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SUPRAMOLECULAR COMPLEX OF 1-METHYL-4- (3-(NAFTYL-1-OXY) PROP-1-INYL)PIPERIDIN-4-OL WITH SULPHATED ARABINOGALACTAN

Abstract. A synthesis of the supramolecular inclusion complex of 1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl)piperidin-4-ol with sulfated arabinogalactan was developed. The optimal conditions for the interaction of the preparation KN-2 with AG-SO_3H were developed, choosing the mass ratios of the starting reagents, solvents and the duration of the reaction. For many years at A.B. Bekturov Institute of Chemical Sciences the fundamental and applied research on creation of new highly effective and environmentally safe plant growth regulators have been carried out. The structure of the supramolecular inclusion complex of 1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl)piperidin-4-ol with sulfated arabinogalactan was studied by the methods of ^{1}H and ^{13}C NMR. The synthesized new supramolecular complex promising as a preparation with low toxicity, biodegradability and high bioavailability for use in the pharmaceutical and agricultural practice.

Keywords: 1-Methyl-4-(3-(naphthyloxy)prop-1-ynyl)piperidin-4-ol, sulfated arabinogalactan, supramolecular inclusion complex, NMR ^{1}H and ^{13}C spectroscopy.

Introduction. The sulfated arabinogalactan (AG-SO_3H) has a great interest for agriculture and medicine. It can act as a matrix for a directed transport of various drugs and biogenic metals due to its polymer structure. Sulfated arabinogalactan derivatives save a water solubility and membranotropy of a natural polysaccharide and possess anticoagulant and lipid-lowering activity. The presence of sulfate groups in the structure of arabinogalactan makes its a potential heparinoid, as well as an antimicrobial agent [1-3].

For many years at A.B. Bekturov Institute of Chemical Sciences the fundamental and applied research on creation of new highly effective and environmentally safe plant growth regulators have been carried out [4]. Previously, supramolecular complexes of arabinogalactan (AG) and cyclodextrin (CD) with 1-methyl-4-(3-(naphthalyl-1-hydroxy)prop-1-ynyl)-piperidin-4-ol (Akpinol-alpha preparation) was developed. Screening the biological activity of the new AG/KN-2 complex was carried out on beans, wheat, barley and grapes. The investigation of the AG/KN-2 complex showed high survival rate of hard-rooted grape varieties (46% and 4%), as well as an increase of root formation (38,5% and 12,5%) compared to the control exapmles and preparation (KN-2), respectively [5].

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra of the samples were recorded in DMSO-D_6 on a JNM-ECA 400 (Jeol) spectrometer by operating frequencies of 400 (^{1}H), 100 MHz (^{13}C). Chemical shifts are measured relative to the signals of residual protons or carbon atoms of deuterated dimethyl sulfoxide. In continuation of our research a synthesis of the supramolecular inclusion complex of 1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl)piperidin-4-ol with sulfated arabinogalactan was developed. For the interaction of the drug KN-2 with AG-SO_3H optimal conditions, choosing the mass ratios of the starting reagents, solvents and the duration of the reaction were developed.

RESULTS and DISCUSSION

It was found that the synthesis inclusion complex of the some substances with AG-SO3H carried out by the highest yield at a mass ratio of the initial reagents 1:1 in DMSO medium, at the temperature of 50-55 ° C, and during the reaction time for 2-4 hours. After completion of the reaction, the resulting KN-2/AG-SO_3H complex was precipitated by acetone or alcohol, after which the formed precipitate was filtered off and dried under vacuum.

The substrate molecules are introduced between the long polysaccharide chains of sulfated arabinogalactan, forming a supramolecular complex that has higher solubility in water compared to the original 1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl)piperidin-4-ol.

The structure of the inclusion complex of 1-methyl-4-(3-(naphthyl-1-oxy)prop-1-ynyl)piperidin-4-ol with sulfated arabinogalactan was studied by the methods of NMR ^{1}H and ^{13}C and scanning electron microscopy. A fragment of the supposed structure of the inclusion complex of 1-methyl-4-(3-(naphthyl-1-oxy)prop-1-ynyl)piperidin-4-ol with AG-SO_3H is shown in the figure 1.

