

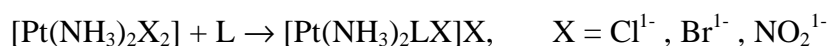
Triamine Complexes of Platinum as Anticancer Agents

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The syntheses and the researches of mono- and dinuclear complexes of platinum (II and IV) with heterocyclic ligands (L = piperazine, Pip, pyrazine, Pyr, 2-aminopyrimidine, 2-AP, cytosine, Cyt, cytidine, Cyt, isicytosine, i-Cyt, 6-fluorocytosine, 6-F-Cyt, 6-fluorisorocytosine, 6-F-i-Cyt, 6-methylisocytosine, 6-CH₃-i-Cyt, imidazole, Imd, benzimidazole, Bimd, benzotriazole, Btaz, theophylline, Thp) and their medical application as antitumor agents are described.

The cis and trans complexes were obtained by general reactions in ratio of the starting complexes and ligands 1:1 (mononuclear) and 2 :1 (dinuclear) :



The purity of the complexes was proved by thin-layer chromatography. The coordination formulae of complexes were confirmed by element analyses and conductometric methods. The presence of intrasphere anions was proved by long-wave IR spectra of complexes. The dinuclear type of complexes was confirmed by the mass-spectrometry (FAB). The nature of donor atoms of ligands was studied by IR and NMR (¹H, ¹³C, ¹⁴N, ¹⁹⁵Pt) spectroscopies.

All ligands in the monocomplexes are coordinated as neutral molecules through heterocyclic nitrogen atom. The bridged coordination of neutral molecules of piperazine, pyrazine and 2-aminopyrimidine was proved also through the nitrogen atom of the ligand ring. The formation of dinuclear complexes with imidazole, benzimidazole, benzotriazole and theophylline is possible only with the anionic forms of the ligands through N(1) and N(3) (Imd, Bimd, cis-Btaz), or N(2) and N(3) (trans-Btaz), or N(7) and N(9) (Thp).

The antitumor properties of the mono- and dinuclear complexes were studied in Cancer Center of Russian Academy of Medicinal Sciences (in vivo on the mouses).

The cis-complexes were indicated to have high antitumor activity, as well as cis-DDP, in respect to leukemia P-388, L-1210 and solid tumors Ca-755, MC-11, LLC.

The trans-complexes had no antitumor activity.

The nature of the intrasphere heterocyclic ligands defines the selective antitumor effect of the dinuclear complexes. The most interest is high antitumor activity of the platinum (II) complex with bridged molecule of pyrazine in respect to resistant cis-DDP tumor L-1210 (ILS - increase life span, %) :

| complex | ILS (L-1210/0) | ILS (L-1210/DDP) |
|---|----------------|------------------|
| (Pt(NH ₃) ₂ Cl) ₂ | 75 | 10 |
| [{Pt(NH ₃) ₂ Cl} ₂ Pyr] ¹⁺ | 78 | 90 |

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