compounds. The missing correlation of the high intracellular drug levels (e.g. approximately 150-fold accumulation grade for Co-ASS into MCF-7 cells), the low drug content of the cell nuclei and the diverging results from the DNA binding experiments made a “Cisplatin-like”-mode of action unlikely. Interestingly, the most antitumor active compounds were potent COX-inhibitors (COX-1 and COX-2). They were by far more active than acetylsalicylic acid (ASS, Aspirin). The presented results indicate that cobalt-alkyne complexes of the Co-ASS type, represent a new class of organometallic cytostatics with a mode of drug action in which COX-inhibition probably plays a major role.