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# Х А Б А Р Л А Р Ы

# ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН

АО «ИНСТИТУТ ТОПЛИВА, КАТАЛИЗА И
ЭЛЕКТРОХИМИИ ИМ. Д.В. СОКОЛЬСКОГО»

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OF THE REPUBLIC OF KAZAKHSTAN

JSC «D.V. SOKOLSKY INSTITUTE OF FUEL,
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## ХИМИЯ ЖӘНЕ ТЕХНОЛОГИЯ СЕРИЯСЫ

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## СЕРИЯ ХИМИИ И ТЕХНОЛОГИИ

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# COMPLEXES OF INCLUSION OF FUNCTIONALLY-SUBSTITUTED HYDRASONS OF ISONICOTHIC ACID WITH CYCLODEXTRINES AND THEIR ANTIRADICAL ACTIVITY

**Abstract.** In the present work, supramolecular complexes based on N- (diethylamino) benzylidenisone-kotinhydrazide and N- (2-bromo-3-phenyl) allylidenisononotinhydohydrazide and cyclodextrins (β-CD, 2-GP-β-CD) were first obtained and studied. Comparison of the integral intensities of the $^1$H NMR signals of substrate (hydrazone) and β- and 2-GP-β-CD-β receptors in supramolecular complexes showed that in all cases complexes of 1 guest molecule composition are formed for 2 host molecules. It was found that during the interaction they form an inclusion complex with the entry of the substrate molecule into the inner cavity of the receptor by the methylamine end. The resulting products form a mixture capable of dissolving in water or forming stable aqueous dispersions. The antiradical effect of synthesized supramolecular complexes on the DPPH radical was estimated. A concentration capable of 50% lowering the optical density of a 100 μM solution of DPPH radical was determined. For a supramolecular complex based on N-(diethylamino)-benzylidenisonocinate-hydrazide and 2-GP-β-cyclodextrin, IC50 (DPPH) was found to be 46.4 μM.

**Key words:** β-cyclodextrin, 2-hydroxypropyl-cyclodextrin, supramolecular inclusion complexes, antiradical activity.

Hydrazones obtained on the basis of known isonicotinic acid hydrazide are used as antibacterial and antitubercular drugs, analytical reagents and dyes [1]. However, some of them have low solubility in water. At present, various ways of increasing the solubility of medicinal substances in water are developed and used: the use of special auxiliaries, including the inclusion of drugs in the complex of cyclodextrin [2].

Cyclodextrins (CD) are cyclic oligosaccharides that have a hydrophobic internal cavity and a hydrophilic outer shell [3]. Cyclodextrins (CD) are cyclic oligosaccharides that have a hydrophobic internal cavity and a hydrophilic outer shell [4]. By forming the inclusion complex, it is possible to increase the stability of low molecular substances sensitive to the action of light and air oxygen, increase their solubility in water, bioavailability, and reduce toxicity. Due to this, CSDs are widely used in the food, cosmetic, pharmaceutical industry, in the production of dyes, in analytical chemistry, in the elimination of environmental pollution by ecotoxicants, etc. [5-7].

The stability of the complexes is caused by the formation of a variety of non-covalent forces of interaction between the molecules of cyclodextrin and the "guest": Van der Waals, hydrophobic and etc. Cyclodextrin in the complex protects the guest molecule from damage by various reactive molecules and thereby reduces the rate of oxidation, steric rearrangement, hydrolysis, racemization and enzymatic degradation [8, 9].

It is promising to use the obtained hydrazones as a constituent supramolecular system (substrate) with a cyclic oligosaccharide - β-cyclodextrin (receptor) having a truncated cone molecule with internal protons $H_3$ and $H_5$ and external $H_2$ and $H_4$ protons (Fig. 1). The possibility of including the active substance in the capsule of β-cyclodextrin is due to hydrophobic interactions between the BAS and the complexing agent.

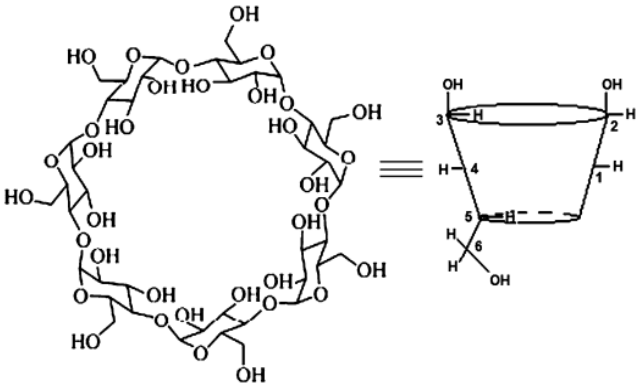
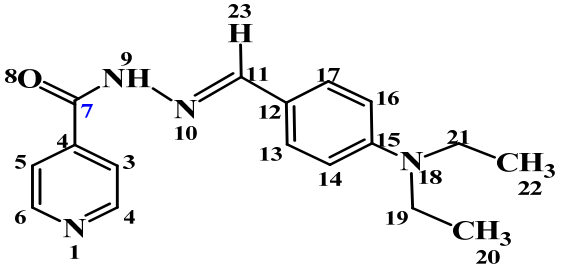
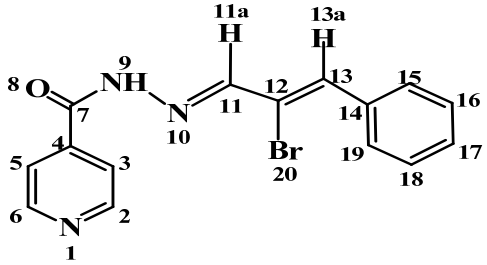


