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SYNTHESIS AND HEMORHEOLOGICAL ACTIVITY OF NEW NAPHTHYL - CONTAINING THIOSEMICARBAZIDES

Mendibayeva A.Zh., Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda, Kazakhstan; Karaganda industrial university, Temirtau, Kazakhstan

Muldakhmetov Z.M., Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda, Kazakhstan

Nurkenov O.A., Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda, Kazakhstan; Karaganda industrial university, Temirtau, Kazakhstan;

Fazylov S.D., Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda, Kazakhstan

Akhmetkarimova Zh.S., National center of biotechnology, Astana, Kazakhstan

Syzdykov A.К., Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda, Kazakhstan; Karaganda industrial university, Temirtau, Kazakhstan;

This paper presents the results of a study of the synthesis, structure, and hemorheological activity of naphthyl-containing thiosemicarbazides (*in vitro*). The main idea in this research was to try to create biologically active molecules with maximum therapeutic activity and a wide range of hemorheological activity and a favorable safety profile. In this context, naphthyl-containing compounds represent as yet unexplored and promising research objects. Their diversity and functional flexibility determine their widespread use as medicines, as well as in the synthesis of other biologically active compounds used in the pharmaceutical, agrochemical and biotechnological industries [1,2]. Naphthyl-containing derivatives, having high antimicrobial activity and significant pharmacological potential, have found wide application in pharmacology. Their ability to participate in a variety of chemical modifications opens up opportunities for the targeted synthesis of compounds with specified properties [3].

Organosulfur compounds represent one of the most widespread and studied classes of organic substances with unique physico-chemical properties and high biological potential. The chemical structure of organosulfur compounds is extremely diverse, due to the content in their structure of fragments with such types of bonds as C–S, C=S, SH, C–N–S, etc. [2]. Compounds based on thiosemicarbazides, which are widely used as components of antimicrobial, anti-tuberculosis and other medicines, are of particular scientific and practical value among organosulfur derivatives. These substances are widely used as a platform for the development of antimicrobial drugs.

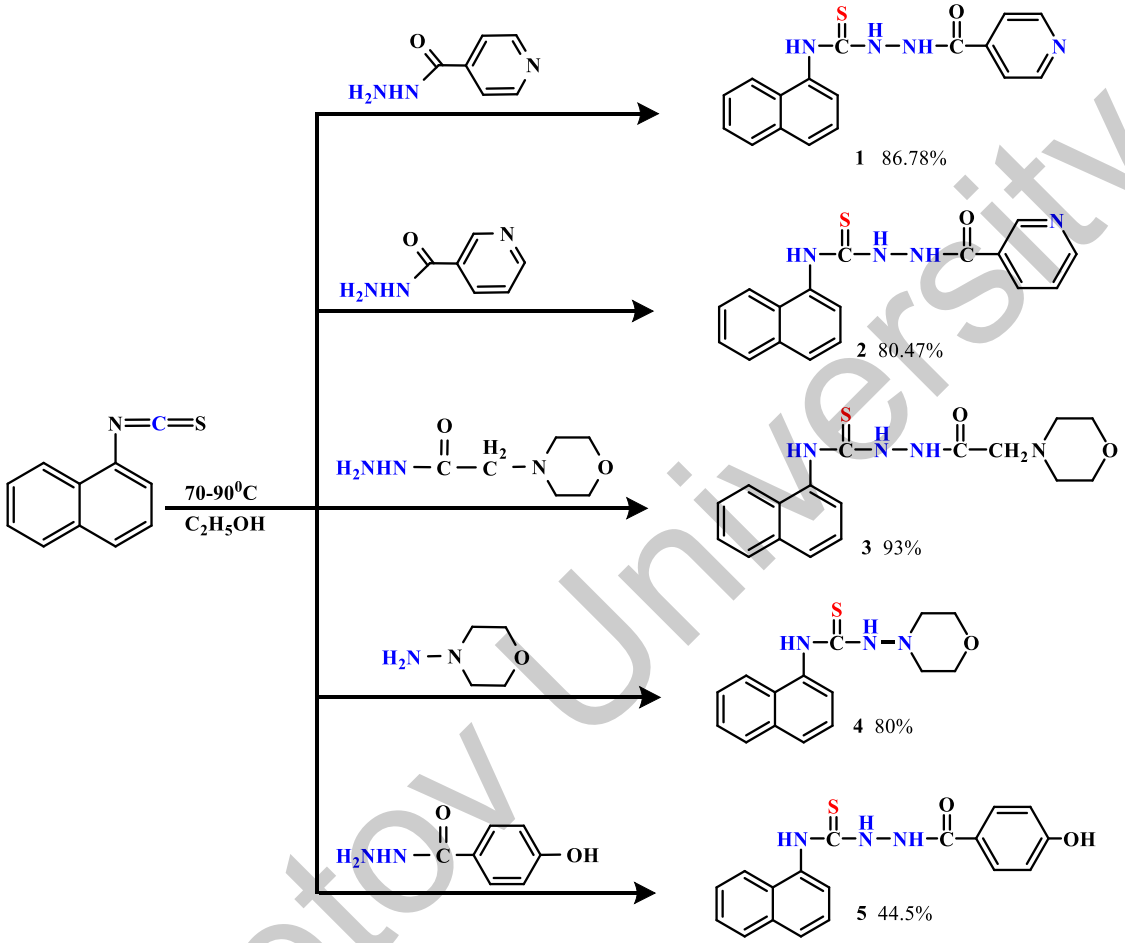
It should be noted that pathological changes in the rheological properties of blood occupy a key place in the pathogenesis of a number of severe chronic and acute diseases, such as ischemic stroke, myocardial infarction, hypertension, bronchial asthma, diabetes mellitus and others. Despite the achievements in the field of studying the molecular mechanisms of hemorheological disorders, the arsenal of effective pharmacological agents capable of correcting these changes remains extremely limited [4]. To date, the most widely used drugs are pentoxifylline, clopidogrel, ticlopidine, aspirin, and lipid-lowering drugs [5]. However, their use is associated with a number of limitations due to insufficient efficacy and a high frequency of side effects, including dyspeptic disorders, intestinal bleeding, skin hemorrhages, leukopenia, thrombocytopenia and agranulocytosis.

