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Production of cyclodextrin nanocomplexes based on N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide and research of their structure by physical and chemical methods

In the present work, the supramolecular complexes of N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide with β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (2-HP-β- CD)were first obtained and studied. The NMR methods of one-dimensional ^{1}H, ^{13}C spectroscopy confirmed the structure of the obtained inclusion complexes. The structure of the compounds was also studied by two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), which allows one to establish spin-spin interactions of a homo- and heteronuclear nature. Comparison of the integral intensities of the ^{1}H NMR signals of the initial substrate and β- and 2-HP-β-CD in supramolecular complexes showed that in both cases complexes of the composition of one substrate molecule per one receptor molecule are formed. It was found that the interaction of N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide with the studied β-cyclodextrins forms inclusion complexes with the penetration of the substrate molecule into the internal cavity of the receptor by the pyridine fragment in the case of using β-CD and the furanose cycle in the case of 2-HP-β-CD. The resulting supramolecular complexes can dissolve in water or form stable aqueous dispersions.

Keywords: hydrazones, N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide, β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, inclusion complexes, NMR spectroscopy, supramolecular complexes, COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C).

Introduction

Hydrazones obtained on the basis of the well-known isonicotinic acid hydrazide are used as antibacterial and anti-tuberculosis drugs, analytical reagents and dyes [1]. However, some of them have low solubility in water. At present, various ways have been developed and are used to increase the solubility of drugs in water: the use of special excipients, including the inclusion of drugs in the structure of water-soluble polymers [2].

A possible solution to the problem of water solubility of hydrophobic substances is the use of complexation technology with cyclodextrins. Using the complexation method to obtain biologically active substance clathrates with cyclodextrins will increase the water solubility of hydrophobic and slightly soluble substances, their bioavailability and chemical stability [3]. This will extend the half-life of the active component and, therefore, reduce the dose of the drug used.

Cyclodextrins (CDs) belong to the group of water-soluble compounds, but do not have high solubility at normal temperature due to the relatively strong intramolecular hydrogen bonds in the crystal lattice [3, 4]. The lowest solubility among all natural cyclodextrins has β-cyclodextrin. Being in a dry crystalline state, cyclodextrins do not have high hygroscopicity [5]. However, in the process of crystallization of cyclodextrins from aqueous solutions, water molecules are actively included in the torus cavity, and are also present in the crystal structure of the substance, binding to the outer surface of the molecules.

The structure of the cyclodextrin crystals is stabilized by intermolecular hydrogen bonds. In the crystalline hydrate state, the aggregates of cyclodextrin molecules have a tubular or network shape, and, due to different orientations, form particles resembling needle-like or prism-like agglomerates in appearance (Fig. 1).

The crystal shape of the cyclodextrin molecules depends on the degree of hydration. With the removal of water, the crystals become amorphous [6]. During the formation of inclusion complexes, water molecules are displaced from the cavities of the cyclodextrin torus as a result of incorporation of the corresponding «guest» substance into the torus cavity.

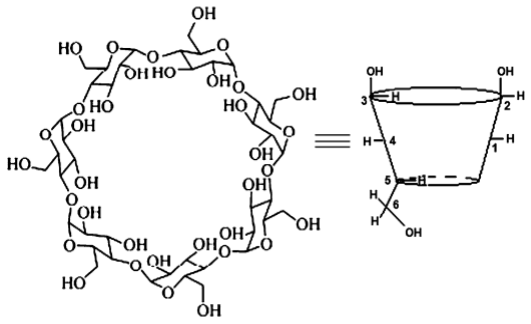


Figure 1. The structure of the cyclodextrin crystals

Cyclodextrins are insoluble in most organic solvents, but are also able to dissolve in some polar aprotic solvents [7]. The temperature dependence of the solubility of cyclodextrin may vary as a result of the complexation process with the molecule of the «guest» substance. Inclusion complexes may have greater solubility in water than intact cyclodextrins, provided that the molecules of the «guest» substance are readily soluble in water. And, on the contrary, during the formation of inclusion complexes with hydrophobic molecules of the «guest» substance, the solubility of cyclodextrins in water may decrease [6]. Despite the decrease in the solubility of cyclodextrin molecules («matrix» molecules), the solubility of a hydrophobic compound in aqueous systems in the inclusion complex may increase [8].

