SMALL-MOLECULES ISOXAZOLE AND ISOTHIAZOLE ADJUVANTS IN COMBINATION WITH FIRST-LINE ANTITUMOR DRUGS IN CHEMOTHERAPY OF NEUROEPITHELIAL TUMORS

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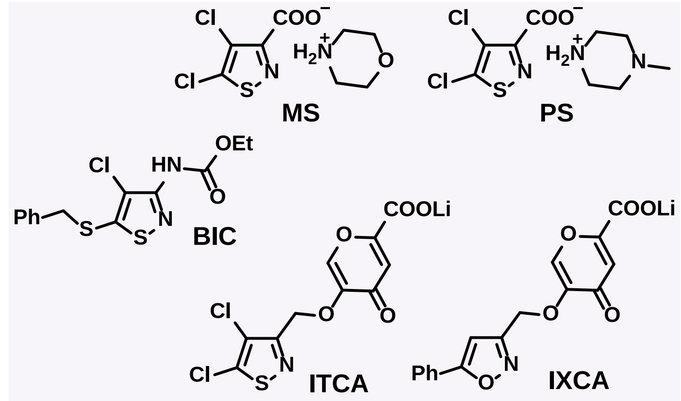
Issue

Chemotherapy remains one of the main options for cancer treatment. But the accompanying side effects often have a strong impact on the patient's body condition and seriously disrupt their quality of life. Using of synergistic adjuvants in combination with therapeutic drugs may be an option to solve this problem. Our goal was to investigate whether some isothiazole and isoxazole small-molecules can act as such adjuvants.

Substances



Experimental methodology

Using original methods we synthesized polysubstituted isothiazole and isoxazole derivatives based on readily available trichlorethylene[1-3]. Their antitumor effect in combination with known cancer-treatment drugs was tested on the cells of neuroepithelial tumors (medulloblastoma, C6 glioma) during standard MTT tests.

Results

Testing MS and BIC in combination with antitumor drugs against medulloblastoma[1]:

Entry	Control	Cytarabine (1 mg/ml)	Cisplatin (0.1 mg/ml) + **MS** (10 mg/ml)	Cisplatin/Cytarabine/Etoposide (0.1 mg/ml) + **BIC** (10 mg/ml)
Cell loss, %	15-19	70	70	60-75

Testing ITCA and IXCA in combination with temobel against glioma C6[2]:

Entry	Control	Temobel (0.4 mg/ml, therapeutic dose)	Temobel (0.004 mg/ml)	Temobel (0.004 mg/ml) + **ITCA** or **IXCA** (0.0004 mg/ml)	**ITCA** (0.0004 mg/ml)
Cell loss, %	5-8	70	5-8	20-25	5-8

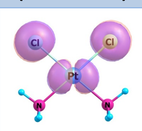
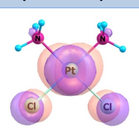
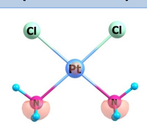
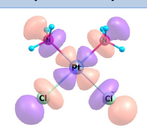
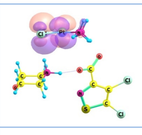
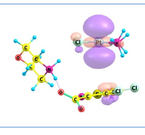
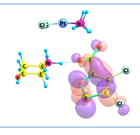
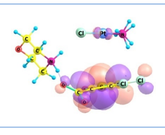
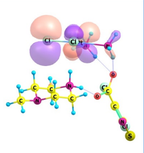
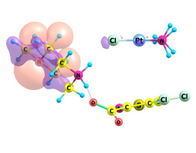
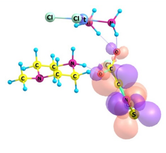
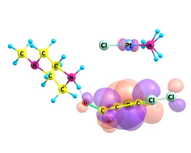
Testing PS in combination with cisplatine against glioma C6[2]:

Entry	Cisplatin (0.3 g/m^2)	Cisplatin (0.03 g/m^2)	**PS** (50 mg/ml)	**PS** (0.5 mg/ml)	Cisplatin (0.03 g/m^2) + **PS** (0.5 mg/ml)
Cell loss, %	82	32	3	3	47

Addition of adjuvante in non-active dose to a reduced dose of toxic chemotherapy drug allows to achieve higher level of tumor cell death *in vitro* than the chemotherapy itself causes at this dose!