These circumstances necessitate the search for new classes of compounds with pronounced hemorheological activity and a favorable safety profile. In this context, naphthyl-containing thiosemicarbazides represent promising research objects that can significantly replenish the arsenal of pharmacological correction of hemorheological disorders. In a series of studies conducted on the basis of the National Center of Biotechnology, the presence of hemorheological activity in a number of naphthyl-containing thiosemicarbazides was established, which confirms the prospects of these compounds for the further development of new effective correctors of disorders of rheological properties of blood.

It is known from the literature [6] that many hydrazides are not only important pharmacologically active drugs and exhibit a wide range of high physiological activity, but also serve as initial synthons for further modifications. One of the well-known methods of using hydrazides is the method of obtaining a thiosemicarbazide framework based on them, since it is known that many thiosemicarbazide and thioamide derivatives (thioacetazone - thiosemicarbazone *n*-acetaminobenzaldehyde, α-methylbenzylthiourea, etc.) have bacteriostatic and antiviral activity [7]. The isothiocyanate

method, due to its high reactivity, allows the introduction of a thioamide group into the structure of hydrazides to form thiosemicarbazides, which not only expands the boundaries of modification of these compounds, but can also lead to the emergence of new types of bioactivity and a possible reduction in the toxicity of compounds.

In connection with the above, it seemed interesting to us to investigate the synthesis of new naphthyl-containing thiosemicarbazides and to study them for the presence of hemorheological activity on the model of high blood viscosity syndrome *in vitro*. New samples of naphthyl-containing thioureas and thiosemicarbazide substances were synthesized at the Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan. By condensation of naphthylisothiocyanate with hydrazides of pyridine carboxylic, 4-hydroxybenzoic and N-morpholinylacetic acids, as well as aminomorpholine in an alcoholic solution with an equimolar ratio of the reagents used, their thiosemicarbazide derivatives **1-5**, potentially possessing biological activity, were synthesized.



The composition and structure of compounds **1-5** are confirmed by IR, NMR ^{1}H and ^{13}C spectroscopy, as well as data from two-dimensional spectra COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C).