Figure 1 - Schematic representation of the structure of β-cyclodextrin molecules

As hydrazones, N-(diethylamino)benzylidenisonconitinohydrazide (1) and N-(2-bromo-3-phenyl)allylidenisonicotinhydohydrazide (7) were selected as substrata for supramolecular self-assembly, which, according to the bioprospecting data, have high antituberculous, antimycobacterial activity and inhibitors of glutamine-phenylurea transaminase and threonine aldolase (see below), as well as poor solubility of the latter in water.



**1**

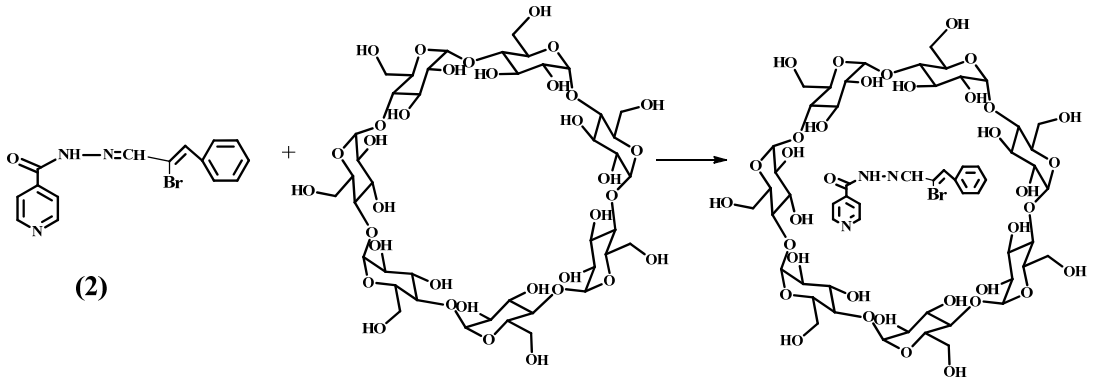


**2**

Supramolecular chemistry is dominated by the size and shape or geometric complementarity of the interacting components, therefore β-CD and its 2-hydroxy derivative-2-GP-β-CD were used to obtain inclusion complexes with substrates **1** and **2**.

Investigation by NMR spectroscopy of supramolecular complexes is based on the determination of the difference in the values of chemical shifts of $^{1}H$ and $^{13}C$ substrates (**1, 2**) and receptors (β-CD, 2-GP-β-CD) in the free state and in the complexes as a result of intermolecular interaction. By the magnitude of chemical shifts of internal or external proton protons, it is possible to detect the formation of internal (inclusion) or external (without inclusion) complexes, respectively. The change in chemical shifts of $^{1}H$ and $^{13}C$ in the spectra of substrates makes it possible to determine the direction of occurrence of the latter in the CD cavity [10, 11].

The structure of substrates of supramolecular self-assembly **1** and **2** was established based on the results of $^{1}H$ and $^{13}C$ NMR spectroscopy obtained in DMSO-$d_6$ (Tables 1, 2 (**1**) and 1, 3, 4 (**2**). The correctness of assigning one-dimensional NMR spectra of $^{1}H$ and $^{13}C$ **1** and **2** was confirmed by two-dimensional correlations of the NMR spectra of $^{1}H$-$^{1}H$ COSY, $^{1}H$-$^{13}C$ HMQC (Table 1).



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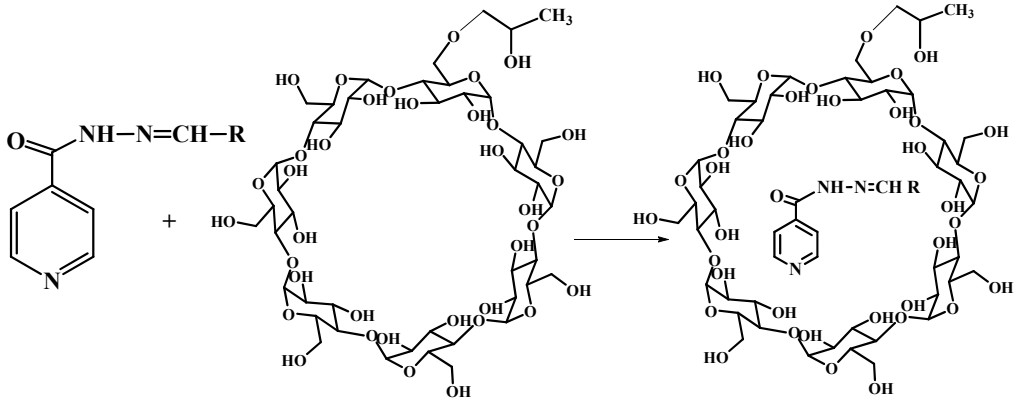