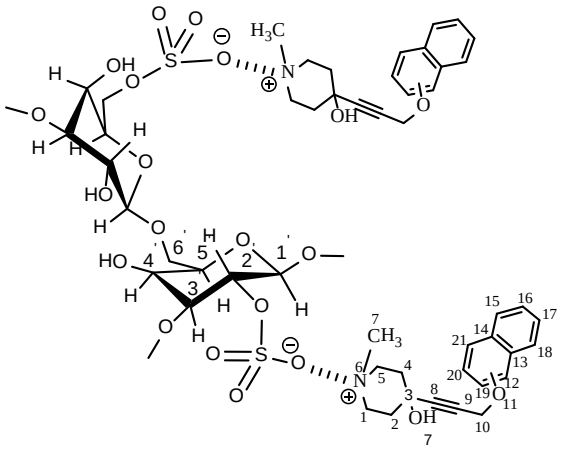

Figure 1 – A fragment of the supposed structure of the inclusion complex of 1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl)piperidin-4-ol with AG-SO_3H

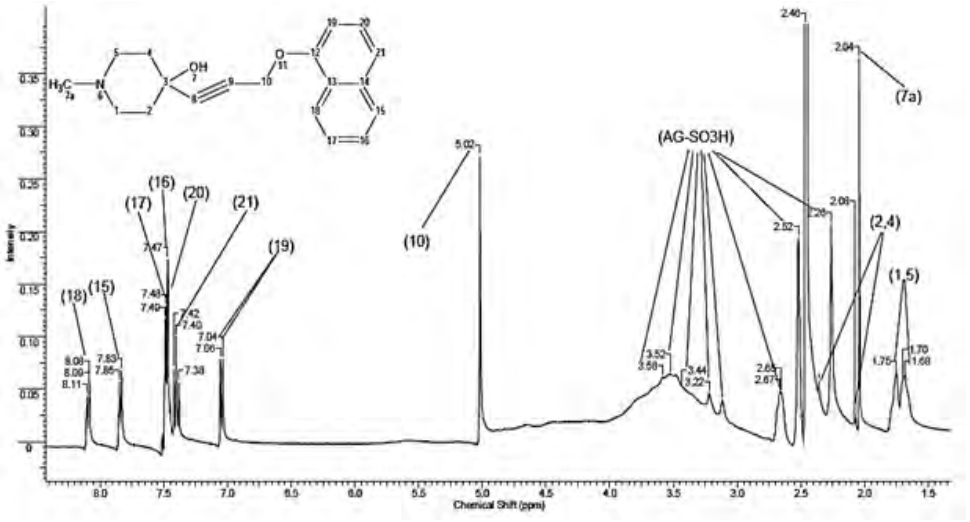

Figure 2 – ^{1}H NMR spectrum of the inclusion complex
of 1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl) piperidin-4-ol with AG-SO_3H

In the ^{1}H NMR spectrum of the supramolecular complex KN-2/AG-SO_3H (figure 2) in the high-field region δ 2.04 ppm is found a singlet signal corresponding to the protons of the N-methyl radical. The axial and equatorial protons H-1 and H-5, H-2 and H-4 of the equivalent CH_2 groups of the piperidine system are resonated in the region of δ 1,68-1,75 and 2,08-2,26 ppm wherein the signals of Ha protons are loca ted in a stronger field than the signals of He protons.

A singlet signal with chemical shift δ 5,02 ppm was assigned to the protons of the secondary carbon atom C-10. In the weak field region are found chemical shifts of protons of the benzene nucleus. The protons H-19, H-15 and H-18 resonate as doublet signals in the region of δ 7,05, 7,83 and 8,09 ppm, respectively. In the range of 7,38 to 7,49 ppm are found the triplet signals of the protons H-16, H-17, H-20 and H-21.

Sulfasubstituted fragment - β-galactopyranose (figure 3) was chosen as a building block for interpretation of the NMR spectra of AG-SO_3H. The protons of methine and methylene groups of galactopyranose unit of the complex AG-SO_3H resonate in the high field region. The protons of the tertiary atoms C-2, C-3 and C-5 resonate at δ 3,22, 3,58 and 3,52 ppm, respectively. The proton H-6 resonates in the region of δ 3,70 ppm. The signals of H-1 and H-4 protons could not be identified.

In the ^{13}C NMR spectrum (figure 4) signals of the equivalent atoms C-1 and C-5, C-2 and C-6 of the guest molecule piperidine are found in the region of δ 39,46 and 51,48 ppm, respectively. Chemical shift at δ 44,89 ppm was assigned to the methyl radical. The secondary carbon atom C-10 resonates in the region of δ 56,78 ppm. *Sp-hybridized* C-8 and C-9 atoms resonate in the weak field of δ 91,59 and 79,41 ppm.

