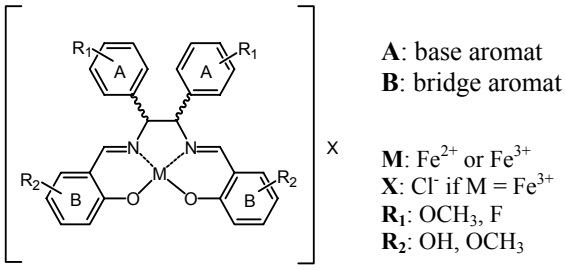
IRON SALEN COMPLEXES AS NOVEL TUMOR THERAPEUTICS: CYTOTOXICITY, DNA CLEAVAGE AND ACCUMULATION STUDIES

Diana Posselt[a]; Axel Bethke[b]; Ronald Gust[a]

[a]Institut für Pharmazie, FU-Berlin, Königin-Luise-Str. 2+4, D-14195 Berlin, Germany
[b]Max Planck Institut für Molekulare Genetik, Ihnestr. 73, D-14195 Berlin, Germany

We synthesized [N,N´-bis(salicylidene)-1,2-diarylethylenediamine]iron(II) and -iron(III) complexes (Fig. 1) in order to develop these compounds as antitumor agents. Similar to the glycopeptide antibiotic Bleomycin, under physiological conditions these iron compounds are expected to catalyse the generation of reactive oxygen species, which subsequently oxidize DNA and RNA, leading to its cleavage up to total degradation.
The introduction of a hydroxyl group into the two salicylidene moieties creates a hydroquinone substructure which can interact with the iron redox system and in this way spontaneously generate free radicals needed for the oxidatitive DNA cleavage.
DNA cleavage properties of the hydroxylated diarylsalen complexes were confirmed *in vitro* using plasmid DNA. In this assay, chinonic salen complexes with hydroxyl groups in position 3 resp. 5 showed higher DNA degradation activity than complexes with the hydroxyl group in position 4. Iron(III)-complexes without hydroxyl groups at the base aromats (B in Fig. 1) only cleaved DNA in presence of a reducing agent.
To determine the antiproliferative activity, we measured the growth inhibition on MCF-7 and MDA-MB-231 breast cancer cell lines. In the cytotoxicity test, iron salen complexes showed a 10-fold higher efficiency on MDA-MB cells compared to MCF-7 cells, despite the significantly lower intracellular uptake.
In both cases the accumulation rate and the influence on cell growth strongly depended on the ligand structure. Complexes with fluorine substituents were taken up to a higher extend than complexes with methoxy groups. And iron salen compounds with the ligand in *d,l* configuration exerted higher cytotoxic activity than their *meso* configured analogues despite their decreased cell uptake.



A: base aromat
B: bridge aromat

M: Fe^{2+} or Fe^{3+}
X: Cl^- if M = Fe^{3+}
R_1: OCH_3, F
R_2: OH, OCH_3

Figure 1: Iron diarylsalen complexes