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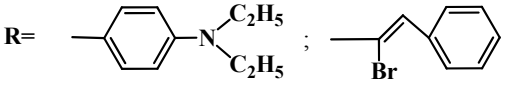

**(1)** **(2)**

Table 1 -NMR data of $^{1}H$, $^{13}C$, $^{1}H$-$^{1}H$ COSY, $^{1}H$-$^{13}C$ HMQC substrates **1** and **2**

| Substrate | δ, ppm, J, Hz | | | |
|---|---|---|---|---|
| | $^{1}H$ | $^{13}C$ | $^{1}H$-$^{1}H$ COSY | $^{1}H$-$^{13}C$ HMQC |
| **1** | 1.06 t (6H, H-20,22, $^{3}J$ 6.9), 3.31-3.35 m (4H, H-19,21), 6.66 d (2H, H-14,16, $^{3}J$ 8.7), 7.48 d (2H, H-13,17, $^{3}J$ 8.7), 7.77 d (2H, H-3,5, $^{3}J$ 4.6), 8.25 s (1H, H-23), 8.72 d (2H, H-2,6, $^{3}J$ 4.6), 11.72 s (1H, H-9). | 12.96 (C-20,23), 44.26 (C-19,21), 111.56 (C-14,16), 120.76 (C-12), 122.00 (C-3,5), 129.56 (C-13,17), 141.37 (C-4,11), 149.57 (C-2,6), 150.41 (C-15), 161.48 (C-7). | $H^{19,21}$-$H^{20,22}$ (1.03, 3.33; 3.32, 1.05); $H^{13,17}$-$H^{14,16}$ (6.65, 7.48; 7.48, 6,66); $H^{3,5}$-$H^{2,6}$ (7.76, 8.72; 8.71, 7.77). | $H^{20,22}$-$C^{20,22}$ (1.03, 12.93); $H^{14,16}$-$C^{14,16}$ (6.63, 111.53); $H^{13,17}$-$C^{13,17}$ (7.45, 129.54); $H^{3,5}$-$C^{3,5}$ (7.76, 121.92); $H^{2,6}$-$C^{2,6}$ (8.70, 150.73). |
| **2** | 7.38-7.43 m (3H, H-15,19,17), 7.67 s (1H, H-13), 7.77 d (2H, H-3,5, $^{3}J$ 1.8), 7.84 d (2H, H-16,18, $^{3}J$ 6.4), 8.34 s (1H, H-11), 8.75 d (2H, H-2,6), 12.19 s (1H, H-9). | 119.50 (C-12), 122.07 (C-3,5), 128.99 (C-15,19), 130.01 (C-17), 130.34 (C-16,18), 135.04 (C-14), 139.37 (C-13), 140.85 (C-4), 149.53 (C-11), 150.90 (C-2,6), 162.27 (C-7). | $H^{16,18}$-$H^{15,17,19}$ (7.40, 7.84; 7.83, 7.43); $H^{2,6}$-$H^{3,5}$ (7.76, 8.75; 8.74, 7.77). | $H^{15,19}$-$C^{15,19}$ (7.40, 129.31); $H^{13}$-$C^{13}$ (7.67, 139.39); $H^{3,5}$-$C^{3,5}$ (7.76, 122.07); $H^{16,18}$-$C^{16,18}$ (7.85, 130.14); $H^{11}$-$C^{11}$ (8.32, 119.49); $H^{2,6}$-$C^{2,6}$ (8.74, 150.97). |

The ratio of the integrated intensities of the protons in the compounds in question corresponded to the structures **1** and **2** presented. NMR spectra of $^{1}H$ and $^{13}C$ β- and 2-GP-β-CD-nanov in the free state and supramolecular complexes 3-5 on their basis with substrates **1** and **2** are presented in Tables 2-4.

Table 2 – Chemical shifts of the $^{1}H$ and $^{13}C$ nuclei of substrate **1** and 2-GP-β-cyclodextrin in the free state ($\delta_0$) and in the complex **3** ($\delta$)

