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Synthesis and investigation of carborane containing hydrindons as potential agents for BNCT

L.I. Lissovskaya[1], I.V. Korolkov[1], S. Irbayeva[2], M. Anisovich[3], M. Vasilyeva[3], K. Ludjik[4], M.V. Zdorovets[1]

i.korolkov@inp.kz

[1]The Institute of Nuclear Physic of the Republic of Kazakhstan, Almaty, Kazakhstan
[2]L.N. Gumilyov Eurasian National University, Nur-Sultan, Kazakhstan
[3]Republican Unitary Enterprise, Scientific-Practical Centre of Hygiene, Minsk, Belarus
[4]Department of Physical Chemistry, University of Lodz, Lodz, Poland

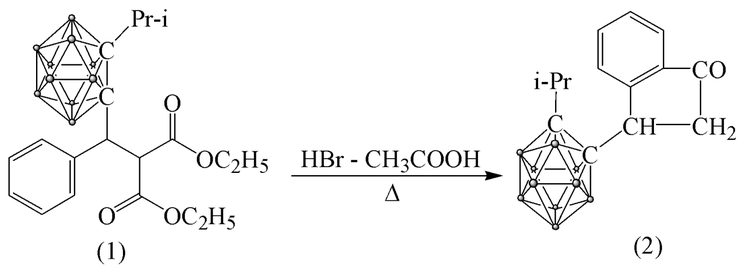
ABSTRACT AND INTRODUCTION

Boron neutron capture therapy (BNCT) is a promising treatment for various oncological diseases [1]. This is due to the selective destruction of cancer cells by the action of neutrons on ^{10}B boron atoms, which selectively accumulate in a tumor without affecting healthy tissue. Therefore, the basic principle of BNCT is that the collision of neutrons with boron isotopes leads to an instantaneous nuclear reaction $^{10}B(n,\alpha)7Li$, the fission effect of which is limited to a range of about 10 μm, which corresponds to the approximate size of a single cell. In this regard, for the practical application of BNCT, it is necessary to create preparations containing a sufficient amount of boron isotopes that can penetrate directly into cancer cells, reach a concentration of the ^{10}B isotope of the order of 20–35 μg/g of the tumor, and also have relatively low toxicity.

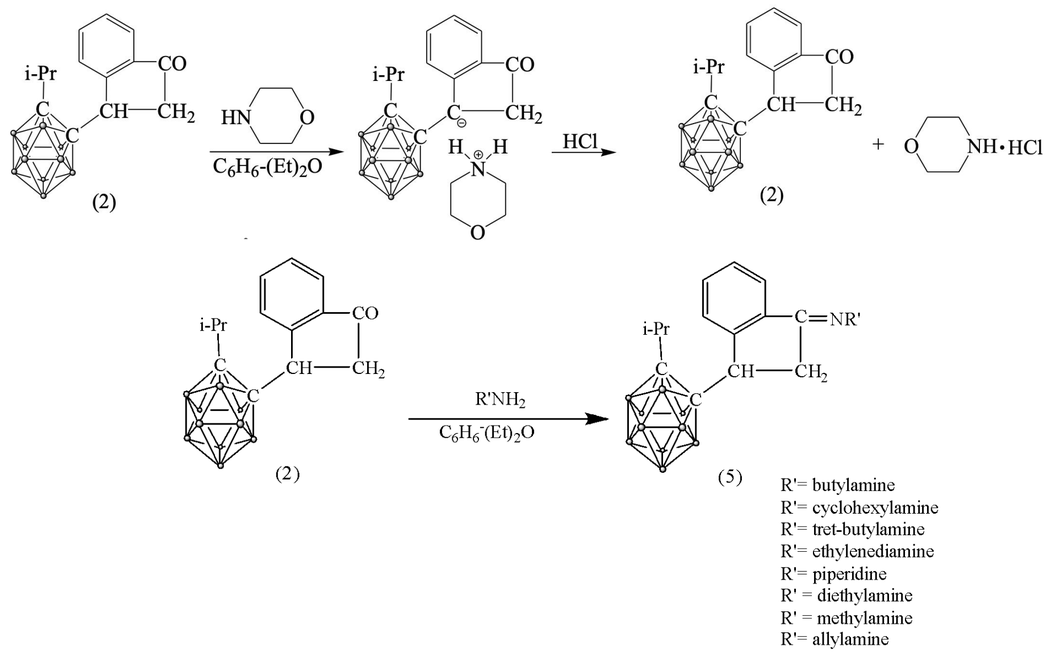
Carboranyl-containing compounds play a key role in medicine as potential drugs for BNCT due to the fact that they contain the necessary number of boron atoms, which allows to achieve the desired concentration of boron in cancer cells. At present, there are many works devoted to derivatives of carboranes in this area [2]. However, the biological properties of carborane derivatives of hydrindone (1-indanone) have not been previously studied as potential drugs for BNCT. Thus, new possibilities for the use of hydrindone derivatives in medicine are opening up.