In order to apply the synthesized compounds in practice, their hemorheological activities have been studied. For the initial assessment of the hemorheological activity of the studied compounds, an *in vitro* model of high blood viscosity syndrome (HBVS) was used, specially designed to reproduce key pathological changes in the rheological properties of blood characteristic of various clinical conditions. The use of this model is due to its high reproducibility, physiological relevance, and the ability to quantify the effects of the tested compounds [8].

The hyperviscosity model was reproduced by incubating blood samples at a temperature of 43,0^{0}C for 60 minutes. It was found that exposure to these temperature conditions leads to a significant increase in blood viscosity due to increased aggregation of red blood cells and a decrease in their deformability. Such changes are key mechanisms for the development of hemorheological disorders characteristic of a wide range of vascular and metabolic pathologies [8]. Blood viscosity was measured using a Brookfield DV2T rotary viscometer, which made it possible to record changes in viscosity at different spindle speeds. (2, 4, 6, 8, 12, 20 and 40 rpm.s^{-1}). This approach provides a comprehensive assessment of the effect of compounds on both the deformability of erythrocytes at high shear rates and their aggregation properties at low rates [8,9]. Blood was taken from healthy male Wistar rats, which ensured the standardization of biological material. After determining the initial viscosity values, the samples were incubated with the test substances (final concentration 10-1 g/ml) in DMSO at 43,0^{0}C for 60 minutes. The control samples contained an equivalent amount of DMSO without active compounds. This protocol made it possible to minimize the effect of the solvent on the rheological properties of blood and to objectively evaluate the effect of the tested compounds. The use of this *in vitro* model made it possible to simulate HBVS in a laboratory experiment, which is an important tool for early detection and pre-screening of substances with potential hemorheological effects (Table 1).

Table 1 - Effect of samples **1-5** on blood viscosity (MPa*s) at different spindle speeds on *in vitro* blood hyperviscosity models (incubation at 43°C)

Indicator	**Blood viscosity (MPa*s) at different spindle speeds, rpm**							
	2	4	6	8	12	20	40	60
compound 1- N-(naphthalene-1-yl)-2-isonicotinoylhydrazino-1-carbotioamide								
Initial viscosity, n=2	3,74±0,04	3,16±0,02	2,59±0,03	1,88±0,03	1,5±0,06	1,08±0,03	0,99±0,01	0,93±0,01
Blood viscosity after 1 h. in control, n=4	5,62±0,17 p1=0,004	4,2±0,07 p1=0,0012	3,17±0,13 p1=0,0758	2,68±0,05 p1=0,0013	2,25±0,05 p1=0,0020	1,97±0,02 p1=0,00002	1,28±0,02 p1=0,029	1,08±0,02 p1=0,0196
Blood viscosity after 1 h. of the sample with a **comp.1** n=4	6,48±0,14 p1=0,0004 p2=0,0193	4,56±0,06 p1=0,0002 p2=0,0185	3,58±0,04 p1=0,0001 p2=0,0508	2,93±0,02 p1=0,0001 p2=0,0207	2,4±0,03 p1=0,0001 p2=0,0625	2,1±0,03 p1=0,0001 p2=0,0163	1,5±0,03 p1=0,0004 p2=0,0021	1,2±0,01 p1=0,00008 p2=0,0072
compound 2- N-(naphthalene-1-yl)-2-nicotinoyl hydrazino-1-carbotioamide								
Initial viscosity, n=2	4,72±0,16	3,47±0,29	2,89±0,24	2,47±0,02	1,92±0,16	1,53±0,21	0,64±0,09	0,23±0,08
Blood viscosity after 1 h. in control, n=4	5,56±0,28 p1=0,1830	4,55±0,14 p1=0,0308	3,68±0,09 p1=0,0361	3,2±0,03 p1=0,0001	2,51±0,16 p1=0,1301	2,27±0,17 p1=0,1079	1,41±0,12 p1=0,0293	0,97±0,14 p1=0,0481
Blood viscosity after 1 h. of the sample with a **comp.2** n=4	7,15±0,04 p1=0,0001 p2=0,0036	5,31±0,06 p1=0,0017 p2=0,0060	4,24±0,02 p1=0,0019 p2=0,0031	3,55±0,03 p1=0,0001 p2=0,0005	3,19±0,01 p1=0,0004 p2=0,0125	2,39±0,08 p1=0,0158 p2=0,6103	2,01±0,07 p1=0,0006 p2=0,0126	1,4±0,04 p1=0,0002 p2=0,0626
compound 3 - 2-(2-morpholinoacetyl)-N-(naphthalene-1-yl)-hydrazino-1-carbotioamide								
Initial viscosity, n=2	4,57±0,38	3,62±0,30	2,73±0,32	2,33±0,25	2,02±0,09	1,53±0,04	0,66±0,36	0,45±0,27
Blood viscosity after 1 h. in control, n=4	8,34±0,08 p1=0,0002	5,67±0,03 p1=0,0009	4,27±0,03 p1=0,0033	3,7±0,05 p1=0,0029	2,92±0,04 p1=0,0005	2,23±0,03 p1=0,0002	1,72±0,03 p1=0,0173	1,28±0,02 p1=0,0155
Blood viscosity after 1 h. of the sample with a **comp.3** n=4	7,60±0,24 p1=0,0043 p2=0,0508	5,31±0,05 p1=0,0023 p2=0,0018	4,11±0,03 p1=0,0051 p2=0,0227	3,07±0,25 p1=0,2080 p2=0,0891	2,44±0,17 p1=0,2434 p2=0,0588	2,09±0,04 p1=0,0031 p2=0,0565	1,32±0,04 p1=0,0727 p2=0,0006	1,09±0,02 p1=0,0359 p2=0,0008
compound 4 - 1-morpholino-3-(naphthalene-1-yl)thiourea								
Initial viscosity, n=2	4,9±0,63	3,54±0,24	2,98±0,10	2,47±0,02	2,07±0,04	1,52±0,12	1,13±0,09	0,99±0,10
Blood viscosity after 1 h. in control, n=4	6,64±0,19 p1=0,0408	4,6±0,30 p1=0,1404	3,63±0,24 p1=0,2209	3,01±0,14 p1=0,1071	2,43±0,11 p1=0,1546	2,04±0,11 p1=0,0747	1,41±0,11 p1=0,2442	1,18±0,06 p1=0,2159