| Atom number | Group | $\delta_0$, ppm. | | $\delta$, ppm. | | $\Delta\delta=\delta-\delta_0$ | |
|---|---|---|---|---|---|---|---|
| | | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ |
| Substrate **1** | | | | | | | |
| 2 | CH | 8.72 | 149.57 | 8.71 | 150.75 | -0.01 | 1.18 |
| 3 | CH | 7.77 | 122.00 | 7.76 | 121.99 | -0.01 | -0.01 |
| 4 | C | | 141.37 | | 141.69 | | 0.32 |
| 5 | CH | 7.77 | 122.00 | 7.76 | 121.99 | -0.01 | -0.01 |
| 6 | CH | 8.72 | 149.57 | 8.71 | 150.75 | -0.01 | 1.18 |
| 7 | C | | 161.48 | | 163.82 | | 2.34 |
| 9 | NH | 11.72 | | 11.63 | | -0.11 | |
| 11 | CH | | 141.37 | | 141.69 | | 0.32 |
| 12 | C | | 120.76 | | 120.94 | | 0.18 |
| 13 | CH | 7.48 | 129.56 | 7.48 | 129.55 | 0 | -0.01 |
| 14 | CH | 6.66 | 111.56 | 6.68 | 111.60 | 0.02 | 0.04 |
| 15 | C | | 150.41 | | 151.53 | | 1.12 |
| 16 | CH | 6.66 | 111.56 | 6.68 | 111.60 | 0.02 | 0.04 |
| 17 | CH | 7.48 | 129.56 | 7.48 | 129.55 | 0 | -0.01 |
| 19 | $CH_2$ | 3.35 | 44.26 | 3.36 | 44.27 | 0.01 | 0.01 |
| 20 | $CH_3$ | 1.06 | 12.96 | 1.00 | 12.84 | -0.06 | -0.12 |
| 21 | $CH_2$ | 3.35 | 44.26 | 3.36 | 44.27 | 0.01 | 0.01 |
| 22 | $CH_3$ | 1.06 | 12.96 | 1.00 | 12.84 | -0.06 | -0.12 |
| 23 | CH | 8.25 | | 8.26 | | 0.01 | |
| 2-HP-β-CD | | | | | | | |
| 1 | CH | 4.79 | 102.33 | 4.80 | 102.29 | 0.01 | -0.04 |
| 2 | CH | 3.26 | 72.56 | 3.28 | 72.94 | 0.02 | 0.38 |
| 3 | CH | 3.70 | 73.56 | 3.73 | 73.55 | 0.03 | -0.01 |
| 4 | CH | 3.18 | 82.11 | 3.21 | 82.20 | 0.03 | 0.09 |
| 5 | CH | 3.56 | 72.56 | 3.60 | 72.30 | 0.04 | -0.26 |
| 6 | $CH_2$ | 3.56 | 60.40 | 3.60 | 60.43 | 0.04 | 0.03 |

Table 3 – Chemical shifts of the $^{1}H$ and $^{13}C$ nuclei of substrate **2** and β-cyclodextrin in the free state ($\delta_0$) and in the complex **4** ($\delta$)

| Atom number | Group | $\delta_0$, ppm. | | $\delta$, ppm. | | $\Delta\delta=\delta-\delta_0$ | |
|---|---|---|---|---|---|---|---|
| | | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ |
| Substrate **2** | | | | | | | |
| 2 | CH | 8.75 | 150.90 | 8.38 | 150.98 | -0.37 | 0.08 |
| 3 | CH | 7.77 | 122.07 | 7.95 | 124.49 | 0.18 | 2.42 |
| 4 | C | | 140.85 | | | | |
| 5 | CH | 7.77 | 122.07 | 7.95 | 124.49 | 0.18 | 2.42 |
| 6 | CH | 8.75 | 150.98 | 8.38 | 150.98 | -0.37 | 0.08 |
| 7 | C | | 162.27 | | | | |
| 9 | NH | 12.19 | | 12.19 | | 0 | |
| 11 | $CH_a$ | 8.34 | 149.53 | 8.38 | | 0.04 | |
| 12 | C | | 119.50 | | | | |
| 13 | $CH_a$ | 7.67 | 139.37 | 7.95 | | 0.28 | |
| 14 | C | | 135.04 | | 133.50 | | -1.54 |
| 15 | CH | 7.43 | 128.99 | 7.53 | 129.42 | 0.10 | 0.43 |
| 16 | CH | 7.84 | 130.34 | 7.95 | 131.17 | 0.11 | 0.83 |
| 17 | CH | 7.43 | 130.01 | 7.53 | 132.11 | 0.10 | 2.10 |
| 18 | CH | 7.84 | 130.34 | 7.95 | 131.17 | 0.11 | 0.83 |
| 19 | CH | 7.43 | 128.99 | 7.53 | 129.42 | 0.10 | 0.43 |
| β-CD | | | | | | | |
| 1 | CH | 4.77 | 102.40 | 4.79 | 102.46 | 0.02 | 0.06 |
| 2 | CH | 3.26 | 72.83 | 3.27 | 72.93 | 0.01 | 0.10 |
| 3 | CH | 3.58 | 73.54 | 3.60 | 73.57 | 0.02 | 0.03 |
| 4 | CH | 3.28 | 81.98 | 3.31 | 82.07 | 0.03 | 0.09 |
| 5 | CH | 3.50 | 72.50 | 3.51 | 72.56 | 0.01 | 0.06 |
| 6 | $CH_2$ | 3.58 | 60.42 | 3.60 | 60.45 | 0.02 | 0.03 |

