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# НОВЫЙ КОМПЛЕКС BODIPY С ПЛАТИНОЙ(II)

**А.А. Кернер[1], Е.П. Борисовская[1], А.Н. Крестова[1], А.А. Ксенофонтов[2], Е.Е. Молчанов[1], К.В. Ксенофонтова[1]**

[1]Ивановский государственный химико-технологический университет, Шереметевский пр., д. 7, г. Иваново, Российская Федерация, 153000
E-mail: borisovskayakatya16@gmail.com, evgenmolch@mail.ru, arenrek@gmail.com, krestova.anka@inbox.ru, kvk@isuct.ru
[2]Институт химии растворов им. Г.А. Крестова Российской академии наук, ул. Академическая, д. 1, г. Иваново, Российская Федерация, 153045
E-mail: ivalex.09@mail.ru

***Комплексы BODIPY с платиной отличаются уникальными спектральными и цитотоксическими свойствами. В настоящей работе был синтезирован новый комплекс такого типа – нитрат хлоридодиаммин[1,3,5,7-тетраметил-8-(2-пиридинил-κN)-4,4-дифтор-2,6-диэтил-4-бор-3a,4a-диаза-s-индацен]платины(II) (cisPt-oP-BODIPY). Исследование спектральных свойств cisPt-oP-BODIPY выявило его потенциал как тераностического агента.***

**Ключевые слова:** BODIPY, цисплатин, комплексообразование

# NOVEL BODIPY-APPENDED PLATINUM(II) COMPLEX

**A.A. Kerner[1], E.P. Borisovskaya[1], A.N. Krestova[1], A.A. Ksenofontov[2], E.E. Molchanov[1], K.V. Ksenofontova[1]**

[1]Ivanovo State University of Chemistry and Technology, 7, Sheremetevskiy pr., Ivanovo, Russia, 153000
E-mail: borisovskayakatya16@gmail.com, evgenmolch@mail.ru, arenrek@gmail.com, krestova.anka@inbox.ru, kvk@isuct.ru
[2]G. A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences, 1, ul. Akademicheskaya, Ivanovo, Russia, 153045
E-mail: ivalex.09@mail.ru

***BODIPY-appended platinum complexes distinguish by unique spectral and cytotoxic properties. In this work, a novel complex diamminechlorido[2,6-diethyl-4,4-difluoro-1,3,5,7-tetramethyl-8-(2-pyridinyl-κN)-4-bora-3a,4a-diaza-s-indacene]platinum(II) nitrate (cisPt-oP-BODIPY) was synthesized. The investigation of spectral properties of cisPt-oP-BODIPY revealed its potential as a theranostic agent.***

**Key words:** BODIPY, cisplatin, complex formation

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## INTRODUCTION

Boron dipyrromethene (BODIPY) fluorescent dyes are well-known for their good stability, high molar extinction coefficients and fluorescence quantum yields, small Stokes shifts, sharp excitation and emission peaks [1–4]. Moreover, an ease of modification of the dipyrrin core provides great opportunities for a synthesis of new phosphors with desired properties.

BODIPY-appended platinum complexes, in turn, are of keen interest to scientists due to their unique spectral and cytotoxic properties [5–18]. Distinguishing by bathochromically shifted absorption and emission bands and/or high light-induced and low dark cytotoxicity, such complexes are promising both for imaging cancer cells and for treatment of cancer.

In this work, we report the synthesis and spectral properties of a novel BODIPY-appended platinum(II) complex, which have potential as theranostic agent.

## EXPERIMENTAL

*Materials*

All reagents and solvents were obtained from commercial sources (Sigma-Aldrich, Reakhim, Panreac AppliChem, EKOS-1) at the highest possible purity and used without further purification.

*Instruments*

$^1$H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 500 NMR spectrometer with the operating frequency of 500.17 MHz. Matrix-assisted laser desorption/ionization (MALDI) time of flight (TOF) mass spectra (MS) were obtained by means of a Shimadzu AXIMA Confidence MALDI TOF-TOF mass spectrometer in a positive ion reflectron mode.

Absorption spectra and emission spectra with the excitation wavelengths of 480 (in case of oP-BODIPY) and 500 (in case of cisPt-oP-BODIPY) nm were recorded on a Solar SM 2203 spectrofluorometer. Fluorescence quantum yields were measured on a PicoQuant FluoTime 300 high performance fluorescence lifetime and steady state spectrometer with an integrating sphere with a PicoQuant LDH-P-C-500 picosecond pulsed laser diode as an excitation source. Fluorescence lifetimes were measured on a PicoQuant FluoTime 300 high performance fluorescence lifetime and steady state spectrometer with a PicoQuant PLS 450 (in case of oP-BODIPY) or a PicoQuant PLS 500 (in case of cisPt-oP-BODIPY) sub-nanosecond pulsed light-emitting diodes as excitation sources. Emission spectra of singlet oxygen were recorded on a PicoQuant FluoTime 300 high performance fluorescence lifetime and steady state spectrometer with a Hamamatsu NIR-PMT detector with a PicoQuant LDH-P-C-500 picosecond pulsed laser diode as an excitation source.