Blood viscosity after 1 h. of the sample with a **comp.4** n=4	6,29±0,23 p1=0,0929 p2=0,3657	4,37±0,19 p1=0,1044 p2=0,6127	3,47±0,14 p1=0,1499 p2=0,6610	2,96±0,13 p1=0,1149 p2=0,8313	2,47±0,10 p1=0,0969 p2=0,8554	1,97±0,09 p1=0,0662 p2=0,6951	1,28±0,08 p1=0,4175 p2=0,4615	1,05±0,06 p1=0,6673 p2=0,2688
compound 5 - 2-(4-hydroxybenzoyl)-N-(naphthalene-1-yl)-hydrazino-1-carbotioamide								
Initial viscosity, n=2	6,2±0,07	4,67±0,51	3,46±0,14	2,85±0,08	2,39±0,04	1,91±0,03	1,27±0,02	0,64±0,24
Blood viscosity after 1 h. in control, n=4	9,47±0,62 p1=0,0458	7,46±0,14 p1=0,0038	6,08±0,05 p1=0,0001	4,65±0,08 p1=0,0003	3,78±0,13 p1=0,0041	3,41±0,12 p1=0,00232	2,23±0,02 p1=0,00003	2,1±0,03 p1=0,0015
Blood viscosity after 1 h. of the sample with a **comp.5** n=4	7,5±0,33 p1=0,1011 p2=0,0631	6,21±0,03 p1=0,0161 p2=0,0004	4.32±0,12 p1=0,0220 p2=0,00003	3,55±0,11 p1=0,0302 p2=0,0006	2,93±0,04 p1=0,0025 p2=0,0022	2,38±0,09 p1=0,0551 p2=0,0013	1,49±0,01 p1=0,0008 p2=0,00005	1,32±0,02 p1=0,0228 p2=0,00001
Note: n - the number of samples in the group; p - the significance level.; p1<0.05 – statistically significant differences compared to baseline values; p2<0.05 – statistically significant differences compared to the corresponding values in the control samples								