Table 4 – Chemical shifts of the $^{1}H$ and $^{13}C$ nuclei of substrate **2** and 2-GP-β-cyclodextrin in the free state (δ0) and in the complex of **5** (δ)

| Atom number | Group | $\delta_0$, ppm. | | δ, ppm. | | Δδ=δ-$\delta_0$ | |
|---|---|---|---|---|---|---|---|
| | | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ |
| Substrate **2** | | | | | | | |
| 2 | CH | 8.75 | 150.90 | 8.78 | 149.72 | 0.03 | -1.82 |
| 3 | CH | 7.77 | 122.07 | 7.87 | 124.04 | 0.10 | 1.97 |
| 4 | C | | 140.85 | | 140.25 | | -0.60 |
| 5 | CH | 7.77 | 122.07 | 7.87 | 124.04 | 0.10 | 1.97 |
| 6 | CH | 8.75 | 150.98 | 8.78 | 149.72 | 0.03 | -1.82 |
| 7 | C | | 162.27 | | 163.61 | | 1.34 |
| 9 | NH | 12.19 | | 12.19 | | 0 | |
| 11 | $CH_a$ | 8.34 | 149.53 | 8.38 | 149.72 | 0.04 | 0.19 |
| 12 | C | | 119.50 | | | | |
| 13 | $CH_a$ | 7.67 | 139.37 | 7.87 | 139.64 | 0.20 | 0.27 |
| 14 | C | | 135.04 | | 131.18 | | -3.86 |
| 15 | CH | 7.43 | 128.99 | 7.52 | 129.00 | 0.09 | 0.01 |
| 16 | CH | 7.84 | 130.34 | 7.87 | 129.42 | 0.03 | -0.62 |
| 17 | CH | 7.43 | 130.01 | 7.52 | 129.42 | 0.09 | -0.59 |
| 18 | CH | 7.84 | 130.34 | 7.87 | 129.42 | 0.03 | -0.62 |
| 19 | CH | 7.43 | 128.99 | 7.52 | 129.00 | 0.09 | 0.01 |
| 2-HP-β-CD | | | | | | | |
| 1 | CH | 4.79 | 102.33 | 4.80 | 102.36 | 0.01 | 0.03 |
| 2 | CH | 3.26 | 72.56 | 3.28 | 72.91 | 0.02 | 0.35 |
| 3 | CH | 3.70 | 73.56 | 3.73 | 73.53 | 0.03 | -0.03 |
| 4 | CH | 3.18 | 82.11 | 3.21 | 82.01 | 0.03 | -0.10 |
| 5 | CH | 3.56 | 72.56 | 3.60 | 72.91 | 0.04 | 0.35 |
| 6 | $CH_2$ | 3.56 | 60.40 | 3.60 | 60.66 | 0.04 | 0.20 |

Comparison of the integrated intensities of the signals of $^{1}H$ NMR of the molecules of substrates **1** and **2** and the receptors of β- and 2-GP-β-CD in supramolecular complexes **3-5** showed that in all cases complexes of the composition of the guest molecule are formed for **2** host molecules.

In the formation of the supramolecular complex **3**, as a result of the supramolecular self-assembly **1** with 2-GP-β-CD, changes in the proton chemical shifts in the cyclodextrin Δδ molecule occurred to a greater extent in the internal hydrophobic protons H-3, H-5, H-6 than in the the external hydrophilic surface of protons H-1, H-2 and H-4. In molecule 1, the largest changes in proton spectra are observed in diethylamine protons H-20, H-22, H-19, H-21 and located closer to the above protons in the phenylidene protons H-14 and H-16. The proton also undergoes screening in the process of complexation, the aromatic pyridine hydrophobic protons H-2,6 and H-3,5. It can be assumed that the greatest supramolecular interaction of host and host molecules is realized by means of the above protons during the formation of complex **3** (Fig. 2).

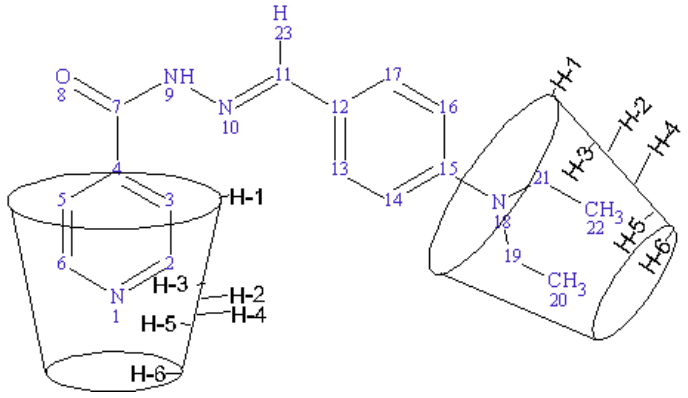


Figure 2 - Supposed supramolecular inclusion complexes **3**

Screening of external cyclodextrin protons is probably due to the intermolecular interaction of hydrophilic protons with external hydroxyl groups of 2-GP-β-CD-N, as well as the possible slight formation of external complexes [12-15]. The water-soluble aggregates formed in this way are capable of solubilizing the molecules of substrates through non-inclusive complexation [16-18]. A significant change in the chemical shifts of the imine proton H-9 is probably due to the hydrophilic interaction of its hydroxy-group receptor.