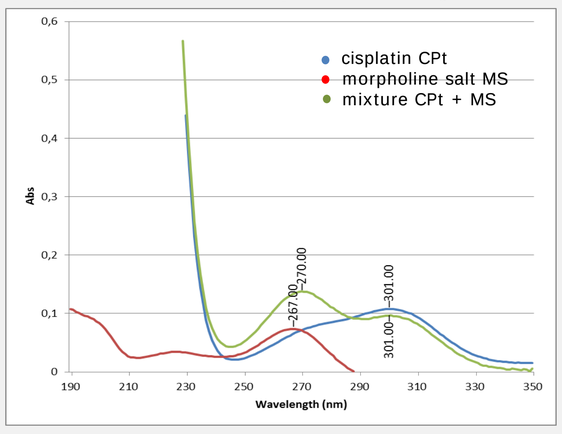
Quantum chemical modeling

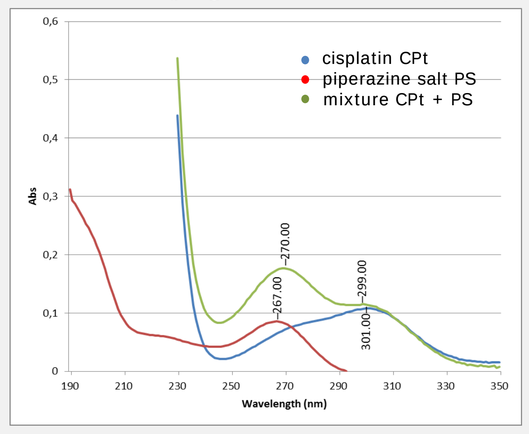
Explaining the adjuvants phenomenon was started with a quantum chemical study of the interaction of morpholinium and 4-methylpiperazinium 4,5-dichloroisothiazol-3-carboxylates with cisplatin. DFT/CAM-B3LYP/aug-cc-pVDZ /LanL2DZ(Pt) level of theory was used. Optimal geometry of molecules, dipole moment, charge distribution, localization and energy characteristics of frontier molecular orbitals (FMO) were calculated both for individual compounds and their conjugates (in vacuum and with consideration to aqueous medium).

	HOMO (vacuum)	HOMO (water)	LUMO (vacuum)	LUMO (water)
Cisplatin				
Cisplatin + **MS**				
Cisplatin + **PS**				

Descriptors	In vacuum			In aqueous medium		
	CPt	CPt-MS	CPt-PS	CPt	CPt-MS	CPt-PS
LUMO (eV)	-0.7946	-0.7215	-0.4042	-0.3053	-0.5667	-0.5550
HOMO (eV)	-7.8982	-8.0759	-8.0815	-8.2420	-8.2638	-8.0346
ΔE (eV)	7.1035	7.3544	7.6773	7.9367	7.6971	7.4796
η	3.5518	3.6772	3.8386	3.9683	3.8486	3.7398
S	0.1408	0.1360	0.1303	0.1260	0.1299	0.1337
Dipole moment (Debye)	10.954	3.271	2.502	**16.438**	**19.032**	**18.990**

UV spectra of cisplatin, adjuvants and their conjugates with cisplatin:





A bathochromic shift of the band at 267 nm to 270 nm and a significant increase in its intensity is observed (hyperchromic effect). Calculated binding energies in water: CPt-PS = 5.48 kkal/mol, CPt-MS = 5.76 kkal/mol.

- Adjuvants of isothiazole series give conjugates with cisplatin with non-covalent interactions between molecules. Conjugate of two molecules acts as a single unit.
- Conjugation leads to relocation of FMO between cisplatin molecules and adjuvant. LUMO localizes on isothiazole heterocycle, which is preferred for binding with DNA.
- Increase in the dipole moment of conjugates in aqueous medium (polarity of their molecules) in comparison with individual cisplatin activate the cytotoxic agent.

Conclusions

- According to *in vitro* tests some isothiazole and isoxazole derivatives can enhance the action of the first-line anti-tumor drugs. This allows to reduce the dose of the drug while maintaining the effectiveness of the action.
- Interaction of cisplatin with heterocyclic adjuvants leads to the formation of conjugates and redistribution of electron density within them. It increases the bioactivity of the system due to enhancing the efficiency of interaction with DNA.
- The data obtained are the basis for the search and design of new effective adjuvants.

References

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Acknowledgements

The work was carried out with financial support from the Belarusian Republican Foundation for Basic Research, grant X23RNF-051. The authors also thank the KAUST Supercomputing Core Lab team for assistance with tasks execution on Skylake nodes.

The 9th International Electronic Conference on Medicinal Chemistry
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