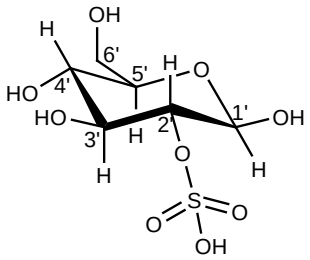

Figure 3 – Signals of a fragment of the elementary unit of sulfated arabinogalactan

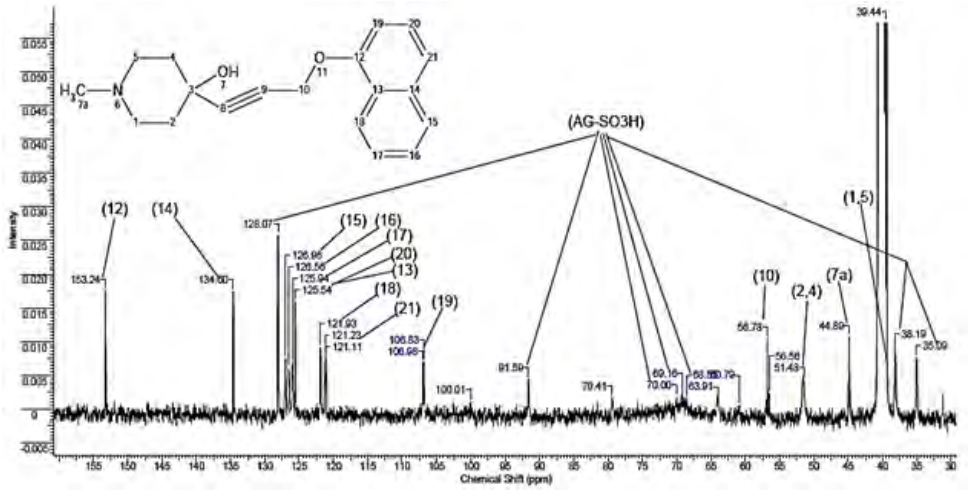

Figure 4 – ^{13}C NMR spectrum of the inclusion complex
of 1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl)piperidin-4-ol with AG-SO_3H

Carbon atoms of the benzene nucleus resonate in a weak field. The following chemical shifts are characteristic for carbon atoms of methine groups: δ (C-19) = 106,98 ppm; δ (C-21) = 121,23 ppm; δ (C-18) = 121,93 ppm; δ (C-20) = 125,54 ppm; δ (C-17) = 125,94 ppm; δ (C-16) = 126,56 ppm; δ (C-15) = 126,96 ppm. The quaternary carbon atoms C-12, C-13 and C-14 resonate in the region of δ 153,24, 125,54 and 134,60 ppm, respectively.

The carbon atoms C-1, C-2, C-3, C-4, C-5 and C-6 of the elementary unit of AG resonate in the region of δ 100,01; 68,55; 70,00; 63,91; 69,16 and δ 60,79 ppm.

The values of chemical shifts of carbon atoms and hydrogen protons of the KN-2/AG-SO_3H complex are shown in the table.

The analysis of spectral data showed that the signals of the H-3 and H-6 protons of the galactopyranose unit of AG-SO_3H are shifted (Δδ = 0,31-3,81 ppm) due to their participation in the complexation process. The chemical shifts most protons of the KN-2 molecule are also shifted (Δδ = 0-0,13 ppm), that indicates formation of the supramolecular inclusion complex KN-2/AG-SO3H.

^{1}H and ^{13}C spectral data of the KN-2 and AG-SO_3H in the free state and as part of the inclusion complex

№	CH		In a free state (δ_0), ppm.		As part of the complex (δ), ppm.		$\Delta\delta(\delta-\delta_0)$, ppm.	
			^{1}H	^{13}C	^{1}H	^{13}C	$\Delta\delta(^{1}H)$	$\Delta\delta(^{13}C)$
1-methyl-4-(3-(naphthyl-1-hydroxy)prop-1-ynyl)piperidin-4-ol								
1	-CH_2-	H*a*	1,58	39,47	1,68	39,46	0,10	-0,01
		Hэ	1,67		1,75		0,08	
2	-CH_2-	H*a*	2,07	52,26	2,08	51,48	0,01	-0,78
		Hэ	2,39		2,26		-0,13	
3	C		–	65,09	–	*	–	–
4	-CH_2-	H*a*	2,07	52,26	2,08	51,48	0,01	-0,78
		Hэ	2,39		2,26		-0,13	
5	-CH_2-	H*a*	1,58	39,47	1,68	39,46	0,10	-0,01
		Hэ	1,67		1,75		0,08	
7	-CH_3		2,02	46,16	2,04	44,89	0,02	-1,27
8	≡C-		–	92,32	–	91,59	–	-0,73
9	≡C-		–	79,15	–	79,41	–	0,26
10	-CH_2-		5,01	56,84	5,02	56,78	0,01	-0,06
12	C=		–	153,29	–	153,24	–	-0,05
13	C=		–	125,60	–	125,54	–	-0,06
14	C=		–	134,61	–	134,60	–	-0,01
15	-CH=		7,84	128,04	7,83	126,96	-0,01	-1,08
16	-CH=		7,48	126,96	7,47	126,56	-0,01	-0,40
17	-CH=		7,48	126,48	7,47	125,94	-0,01	-0,54
18	-CH=		8,11	121,94	8,09	121,93	-0,02	-0,01
19	-CH=		7,05	106,93	7,04	106,98	-0,01	0,05
20	-CH=		7,45	125,95	7,47	125,54	0,02	-0,41
21	-CH=		7,40	121,12	7,42	121,11	0,02	-0,01
AG-SO_3H								
1	>CH-		4,81	103,82	*	100,01	–	-3,81
2	>CH-		3,22	68,87	3,22	68,55	0	-0,32
3	>CH-		3,80	70,32	3,58	70,00	-0,22	-0,32
4	>CH-		4,16	66,55	*	63,91	–	-2,64
5	>CH-		3,52	69,68	3,52	69,16	0	-0,52
6	-CH_2-		3,76	61,10	3,70	60,79	-0,06	-0,31
*Signal not interpreted.								

