Abstract

Synthesis of novel ligands for the stabilization of organometallic complexes having potential antitumor activity

The design of new metal complexes as anticancer agents has received considerable interest in recent years. Complexes of titanium (e.g.: titanocene dichloride), lanthanides complexes (e.g.: texaphyrrins lanthanide) and carbenic complexes of gold, silver and copper showed significant biological activity, and have progressed into clinical trials.

Thus, the target of this PhD project are the synthesis of new ligands and metal complexes. Firstly 5 cyclopentadienyl pro-ligands were synthesised: *6-phenylfulvene*, *6-(p-metoxyphenyl)-fulvene* e *6-(3',4'-dymethoxyphenyl)fulvene*, *6-(3',5')-dymethoxyphenyl)fulvene* and *6-(2',4')-dymethoxyphenyl)fulvene*. Then, the synthesis of 12 novel scandium, yttrium and neodymium complexes with these cyclopentadienyl ligands was carried out.

The complexes were tested on DU146 (Prostatic carcinoma) and MDA.MB213 (Breast cancer) to verify inhibition of cell-proliferation, using MTT test with standard procedures. All the complex showed a strong concentration-dependent ability of inhibiting the growth tumor cell, referring to antiblastic activity.

In the last years the synthesis of new carbenic ligands (*N-methyl-N'-[2-hydroxycyclopentan]-4,5-dychloroimydazole iodide*, *N-methyl-N'-[2-hydroxycyclopentan]-4,5-dyphenylimydazole iodide, N-methyl-N'-[(2-hydroxy-2-phenyl)ethyl]-imydazole iodide)* and 8 new complexes of gold, silver and copper was carried out.

The complexes were tested on MCF-7 (human mammary carcinoma expressing the estrogen receptor ERα/ER-positive), MDA-MB-231 (human mammary carcinoma not expressing the estrogen receptor/ER-negative), MCF-10 (breast glandular epithelium), using MTT test with standard procedures. All the molecules showed a good inhibitory effect on the proliferation of two cancer cell lines. Many of them did not showed a any inhibitory effect on healthy cell. Instead, some compounds showed a only a mild effects only at very high concentrations.

Then, it was investigated if the antiproliferative activity of the complex AuL20 on MCF-7 was connected to the mechanisms of regulation of the cell cycle. Therefore, it was evaluated the level of expression of two proteins involved in the regulation of the cell cycle, p53 and p21 with *immunoblotting*, using β-actina as "loading control". Results showed a marked modulation of the expression of p21 and p53, confirming that AuL20 can stop cell proliferation between the G1 and S phase.