*Synthetic procedures*

**Synthesis of 2,6-diethyl-4,4-difluoro-1,3,5,7-tetramethyl-8-(2-pyridinyl)-4-bora-3a,4a-diaza-s-indacene (oP-BODIPY).** Synthesis was carried out on the basis of the previously described procedure [19] (Scheme 1, Fig. S1, Fig. S2, http://rcj-isuct.ru/article/view/5902/3540). After the synthesis and all workups, 76 mg of dark red powder of the desired product was obtained resulting in 38% yield. $^1$H NMR ($CDCl_3$): δ (ppm) 8.76 (d, J = 4.7 Hz, 1H, $–CH_{aryl}$), 7.83 – 7.79 (m, 1H, $–CH_{aryl}$), 7.44 – 7.38 (m, 2H, $–CH_{aryl}$), 2.52 (s, 6H, $–CH_3$), 2.28 (q, J = 7.7 Hz, 4H, $–CH_2–$), 1.19 (s, 6H, $–CH_3$), 0.96 (t, J = 7.6 Hz, 6H, $–CH_3$). MS (MALDI-TOF): m/z calculated for $C_{22}H_{26}BF_2N_3^+$ $[M]^+$ – 381.22, found – 381.46.

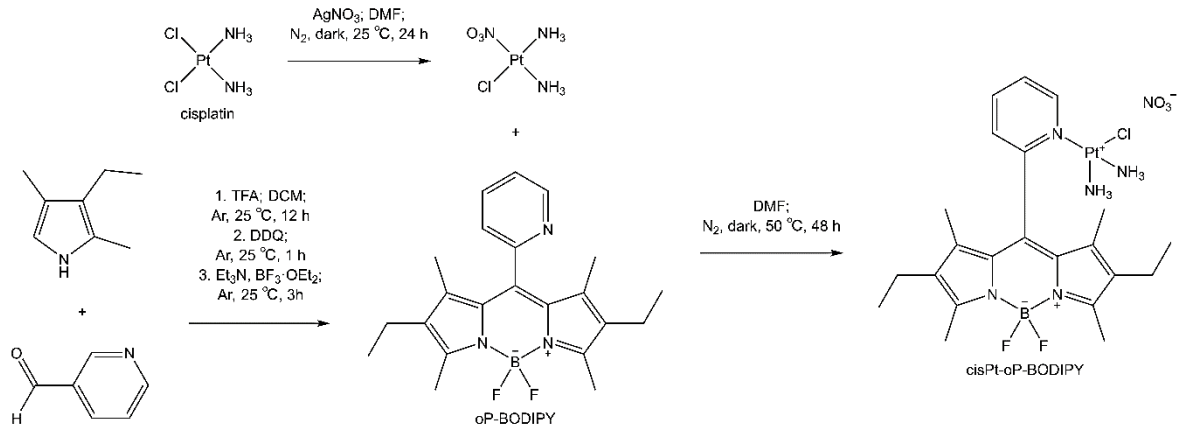
**Synthesis of diamminechloridonitratoplatinum ($[PtCl(NH_3)_2(NO_3)]$).** Synthesis was carried out on the basis of the previously described procedure [7] (Scheme 1). After the synthesis and all workups, light yellow solution of the desired product in dimethylformamide (DMF) was obtained.

**Synthesis of diamminechlorido[2,6-diethyl-4,4-difluoro-1,3,5,7-tetramethyl-8-(2-pyridinyl-κ*N*)-4-bora-3a,4a-diaza-*s*-indacene]platinum(II) nitrate (cisPt-oP-BODIPY).** Synthesis was carried out following the procedure [7] (Scheme 1, Fig. S3, Fig. S4, http://rcj-isuct.ru/article/view/5902/3540). A solution of oP-BODIPY (40 mg, 1 equiv.) in DMF was added dropwise to a solution of $[PtCl(NH_3)_2(NO_3)]$ (1 equiv.) in DMF. The mixture was stirred under an inert atmosphere of nitrogen in the dark at 50 °C for 48 h. After completion of the reaction, which was monitored by thin-layer chromatography, DMF was evaporated under reduced pressure. The crude residue was dissolved in cold methanol, filtered from the precipitated unreacted yellow $[PtCl(NH_3)_2(NO_3)]$, and then methanol was evaporated under reduced pressure. The crude residue was dissolved in cold diethyl ester, the resulting dark red precipitate of cisPt-oP-BODIPY was separated from the solution of unreacted oP-BODIPY by a series of successive centrifugations and decantations. After the removal of diethyl ester and recrystallization from acetonitrile, 15 mg of dark red powder of the desired product was obtained resulting in 20% yield. $^1$H NMR (DMSO-$d_6$): *δ* (ppm) 9.11 (d, *J* = 6.1 Hz, 1H, $–CH_{aryl}$), 8.15 (t, *J* = 7.8 Hz, 1H, $–CH_{aryl}$), 7.91 (d, *J* = 7.9 Hz, 1H, $–CH_{aryl}$), 7.78 (t, *J* = 6.8 Hz, 1H, $–CH_{aryl}$), 4.17 (s, 3H, $–NH_3$), 3.84 (s, 3H, $–NH_3$), 3.48 (s, 6H, $–CH_3$), 2.47 (s, 6H, $–CH_3$ (DMSO overlapping)), 2.29 (q, *J* = 7.4 Hz, 4H, $–CH_2–$), 0.92 (t, *J* = 7.5 Hz, 6H, $–CH_3$). MS (MALDI-TOF): m/z calculated for $C_{22}H_{32}BClFN_5Pt^+$ $[M – F – NO_3]^+$ – 626.21, found – 628.97.