Conclusion. For the interaction of the drug KN-2 with AG-SO_3H optimal conditions, choosing the mass ratios of the initial reagents, solvents and the duration of the reaction were developed. Thus, the synthesized new supramolecular complex promising as a preparation with low toxicity, biodegradability and high bioavailability for use in the pharmaceutical and agricultural practice.

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Резюме

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1-МЕТИЛ-4-(3-(НАФТИЛ-1-ОКСИ)ПРОП-1-ИНИЛ)ПИПЕРИДИН-4-ОЛДЫҢ СУЛЬФАТТЫ АРАБИНОГАЛАКТАНМЕН СУПРАМОЛЕКУЛАЛЫҚ ҚОСЫЛЫСЫ

Асқын молекулалық кіріккен 1-метил-4- (3-(нафтил-1-гидрокси) проп-1-инил) пиперидин-4-олдың сульфатты арабиногалактан алу жүзеге асырылды. КН-2 және AG-SO_3H препараттарының массалық өзарара қатынастарына қарай, еріткіш бойында әрекеттесу уақыты ескерілген тиімді жағдайлар анықталынды. Аталған тұрғыдағы экологиялық таза және жоғары тиімділікті өсімдіктер мен жеміс ағаштарына арналған өсу стимуляторларын синтездеу жұмыстары Ә.Бектуров атындағы Химия ғылымдары институтының іргелі және қолданбалы көпжылғы зерттеулерінің жалғасы болып табылады. Асқын молекулалық кіріккен 1-метил-4- (3-(нафтил-1-гидрокси) проп-1-инил) пиперидин-4-олдың сульфатты арабиногалактанның құрылымы ^1H және ^{13}C ЯМР әдістерімен зерттелінді. Алынған асқын молекулалық кіріккен 1-метил-4- (3-(нафтил-1-гидрокси) проп-1-инил) пиперидин-4-олдың сульфатты

арабиногалактан қосылысының токсикалық улы қасиеті төмен, биологиялық ыдырау мен қол жетімділігі олардың фармацевтика және ауыл шаруашылық салаларында пайдалануға кең жол ашады.

Түйін сөздер: 1-метил-4-(3-(нафтил-1-окси)проп-1-инил)пиперидин-4-ол, сульфатты арабиногалактан, супрамолекулалық кешенді қосылыс, ЯМР ^{1}H және ^{13}C спектроскопия.

Резюме

Е. С. Сычева, И. Н. Әнуарбекова, М. С. Муканова, Т. М. Сейлханов

СУПРАМОЛЕКУЛЯРНЫЙ КОМПЛЕКС
1-МЕТИЛ-4-(3-(НАФТИЛ-1-ОКСИ)ПРОП-1-ИНИЛ)ПИПЕРИДИН-4-ОЛА
С СУЛЬФАТИРОВАННЫМ АРАБИНОГАЛАКТАНОМ

Разработан синтез надмолекулярного комплекса включения 1-метил-4-(3-(нафтил-1-гидрокси) проп-1-инил) пиперидин-4-ола с сульфатированным арабиногалактаном. Определены оптимальные условия взаимодействия препарата КН-2 с AG-SO_3H с выбором массовых соотношений исходных реагентов, растворителей и продолжительности реакции. В течение многих лет в Институте химических наук им. А.Б. Бектурова проводились фундаментальные и прикладные исследования по созданию новых высокоэффективных и экологически безопасных регуляторов роста растений. Структура надмолекулярного комплекса включения 1-метил-4- (3- (нафтил-1-гидрокси) проп-1-инил) пиперидин-4-ола с сульфатированным арабиногалактаном была изучена методами ЯМР ^{1}H и ^{13}C. Синтезирован новый надмолекулярный комплекс, перспективный в качестве препарата с низкой токсичностью, биоразлагаемостью и высокой биодоступностью для использования в фармацевтической и сельскохозяйственной практике.

Ключевые слова: 1-метил-4-(3-(нафтил-1-окси)проп-1-инил)пиперидин-4-ол, сульфатированный арабиногалактан, супрамолекулярный комплекс включения, спектроскопия ЯМР ^{1}H и ^{13}C.