The stability of the formed complexes is due to the formation of various non-covalent forces of interaction between the cyclodextrin and «guest» molecules: van der Waals, hydrophobic, etc. Cyclodextrin in the complex protects the «guest» molecule from damage by various reactive molecules and thereby reduces the oxidation rate of steric rearrangements, hydrolysis, racemization and enzymatic destruction [3].

In this regard, the use of cyclic oligosaccharides, β-cyclodextrins (receptor), as a component of the supramolecular system for obtaining a water-soluble complex with hydrazone (substrate) is promising. The possibility of inclusion of the active substance in the capsule of β-cyclodextrin is due to hydrophobic interactions between the BAC and the complexing agent.

When complexing with cyclodextrins, the molecules of the «guest» substance transform into a nanostructured («encapsulated») state, in which each substrate molecule is placed in the cavity of a native or modified cyclodextrin molecule [6]. This causes significant changes in the physicochemical properties of the molecules of the substance bound by cyclodextrins: the stability of compounds sensitive to oxygen or light increases [6]; the reactivity and activity of the substrate molecules changes; stabilization of easily volatile compounds occurs [9]; the solubility of a number of substances increases [9]; the possibility of converting liquids into powder form is realized [2]; the resistance of the substrate to biodegradation by microorganisms increases [9]; disagreeable odors and taste are masked [10]; the color or color intensity of the compounds changes; the catalytic activity of cyclodextrins, etc., can be observed [9]. Such properties of cyclodextrins and their derivatives makes them suitable for use in analytical chemistry, agriculture, pharmaceuticals, food and cosmetic production [10].

The aim of this work was to obtain inclusion complexes N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide **1** (Fig. 2) with β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD), as well as the establishment of structural features of the obtained supramolecular complexes.

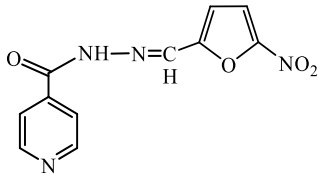


Figure 2. N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide **(1)**

Experimental

β-Cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD) were used by Fluka, 99 % pure. ^{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 of DMSO-d_6.

To obtain complexes for the inclusion of functionally substituted N'-((5-nitrofuran-2-yl)methylene)-isonicotinohydrazide **1** with β-cyclodextrins, the coprecipitation method was chosen, since this method is simple and easy to implement. A concentrated solution of β-cyclodextrin in water was added dropwise to a concentrated solution of N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide **1** in DMF in the ratio 1:1. Then they were interfered with a magnetic stirrer at a temperature of 50–60 ºC. The identity of the proposed complexes was checked by thin-layer chromatography on Silufol UV-254 plates in the isopropyl alcohol system — 25 % ammonia-water solution 7:2:1. The final product was dried at a temperature of 350 ºC in vacuum drying at atmospheric pressure of 0.4 kgf/cm^2. The inclusion complex of hydrazone **1** with β-cyclodextrin was obtained in powder form. The yield of product 2 was 71.6 %, mp. 300–303 ºC. The inclusion complex **3** N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide **1** with 2-hydroxypropyl-β-cyclodextrin was obtained similarly. The product yield was 70.5 %, mp. 289–292 ºC.

Results and Discussion

In supramolecular chemistry, the size and shape or geometric complementarity of the interacting components play a decisive role; therefore, β-CD and its 2-hydroxy derivative, 2-hydroxypropyl-β-CD, were used to obtain inclusion complexes with substrate **1**.