Supramolecular self-assembly of substrate **2** with β- and 2-GP-β-CDs with the formation of supracomplexes **4** and **5** was also accompanied by a change in internal hydrophobic protons of CD and insignificant screening of external proton receptors. In molecule **1**, the largest changes in proton chemical shifts occurred in the phenyl and pyridine fragments. When β-CD-β was used as the receptor, the greatest changes in proton chemical shifts were observed in the protons of the pyridine fragment of complex **4**, whereas the use of 2-GP-β-CD in supramolecular self-assembly with substrate **2** leads to the greatest change in the chemical shifts of the protons of the phenyl radical in the supracomplex **5**.

The proposed models of supracomplexes **4** and **5** are similar in structure and are shown in Figure 3. In order to study the biological activity of the obtained supramolecular inclusion complexes 3-5, their antiradical effect on the DPPH radical was evaluated. The antiradical action of the presented samples was investigated with respect to the radical 2,2-diphenyl-1-picryl hydrazyl (DPPH •) [19].

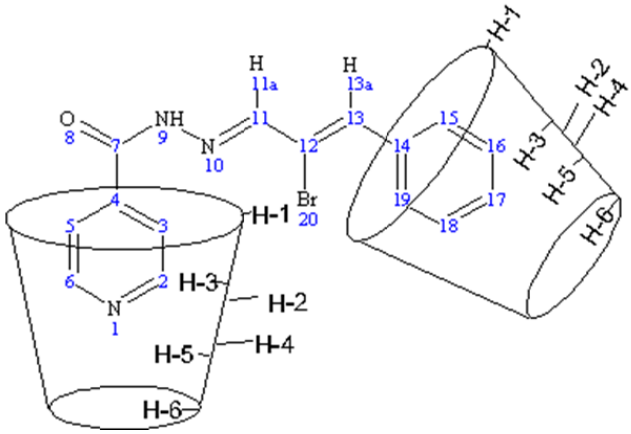


Figure 3 - Supposed supramolecular inclusion complexes **4** and **5**

A methanol solution of DPPH (100 μM) was used for the initial evaluation of the antiradical activity of the samples under study in the DPPH-radical test. For the selection of substances with a pronounced antiradical activity, 2 ml of a 100 μM methanolic solution of DPPH was mixed with 20 μl of the test object dissolved in DMSO at a concentration of 5 mM. Thus, the final concentration of the test substance in the reaction mixture was 50 μM. 10 minutes after the solution of the test compound was added to the DPPH radical solution, the optical density reduction at 515 nm was measured. For substances capable of reducing the optical density by more than 30%, an interaction test with DPPH radical was carried out at the final concentrations of the test substances 100, 75, 50, 25, 20, 10 and 5 μM. Then, the concentration of the test substance was determined, which was able to reduce the optical density by 50% - $IC_{50}$ (DPPH) (Table 5). In control, a 100 μM solution of DPPH was added with 20 μl of a solvent - DMSO.

Table 5 - Optical density of the solution of a 100 μM DPPH radical
after a 10-minute incubation with the test substance at a final concentration of 50 μM

| № | Connection cipher | Optical density | The decrease in the optical density of the initial solution of DPPH-radical, in% of the control |
|---|---|---|---|
| 1. | **(3)** | 0,535 | 52,3 |
| 2. | **(4)** | 1,094 | 2,5 |
| 3. | **(5)** | 1,058 | 5,7 |
| 4. | Control (DPPH solution without test sample) | 1,122 | - |

From Table 5 we see that Compound **3** in the final concentration of 50 μM reduces the optical density of the initial solution of DPPH radical by 52.3%, which means it is promising for further studies. The remaining compounds showed no pronounced antiradical activity under the conditions of this test system.

In the second series of experiments, we studied the ability of compound **3** at various concentrations (from 5.0 to 100 μM) to interact with the DPPH radical (Table 6).

Table 6 - Optical density of the solution of a 100 μM DPPG radical after a 10-minute incubation with **3** at the final concentrations in the reaction mixture of 100, 75, 50, 25, 20, 10 and 5 μM

| № | The final concentration of **3** in the reaction mixture, μM | Optical density |
|---|---|---|
| 1. | 100 | 0,079 |
| 2. | 75 | 0,275 |
| 3. | 50 | 0,491 |
| 4. | 25 | 0,723 |
| 5. | 20 | 0,798 |
| 6. | 10 | 0,907 |
| 7. | 5 | 0,963 |
| | Control (DPPH solution without test sample) | 1,042 |

Using the constructed calibration curve (Fig. 4), the concentration of Compound **3** was determined, capable of 50% decrease in the optical density of a 100 μM solution of DPPH radical. For compound **3**, $IC_{50}$ (DPPH) was found to be 46.4 μM.