RESULTS AND DISCUSSION

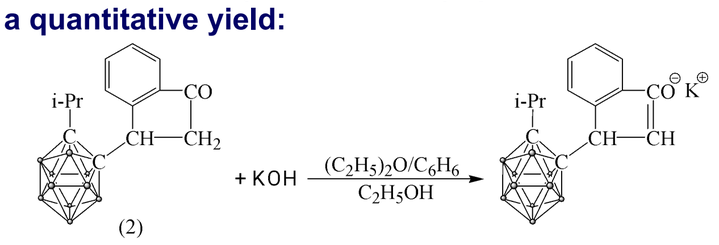
In this research, carborane derivatives hydrindones were synthesized. The reactions of C-metal derivatives of isopropyl-o-carborane with benzylidenemalonic ether and their derivatives were studied. 3- (isopropyl-o-carboranyl) -hydrindone was obtained by cyclization with bromohidric acid.



The reactions of 3-(isopropyl-o-carboranyl)-hydrindones with various amines (butylamine, methylamine, morpholine, cyclohesylamine), alkali metals and their hydroxides were studied. It was found that amines with higher basicity selectively interact with hydrindone derivatives at the carbonyl group, forming Schiff bases. Whereas the weaker amine (morpholine) forms a salt at a reagent ratio of 1:1, predominantly interacts with the acidic proton of the C-H group of 3-(isopropyl-o-carboranyl) -hydrindone.



Under the action of KOH or K on hydrindone (2) in a benzene-ether medium, ethanol and DMF (in case of K), potassium enolate anion is formed with a quantitative yield:



The cytotoxic properties of the water soluble potassium salt of hydrindone were studied. Studies of the cytotoxicity of the obtained compounds were carried out using the example of human hepatocarcinoma cells (HepG2) and human fibroblasts. LD50 is around 1 mg/ml for HepG2 and 0.5 mg/ml for human fibroblasts.
Analysis of the content of carboranyl-containing hydrindons in healthy tissues and tumors when injection to laboratory mice with transplanted tumors (Ehrlich's carcinoma).

Table 1 - The content of boron in tumor and healthy tissues 3 hours after the injection of carboranyl-containing hydrindons.

Compound	Boron content, μg/g					
	Tumor	Liver	Blood	Kidneys	Bone marrow	Muscular adjacent tissue
Reference measurement	-	-	-	-	-	-
Intraperitoneally						
1) isopropyl-o-carboranyl-hydrindone	6,9±1,4	4,4±2,3	0,12±0,03	1,8±0,3	-	0,8±0,8
2) isopropyl-o-carboranyl-hindrindone potassium salt	18,7±4,2	37,5±1,7	0,18±0,05	3,2±0,8	0,05±0,01	1,2±0,47
3) isopropyl-o-carboranyl-p-dimethylamino-hydrindone potassium salt	7,3±2,6	26,4±12,7	0,11±0,04	8,1±2,2	-	1,1±0,36
4) isopropyl-o-carboranyl-m-nitro-hyndrindone potassium salt	17,8±5,7	98,4±12,6	0,05±0,04	38,8±7,9	0,04±0,02	1,6±0,6
5) butylamine-hydrindone	12,8±2,9	88,6±11,8	0,11±0,04	27,7±10,2	0,06±0,02	1,4±1,8
Introduction to tumor tissue						
1) isopropyl-o-carboranyl-hydrindone	11,6±3,4	38,8±10,2	0,09±0,02	19,7±2,9	0,09±0,04	3,9±2,2
2) isopropyl-o-carboranyl-hindrindone potassium salt	33,8±4,7	10,4±4,9	0,08±0,08	3,9±3,0	0,11±0,08	2,7±1,8
3) isopropyl-o-carboranyl-p-dimethylamino-hydrindone potassium salt	68,7±11,3	14,2±2,8	0,08±0,05	7,7±2,4	0,14±0,1	3,7±2,9
4) isopropyl-o-carboranyl-m-nitro-hyndrindone potassium salt	28,9±7,7	54,2±10,8	0,14±0,03	12,6±5,8	0,21±0,09	7,9±2,1
5) butylamine-hydrindone	164,2±28,7	16,6±2,8	0,09±0,02	5,7±3,1	0,08±0,04	9,3±3,6

CONCLUSION

Analysis of the obtained results showed that the synthesized compounds are able to selectively accumulate in tumor cells (A549, HepG2, MCF7), in comparison with normal fibroblasts. The concentration in tumors (Ehrlich's carcinoma) inoculated into mice was more than 30 μg/g. The condition for effective cancer therapy, in which the biodistribution of carboranil-containing compounds in the system "normal tissue:tumor" should not be less than 1:3, is fulfilled in comparison with the muscle tissue adjacent to the tumor.

Based on the obtained results, it can be concluded that carboranil-containing hydrindones synthesized in the framework of this study are promising drugs for BNCT and they are recommended for further research.

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Contacts: i.korolkov@inp.kz, +77051799083