To analyze the physicochemical properties of inclusion complexes of cyclodextrins with substances from various classes of organic and inorganic compounds, as well as aggregates of inclusion complexes, various instrumental methods are used [11]. The choice of specific analysis methods is determined by the physicochemical properties of the complexant substance and the state of aggregation of inclusion complexes [6]. Nanostructures of inclusion complexes formed as a result of substrate-ligand interaction of guest substance molecules with cyclodextrin molecules can be studied and characterized both in dry crystalline form and in the state of solutions [12].

To determine the change in the properties of the ligand substance and the substrate as a result of the formation of nanocomplexes of cyclodextrincavitates obtained in the crystalline state, thermal analysis methods, microscopy methods, spectral, chromatographic methods, etc. can be used [13–15]. To control the physicochemical properties of inclusion complexes It is recommended to use the methods of thermal analysis, scanning electron microscopy, X-ray diffraction analysis, IR spectroscopy, NMR, CD, EPR spectroscopy, microcalorimetry and etc.

For analysis of inclusion complexes, the methods of proton magnetic resonance spectroscopy on ^{1}H nuclei and nuclear magnetic resonance spectroscopy on ^{13}C nuclei are mainly used. The most informative method for confirming the formation of inclusion complexes is ^{1}H-NMR spectroscopy [9]. This analysis method allows you to fix the pronounced chemical shift in the vibrational spectra of H-3 and H-5 protons oriented inside the torus cavity, which is due to the placement of the «guest» substance molecule in the hydrophobic cyclodextrin cavity. Moreover, insignificant chemical shifts are observed in the vibrational spectra of H-1, H-2, and H-4 atoms localized on the outer surface of the molecule [16]. The ^{13}C-NMR spectroscopy method allows one to record chemical shifts in the electronic environment of carbon atoms of the cavity of a cyclodextrin molecule resulting from the van der Waals and electrostatic interaction of the molecules of the «guest» substance with the molecules of the host substance [17–20]. With an increase in the concentration of the «guest» substance in the system, a proportional increase in the chemical shift in the vibrational spectra is observed, due to a shift in the equilibrium state towards the formation of inclusion complexes [21].

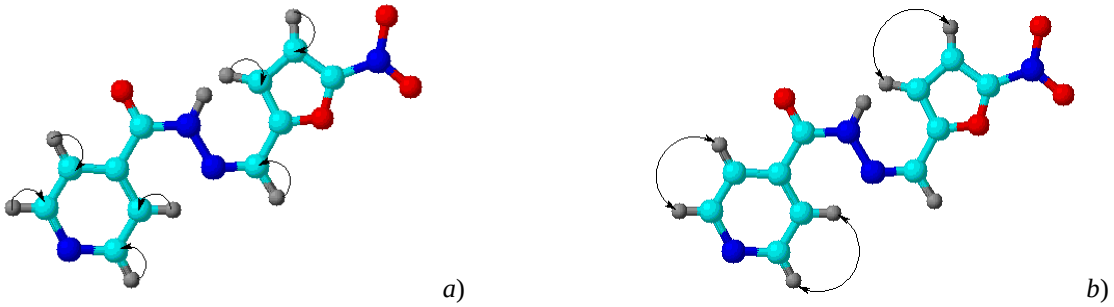
The synthesis of the initial N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide **1** (substrate) was previously described by us in [11–13]. The substance during screening studies showed pronounced antimicrobial and antifungal activity.

In the ^{1}H NMR spectrum of compound **1**, the proton H-4 of the furan fragment appeared as a single-proton doublet at 7.29 ppm. with ^{3}J 4.4 Hz. The remaining furan proton H-3 resonated with the pyridine protons H-15,19 with a three-proton multiplet at 7.76–7.79 ppm. The pyridine protons H-16,18 were manifested by a two-proton doublet at 8.77 ppm. with ^{3}J 5.6 Hz. The proton H-8 at the unsaturated carbon atom and the amide proton H-10 appeared as single-proton singlets at 8.36 and 12.41 ppm. respectively.