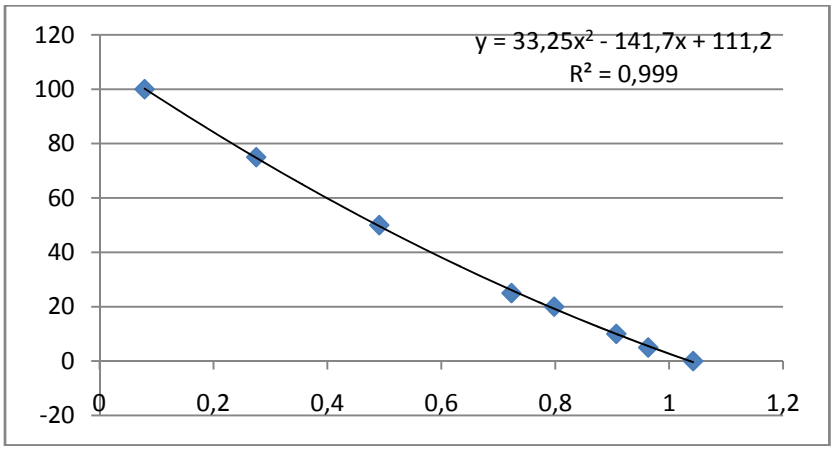


Figure 4 - Dependence of the optical density of the DPPH radical solution on the concentration of **3**

Using the constructed calibration curve (Table 7, Fig. 5), the concentration of ascorbic acid, capable of 50% lowering the optical density of 100 μM DPPH radical solution, was determined. For ascorbic acid, $IC_{50}$ (DPPH) was found to be 21.14 μM.

Thus, supramolecular complexes based on the functionally substituted N-benzylidene- and allylidene-isonicotinohydrate with cyclodextrins (β-CD, hydroxypropyl-β-CD) were obtained and their structures studied by NMR spectroscopy. It is shown that the products obtained from a mixture that is capable of dissolving in water or forming stable aqueous dispersions.

Table 7 - Optical density of the solution of a 100 μM DPPG radical after a 10-minute incubation with ascorbic acid at the final concentrations in the reaction mixture of 25, 20, 10 and 5 μM

| № | The final concentration of ascorbic acid in the reaction mixture, μM | Optical density |
|---|---|---|
| 1. | 25 | 0,429 |
| 2. | 20 | 0,545 |
| 3. | 10 | 0,792 |
| 4. | 5 | 0,914 |
| | Control (DPPH solution without test sample) | 1,042 |

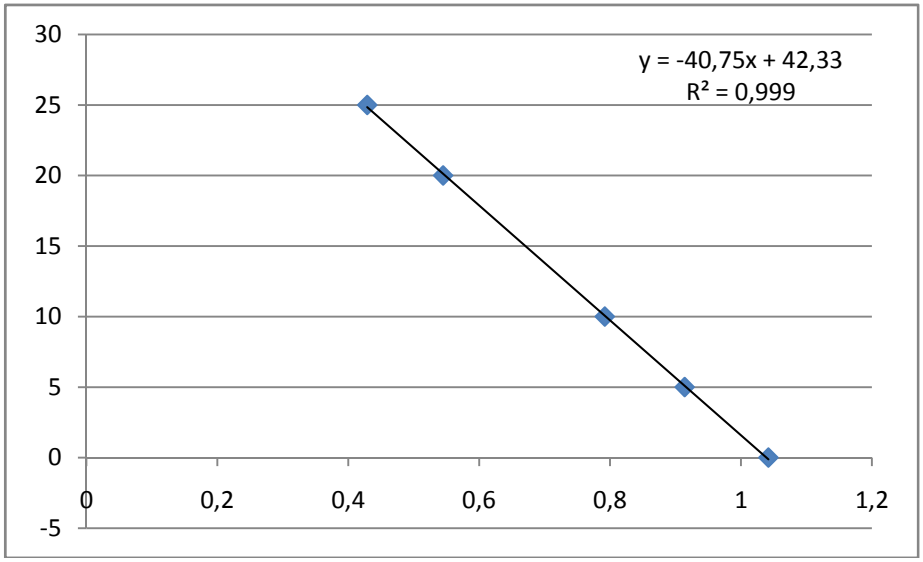


Figure 5 - Dependence of the optical density of the DPPH radical solution on the concentration of ascorbic acid

The antiradical effect of synthesized supramolecular inclusion complexes against DPPH radical was estimated. Antiradical activity under the conditions of this test system was shown in Sample 3, for which a concentration was determined capable of 50% decrease in the optical density of a 100 μM solution of DPPH radical. For compound 3, IC50 (DPPH) was found to be 46.4 μM.

According to our data, the IC50 (DPPH) (μM) for the reference sample, in this case for ascorbic acid, was 21.1 μM. The activity of the sample of Compound 3, for which IC50 (DPPH) was 46.4 μM is inferior to the reference sample of ascorbic acid.

According to the literature data [20] IC50 (DPPH) (μM) for ascorbic acid is 27, for glutathione - 49, for hydroquinone - 27, for trolox - 28, for α-tocopherol - 28. Thus, the activity of compound 3 is comparable with activity known antioxidant - glutathione.

**Experimental part**

β- and 2-GP-β-CDDs were used by Fluka companies with a purity of 99%. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Jeol JNM-ECA 400 spectrometer (399.78 and 100.53 MHz on $^{1}H$ and $^{13}C$ nuclei, respectively) in a DMSO-$d_6$ solution at room temperature. Chemical shifts are measured relative to the residual signals of protons or carbon atoms DMSO-$d_6$.