## RESULTS AND DISCUSSION

*Synthesis of BODIPY-appended platinum(II) complex*

The novel BODIPY-appended platinum(II) complex diamminechlorido[2,6-diethyl-4,4-difluoro-1,3,5,7-tetramethyl-8-(2-pyridinyl-κ*N*)-4-bora-3a,4a-diaza-*s*-indacene]platinum(II) nitrate (cisPt-oP-BODIPY) was synthesized from fluorescent dye with σ-donor pyridine subunit 2,6-diethyl-4,4-difluoro-1,3,5,7-tetramethyl-8-(2-pyridinyl)-4-bora-3a,4a-diaza-*s*-indacene (oP-BODIPY) and platinum-based antineoplastic drug cisplatin following the common three-step procedure [7] in 20% yield (Scheme 1). Synthetic details and characterization of the obtained compounds are given in Section 3




Scheme 1. Scheme of cisPt-oP-BODIPY synthesis

*Spectral properties of BODIPY-appended platinum(II) complex*

The comparative analysis of spectral properties (Fig. 1, Table 1) of oP-BODIPY and cisPt-oP-BODIPY showed that conjugation of BODIPY core with platinum-containing subunit leads to a pronounced bathochromic shift of absorption and emission bands due to the heavy atom effect [20–22]. Moreover, such chemical modification brings to fluorescence quenching as a result of an increase of a probability of internal conversion and intersystem crossing. The evidence of the latter is a singlet oxygen generation in cisPt-oP-BODIPY solution (Fig. S5, http://rcj-isuct.ru/article/view/5902/3540).

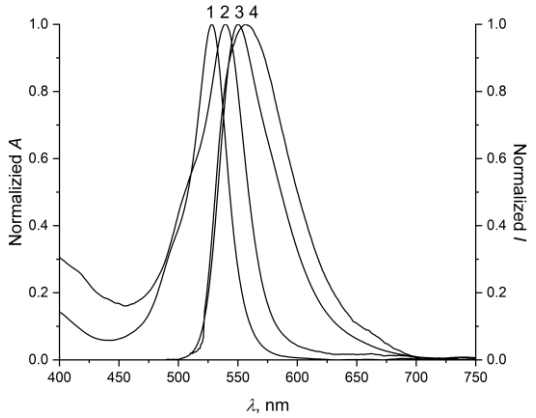



Fig. 1. Absorption and emission spectra of oP-BODIPY (1 and 3, respectively) and cisPt-oP-BODIPY (2 and 4, respectively) in chloroform

***Table 1***

**Photophysical characteristics of oP-BODIPY and cisPt-oP-BODIPY in chloroform**

| | oP-BODIPY | cisPt-oP-BODIPY |
|---|---|---|
| $\lambda_{abs\ max}$, nm | 528 | 540 |
| $\lambda_{em\ max}$, nm | 550 | 556 |
| $\Delta\nu$, $cm^{-1}$ | 758 | 533 |
| $\Phi$ | 0.11 | 0.03 |
| $\tau$, ns | 1.37 | 4.09 |
| $k_r$, $ns^{-1}$ | 0.08 | 0.01 |
| $k_{nr}$, $ns^{-1}$ | 0.65 | 0.24 |

where $\lambda_{abs\ max}$ is the maximum absorption wavelength; $\lambda_{em\ max}$ is the maximum emission wavelength; $\Delta\nu$ is the Stokes shift; $\Phi$ is the fluorescence quantum yield; $\tau$ is the average fluorescence lifetime; $k_r$ is the radiative rate constant; $k_{nr}$ is the non-radiative rate constant.

Thus, the novel BODIPY-appended platinum(II) complex cisPt-oP-BODIPY possessing attractive spectral and photosensitizing properties appear to be promising theranostic agent.

## CONCLUSIONS

A novel BODIPY-appended platinum(II) complex diamminechlorido[2,6-diethyl-4,4-difluoro-1,3,5,7-tetramethyl-8-(2-pyridinyl-κ*N*)-4-bora-3a,4a-diaza-*s*-indacene]platinum(II) nitrate (cisPt-oP-BODIPY) was synthesized. Spectral properties of cisPt-oP-BODIPY were investigated. cisPt-oP-BODIPY was found to be a promising theranostic agent.

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*The authors declare the absence a conflict of interest warranting disclosure in this article.*

*Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.*

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