In the ^{13}C NMR spectrum of compound **1**, the signals of the carbon atoms of the furan fragment appeared at 115.08 (C-3), 11.61 (C-4), 151.83 (C-5) and 152.59 (C-2) ppm. The signals of the carbon nuclei of the pyridine ring are observed at 122.07 (C-15,19), 140.35 (C-14) and 150.99 (C-16,18) ppm. The unsaturated carbon atom C-8 resonated at 137.20 ppm. Chemical shift signal at 162.53 ppm corresponds to the carbon atom C-11 of the urea group.

The structure of compounds **1** was also confirmed by the methods of two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), which allows one to establish spin-spin interactions of a homo- and heteronuclear nature. The observed correlations in molecule **1** are presented in Figure 3.

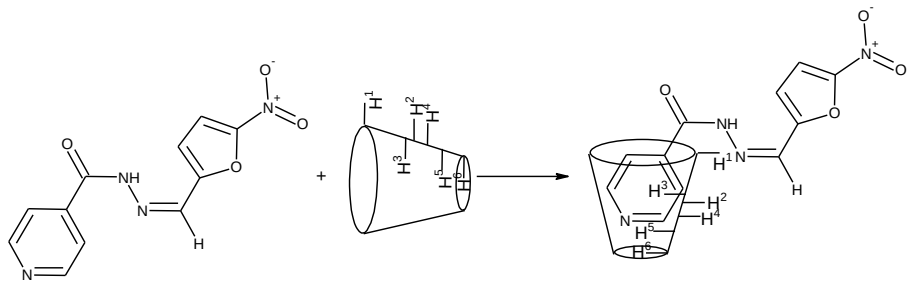
In the spectra of the ^{1}H-^{1}H COSY compound, spin-spin correlations are observed through three bonds of the neighboring methine-methine protons of the H^{4}-H^{3} furan ring (cross-peak coordinates, ppm: 7.28, 7.76 and 7.76, 7.28) and aromatic protons $H^{15,19}$-$H^{16,18}$ (coordinates of cross peaks, ppm: 7.78, 8.76 and 8.7, 7.77) of the pyridine ring. Heteronuclear interactions of protons with carbon atoms through one bond were established using ^{1}H-^{13}CHMQC spectroscopy (Fig. 3*b*) for all pairs present in the compound: H^{4}-C^{4} (7.27, 116.62), H^{3}-C^{3} (7.75, 115.04), $H^{15,19}$-$C^{15,19}$ (7.76, 122.10), H^{8}-C^{8} (8.35, 137.21), $H^{16,18}$-$C^{16,18}$(8.77, 150.96).



a) *b*)

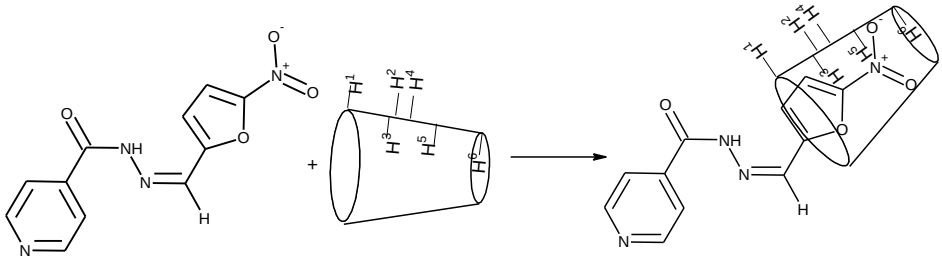
Figure 3. Correlation scheme in the spectra of HMQC (*a*) and COSY (*b*) of compound **1**

As a result of the studies, the supramolecular complexes **2** and **3** based on the functionally substituted N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide with cyclodextrins (β-CD, 2-hydroxypropyl-β-CD) were first obtained. The study of supracomplexes with β-CD **2** and 2-HP-β-CD **3** showed that in both cases, inclusion complexes of substrate **1** with a cyclodextrin receptor cavity are formed. The greatest change in the chemical shifts of protons in the process of formation of supramolecular complexes occurs with the internal protons H-3 and H-5 of the cyclodextrin cavity. In the formation of the inclusion complex of substrate **1** with β-CD, the greatest change in chemical shifts occurs with protons of the pyridine fragment. In the case of using 2-HP-β-CD, a proton of the furan cycle undergoes a greater change in chemical shifts. This indicates the incorporation of the substrate molecule into the cyclodextrin cavity by the pyridine fragment in the case of using β-CD (Fig. 4) and the furanose cycle in the case of 2-HP-β-CD (Fig. 5).