The results of the study convincingly demonstrated the effectiveness of the *in vitro* blood hyperviscosity model used to identify compounds with promising hemorheological activity. The control drug, pentoxifylline, demonstrated the expected hemorheological effect, thereby confirming the reliability, reproducibility and physiological relevance of the chosen screening methodology. Among the five new compounds studied, 2-(2-morpholinoacetyl)-N-(naphthalene-1-yl) hydrazino-1-carbotioamide **3** and 2-(4-hydroxybenzoyl)-N-(naphthalene-1-yl) hydrazino-1-carbotioamide **5**, showed the greatest activity. contributing to a decrease in blood viscosity under conditions of induced hyperviscosity *in vitro*.

Against the background of the induced syndrome of increased viscosity, compounds **1, 3** and **5** showed pronounced hemorheological activity, significantly limiting the increase in blood viscosity. These compounds demonstrated the ability to simultaneously influence the deformability of red blood cells and their aggregation characteristics, which makes them promising candidates for further research. The results obtained indicate the potential of these compounds as the basis for the development of new pharmacological agents aimed at correcting microcirculation disorders associated with a pathological increase in blood viscosity.

The results of the study convincingly demonstrated the effectiveness of the *in vitro* blood hyperviscosity model used to identify compounds with promising hemorheological activity. Screening of the new five substances under study revealed that three of them have the ability to significantly reduce blood viscosity in conditions of induced hyperviscosity. These compounds showed activity in the full range of shear rates studied, which indicates their complex effect on both erythrocyte deformability and aggregation processes results of the study convincingly demonstrated the effectiveness of the *in vitro* blood hyperviscosity model used to identify compounds with promising hemorheological activity. The new naphthyl-containing derivatives of thiosemicarbazides synthesized by us can be considered as potential candidates for the development of new highly effective hemorheological agents. Subsequently, a detailed study of the mechanisms of their action on cellular and plasma components of blood, pharmacokinetic characteristics, and toxicological profiles is required.

Experimental part

The ^{1}H and ^{13}C NMR spectra were recorded on a JNM-ECA Jeol 400 spectrometer (frequency 399.78 and 100.53 MHz, respectively) using DMSO-d_6 and $CDCl_3$ solvents. Chemical shifts were measured relative to the signals of residual protons or carbon atoms of the deuterated solvent. The melting temperatures were determined on the SMP10 device. TLC analysis was performed on Silufol UV-254 plates, developed with iodine vapor.

N-(naphthalene-1-yl)-2-isonicotinoylhydrazino-1-carbotioamide (1) – 0.5 g (0.0027 M) of nicotinic acid hydrazide in 15 ml of ethanol was added to the mixture while stirring 0.5 g (0.0027 M) of 1-naphthylisothiocyanate in 15 ml of ethanol. The reaction mixture was stirred at 90 °C for 5 hours, then cooled to room temperature, the crude product was filtered and dried. Recrystallization gave **1** in the form of a white powder (0.75 g, 86.78%, m.p. 221-225°C).

N-(naphthalene-1-yl)-2-nicotinoylhydrazino-1-carbotioamide (2) was obtained similarly to compound **1** from 0.37 g (0.0027 M) of nicotinic acid hydrazide and 0.5 g (0.0027 M) of 1-naphthylisothiocyanate. The yield of product **2** was 0.70 g (80.47%), white powder, m.p. 202-204ºC.

2-(2-morpholinoacetyl)-N-(naphthalene-1-yl)-hydrazino-1-carbotioamide (3) was prepared similarly to compound **1** from 0.43 g (0.0027 M) morpholinoacetohydrazide and 0.5 g (0.0027 M) 1-naphthylisothiocyanate. The yield of product **3** was 0.90 g (93%), white powder, m.p. 207-208oC.

1-morpholino-3-(naphthalene-1-yl)thiourea (4) was obtained similarly to compound **1** from 0.26 g (0.0027 M) morpholino acetohydrazide and 0.5 g (0.0027 M) 1-naphthylisothiocyanate. The yield of product **4** was 0.62 g (80%), a light yellow powder, m.p. 164-165 °C.