Preparation of inclusion complexes (3-5) of functionally substituted N-benzylidene- and allylidene-isonicotinhydrazide (1, 2) with β- and hydroxypropyl-β-cyclodextrin. We chose the method of coprecipitation, since this method makes it possible to obtain a very pure preparation of the inclusion complex in a crystalline form. In a 1: 1 ratio, a saturated solution of cyclodextrin in water was added dropwise to a concentrated solution of the functionally substituted N-benzylidene- and allylidenisonicotinhydrazide in an organic solvent (ethanol, dioxane, DMF, etc.). After that, they interfered with a magnetic stirrer at a temperature of 85-90°C. The individuality of the proposed complexes was checked by thin-layer chromatography on Silufol UV-254 plates in isopropyl alcohol-25% ammonia-water 7:2:1 solution. The final product was dried at a temperature of 600°C in vacuum drying at atmospheric pressure of 0.4 kgf/cm2. The inclusion complexes of hydrazones with cyclodextrins were obtained in the form of a powder.

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## ФУНКЦИОНАЛДЫҚ-ОРЫНБАСЫЛҒАН ИЗОНИКОТИН ҚЫШҚЫЛЫНЫҢ ГИДРАЗОНДАРЫ МЕН ЦИКЛОДЕКСТРИНДЕРДІҢ КОМПЛЕКСТІК КЕШЕНДЕРІ ЖӘНЕ ОЛАРДЫҢ АНТИРАДИКАЛДЫҚ БЕЛСЕНДІЛІКТЕРІ

**Аннотация.** Берілген жұмыста алғаш рет циклодекстриндердегі (β-ЦД, 2-ГП-β-ЦД) N-(диэтиламино) бензилиденизоникотиногидразид және N-(2-бромо-3-фенил)аллилиденизоникотиногидразидінің негіздегі супрамолекулярлық кешендердің реакциялары қарастырылып, зерттелді. β- және 2-ГП-β-ЦД рецепторлары мен субстраттар (гидразондар) молекулаларының $^1$Н ЯМР интегралдық қарқындылық дабылдарын сәйкестендіру кезінде барлық жағдайда 1 қонақ молекуласының 2 рецептордың молекуласы құрамында болатын кешендер түзілетіні байқалды. Олардың субстрат молекуласының метиламиндік тобы жағынан рецептордың ішкі жағына кіруі арқылы қосылу кешенін түзетіні анықталды. Алынған өнімдер суда ери алатын қоспа түзеді немесе суда тұрақты дисперсиялар түзеді. Сонымен қатар, ДФПГ-радикалы қатысында циклодекстриндердегі гидразондардың супрамолекулярлық кешенінің антирадикалдық әсері бағаланды. ДФПГ-радикалының ерітіндісінің 100 μМ оптикалық тығыздықты 50%-ға дейін төмендете алатын концентрациясы анықталды. N-(диэтиламино)-бензилиденизоникотиногидразиді мен 2-ГП-β-циклодекстриннің супрамолекулярлық кешені үшін $IC_{50}$(DPPH) 46,4 μМ тең.

**Түйін слова:** β-циклодекстрин, 2-гидроксипропил-β-циклодекстрин, супрамолекулярлық қосылу кешендері, антирадикалдық белсенділік.

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## КОМПЛЕКСЫ ВКЛЮЧЕНИЯ ФУНКЦИОНАЛЬНО-ЗАМЕЩЕННЫХ ГИДРАЗОНОВ ИЗОНИКОТИНОВОЙ КИСЛОТЫ С ЦИКЛОДЕКСТРИНАМИ И ИХ АНТИРАДИКАЛЬНАЯ АКТИВНОСТЬ

**Аннотация.** В настоящей работе впервые были получены и изучены супрамолекулярные комплексы на основе N-(диэтиламино)бензилиденизони-котиногидразида и N-(2-бромо-3-фенил)аллилиденизоникотиногиддразида и циклодекстринами (β-ЦД, 2-ГП-β-ЦД). Сопоставление интегральных интен-сивностей сигналов $^1$Н ЯМР молекул субстратов (гидразонов) и рецепторов β- и 2-ГП-β-ЦД-на в супрамолекулярных комплексах показало, что во всех случаях образуются комплексы состава 1 молекула гостя на 2 молекулы хозяина. Установлено, что при взаимодействии они образуют комплекс вклю-чения с вхождением молекулы субстрата во внутреннюю полость рецептора метиламинным концом. Полученные продукты образуют смесь, способную растворяться в воде или образовывать устойчивые водные дисперсии. Оценено антирадикальное действие синтезированных супрамолекулярных комплексов в отношении ДФПГ-радикала. Определена концентрация, способная на 50% снижать оптическую плотность 100 μМ раствора ДФПГ-радикала. Для супрамолекулярного комплекса на основе N-(диэтиламино)-бензилиденизоникотиногидразида и 2-ГП-β-циклодекстрина, $IC_{50}$(DPPH) оказалась равной 46,4 μМ.

**Ключевые слова:** β-циклодекстрин, 2-гидроксипропил-β-циклодекстрин, супрамолекулярные комплексы включения, антирадикальная активность.

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