1 **2**

Figure 4. Scheme of the formation of supramolecular complex 2



1 **3**

Figure 5. Scheme of the formation of supramolecular complex **3**

^{1}H and ^{13}C NMR spectra of compound **1** in the free state and in the composition of supramolecular complexes **2** and **3** obtained in DMSO-d_6 are presented in Tables 1 and 2.

Table 1

Chemical shifts of ^{1}H and ^{13}C nuclei of substrate 1 in the free state (δ_0) and in the composition of complexes 2 (δ_1), 3 (δ_2)

Atom number	Group	^{13}C	^{1}H				
		δ_0	δ_0	δ_1	$\Delta\delta_1 = \delta_1 - \delta_0$	δ_2	$\Delta\delta_2 = \delta_2 - \delta_0$
2	>C<	152.59					
3	CH	115.08	7.78	7.77	–0.01	7.90	0.12
4	CH	140.35	7.29	7.28	–0.01	7.26	–0.03
5	>C<	151.83					
8	=CH	137.20	8.36	8.35	–0.01	8.38	0.02
10	NH		12.41	12.41	0		
11	>CO	162.53					
14	>C<	140.35					
15	CH	122.07	7.78	7.75	–0.03	7.78	0
16	CH	150.99	8.77	8.75	–0.02	8.75	–0.02
18	CH	150.99	8.77	8.75	–0.02	8.75	–0.02
19	CH	122.07	7.78	7.75	–0.03	7.78	0

Table 2

Chemical shifts of ^{1}H nuclei of β- and 2-HP-β-CD in the free state (δ_0) and in complexes 2 (δ_1) and 3 (δ_2), ppm

Atom number	β-CD			2-HP-β-CD		
	δ_0	δ_1	$\Delta\delta_1 = \delta_1 - \delta_0$	δ_0	δ_2	$\Delta\delta_2 = \delta_2 - \delta_0$
1	4.77	4.77	0	4.79	4.79	0
2	3.26	3.25	–0.01	3.26	3.27	0.01
3	3.58	3.52	–0.06	3.70	3.73	0.03
4	3.28	3.28	0	3.26	3.27	0.01
5	3.50	3.58	0.08	3.54	3.50	–0.04
6	3.58	3.55	–0.03	3.56	3.58	0.02
7				3.26	3.26	0
8				3.70	3.70	0
9				0.98	0.96	–0.02

A comparison of the integral intensities of ^{1}H NMR signals of molecule **1** with β- and 2-HP-β-CD in supracomplexes showed that in both cases complexes of the composition of one substrate molecule per one receptor molecule are formed. It was shown that the products obtained form a mixture capable of dissolving in water or forming stable aqueous dispersions.

Conclusions

The supramolecular complexes of N'-((5-nitrofuran-2-yl)methylene)isonicotinohydrazide with β-cyclodextrin (β-CD) and 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD) were first obtained and studied in the work. Using the ^{1}H, ^{13}C NMR and two-dimensional NMR COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) spectroscopy, the structure of the obtained inclusion complexes was confirmed, and spin-spin interactions of a homo- and heteronuclear nature were established. A comparison of the integral intensities of the ^{1}H NMR signals of the initial substrate with β-CD and 2-HP-β-CD-us in supramolecular complexes showed that in both cases complexes are formed with the penetration of the substrate molecule into the internal cavity of the receptor by the pyridine fragment in the case of β-CD and furanose cycle in the case of 2-HP-β-CD. It was shown that the obtained supramolecular complexes are able to dissolve in water or form stable aqueous dispersions.