2-(4-hydroxybenzoyl)-N-(naphthalene-1-yl)-hydrazino-1-carbotioamide (5) was prepared similarly to compound **1** from 0.41 g (0.0027 M) of 4-hydroxybenzohydrazide and 0.5 g (0.0027 M) of 1-naphthylisothiocyanate. The yield of product **5** was 0.4 g (44.5%), white powder, m.p. 198-200 °C.

Thus, the identified new compounds can be considered as potential candidates for the development of new highly effective hemorheological agents capable of filling the existing shortage of drugs aimed at correcting microcirculation disorders in various pathological conditions.

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АЛТАЙ МЕМЛЕКЕТТІК УНИВЕРСИТЕТІ ОҚЫТУШЫЛАРЫНЫҢ ФИЗИКАЛЫҚ ДЕНСАУЛЫҒЫН ЗЕРТТЕУ

Мырзабаев А.Б., академик Е.А. Бөкетов атындағы Қарағанды университеті, Қарағанды, Қазақстан
Тнимова Г.Т., «Bolashaq» академиясы Қарағанды, Қазақстан.
Кабдолла Е., академик Е.А. Бөкетов атындағы Қарағанды университеті, Қарағанды, Қазақстан
Бөдеев М.Т, академик Е.А. Бөкетов атындағы Қарағанды университеті, Қарағанды, Қазақстан
Дүйсебаев Б.Т., академик Е.А. Бөкетов атындағы Қарағанды университеті, Қарағанды, Қазақстан

Мақалада Алтай мемлекеттік университетінің 59 оқытушысының (21 ер және 38 әйел) негізгі физиологиялық көрсеткіштері мен анонимді сауалнама және зерттеу деректері берілген. Зерттеу В. П. Войтенконың экспресс-әдісі бойынша паспорттық және биологиялық жастағы айырмашылықтарды бағалауға бағытталған. Биологиялық жастың (БЖ) мәнін есептеу үшін денсаулықты өз денсаулығын бағалаудың арнайы сауалнамасы және бірқатар физиологиялық көрсеткіштер мен математикалық формулалар қолданылды; тиісті биологиялық жастың мәні (ТБЖ) есептелді; алынған биологиялық жас және тиісті биологиялық жас салыстырылды, зерттелушілердің қартаю жылдамдығы құрдастарынан қанша жыл бұрын немесе артта қалғаны анықталды. Мұндай тәсіл жастары бірдей адамдарды «жасына қарай қартаю» дәрежесі бойынша, сонымен қатар денсаулығының "қоры" бойынша бірнеше дәрежеге бөлуге мүмкіндік береді (I және II дәрежелер – баяу қартаю, III – БЖ популяциялық стандартқа сәйкес келеді, IV және V – жеделдетілген қартаю).

Кілт сөздер: денсаулық, стресс, қашықтықтан білім беру, пандемия, жас, биологиялық жас, университет оқытушылары, гендер.

Адамның қартаюы - бұл биологиялық дамудың барлық деңгейлеріне белгілі бір дәрежеде бірте-бірте әсер ететін, біркелкі емес және тұрақты прогрессиямен сипатталатын әмбебап және табиғи үдеріс. Адамның денсаулығы мен оның өмір сүру ұзақтығы дененің қартаю сипатымен тығыз байланысты.

Биологиялық қартаю – бұл тірі жүйелердің уақыт бойынша өзгеру үдерісі ол организмнің, құрылымы мен функциясының бұзылуын тудырады, бұл адам организмінің көптеген жүйелерінің тіршілік қорының мүмкіндіктерінің төмендеуіне әкеліп соғады. Сонымен қатар, ол онымен байланысты аурулардың пайда болуымен, сондай-ақ өлім-жітімнің жоғарылауымен бірге жүреді [1]. Қартаю бұлшықет массасының, сапасы мен күшінің біртіндеп төмендеуімен қатар жүреді. [2]. Сонымен, биологиялық жас деген (БЖ) ұғым бар. [3] Биологиялық жас - бұл өмір сүрген жылдар саны емес, адам денесінің (денсаулығының) жасы. Адамдар өздері шынайы жастарын білуге мүдделі. Ол үшін адамның биологиялық жасын анықтау қажет.