Acknowledgements

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N'-((5-нитрофуран-2-ил)метилен)изоникотиногидразид негізінде циклодекстриндік нанокешендерді алу және олардың құрылымын физикалық-химиялық әдістермен зерттеу

Мақалада N'-((5-нитрофуран-2-ил)метилен)изоникотиногидразидтің β-циклодекстринмен (β-ЦД) және 2-гидроксипропил-β-циклодекстринмен (2-ГП-β-ЦД) супрамолекулярлық кешендер алынып, зерттелген. Бір өлшемді ^{1}H, ^{13}C спектроскопия ЯМР әдістерімен алынған қосу кешендерінің құрылысы расталды. Гомо-және гетероядер табиғатының спин-спинді өзара әрекеттесуін орнатуға мүмкіндік беретін ЯМР COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) екі өлшемді спектроскопия әдістерімен анықталған.

Супрамолекулярлы кешендерде ^{1}H ЯМР сигналдарының интегралдық қарқындылығын β- және 2-ГП-β-ЦД-мен салыстыру екі жағдайда да рецепторлардың бір молекуласына субстраттың бір молекуласының құрам кешені түзілетіндігін көрсетті.N'-(5-нитрофуран-2-ил)метилен)изоникотиногидразидтің зерттелетін β-циклодекстриндермен өзара әрекеттесуі кезінде субстрат молекуласының рецептордың қуысына пиридин фрагменімен кіруімен β-ЦД қолданғанда және фураноздық циклмен кіруімен 2-ГП-β-ЦД қолданғанда қосу кешендері пайда болатыны байқалды. Алынған супрамолекулярлық кешендер суда еруі немесе тұрақты су дисперсияларын құруы мүмкін.

Кілт сөздер: гидарзидтер, N'-((5-нитрофуран-2-ил)метилен)изоникотиногидразид, β-циклодекстрин, 2-гидроксипропил-β-циклодекстрин, қосу кешендері, ЯМР спектроскопиясы, супромолекулярлы кешендер, COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C).

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Получение циклодекстриновых нанокомплексов на основе N'-((5-нитрофуран-2-ил)метилен)изоникотиногидразида и исследование их структуры физико-химическими методами

В статье впервые были получены и изучены супрамолекулярные комплексы N'-((5-нитрофуран-2-ил)метилен)изоникотиногидразида с β-циклодекстрином (β-ЦД) и 2-гидроксипропил-β-циклодекстрином(2-ГП-β-ЦД). Методами ^{1}H, ^{13}C ЯМР спектроскопии было подтверждено строение полученных комплексов включения. Строение соединений было изучено также методами двумерной спектроскопии ЯМР COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C), позволяющей установить спин-спиновые взаимодействия гомо- и гетероядерной природы. Сопоставление интегральных интенсивностей сигналов ^{1}H ЯМР исходного субстрата с β- и 2-ГП-β-ЦД-нами в супрамолекулярных комплексах показало, что обоих случаях образуются комплексы состава: одна молекула субстрата на одну молекулу рецептора. Установлено, что при взаимодействии N'-((5-нитрофуран-2-ил)метилен)изоникотиногидразида с изучаемыми β-циклодекстринами образуются комплексы включения с вхождением молекулы субстрата во внутреннюю полость рецептора пиридиновым фрагментом в случае использования β-ЦД и фуранозным циклом — в случае 2-ГП-β-ЦД. Полученные супрамолекулярные комплексы способны растворяться в воде или образовывать устойчивые водные дисперсии.

Ключевые слова: гидразиды, N'-((5-нитрофуран-2-ил)метилен)изоникотиногидразид, β-циклодекстрин, 2-гидроксипропил-β-циклодекстрин, комплексы включения, спектроскопия ЯМР, супромолекулярные комплексы, COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C).

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