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РЕСПУБЛИКИ КАЗАХСТАН

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OF THE REPUBLIC OF KAZAKHSTAN

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Адрес редакции: 050100, г. Алматы, ул. Кунаева, 142,
Институт органического катализа и электрохимии им. Д. В. Сокольского,
каб. 310, тел. 291-62-80, факс 291-57-22, e-mail:orgcat@nursat.kz

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СИНТЕЗ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ ВИНИЛОВОГО ЭФИРА МОНОЭТАНОЛАМИНА N-2-ВИНИЛОКСИЭТИЛ-N'-АМИНОТИОМОЧЕВИН

А.М. Газалиев, А.Т. Такибаева, С.К. Кабиева,
А.А. Дудкина, Ж.Б. Рахимберлинова

Ключевые слова: винилоксиэтилизотиоцианат, анабазин, N-2-винилоксиэтил- N'-аминотиомочевина, виниловый эфир моноэтаноламина

Аннотация. В статье приведены данные по изучению и подробно интерпретированы N-2-винилоксиэтил-N'-аминотиомочевины (**2.1-2.6**). Соединения (**2.3, 2.4** и **2.6**) были исследованы на антимикробную, гепатопротекторную, фунгицидную и афицидную активности. Установлено, что 2(винилокси)этилтиосемиркарбазид изоникотиновой кислоты (**2.6**) обладает антимикробной активностью по отношению к грибам Candida albicans и фунгицидной активностью. Подавление роста грибка Botrytis cinerea составляет 69-73%. 2-(Винилокси)этиланабазинотиомочевина (**2.4**) показала афицидную активность с подавлением роста бахчевой и персиковой тлей на 84,2%. Соединения (**2.1, 2.3-2.6**) представляют собой хорошо кристаллизующиеся бесцветные соединения, а тиомочевина (**2.2**) – маслообразное общество, хорошо растворимые в органических растворителях.

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Synthesis and biological activity of monoethanolamine vinyl ether N-2-vinyloxyethyl-N'-aminothiourea

A.M. Ghazaliev, A.T. Takibayeva, S.K. Kabieva,
A.A. Dudkina, Zh.B. Rakhimberlinova

«Karaganda State Technical University», Karaganda, Kazakhstan
altynarai81@mail.ru

Key words: vinyloxyethyl isothiocyanate, anabasine, N-2-vinyloxyethyl-N'-aminothiourea, vinyl ether of monoethanol amine

The article presents the results of analysis and detailed interpretation of N-2-hydroxy ethyl vinyl-N'-amino thio urea (**2.1-2.6**). The compounds (**2.3, 2.4** and **2.6**) were tested for antimicrobial, hepatoprotective, and fungicidal activity aphicidal. 2 (vinyloxy) etiltiosemirkarbazid isonicotinic acid is found to have (**2.6**) an antimicrobial activity against fungi Candida albicans and fungicidal activity. Suppression of growth of the fungus Botrytis cinerea is 69-73%. 2- (vinyloxy) etilanabazinotiourea (**2.4**) showed aphicidal activity to inhibit the growth of melon and peach aphids by 84.2%. The compounds (**2.1, 2.3-2.6**) are well crystallized colorless compounds and thiourea (**2.2**) is an oil company. They are readily soluble in organic solvents.

At present improving the fundamental concepts of organic chemistry, reactivity, stereochemistry and conformational analysis is accompanied by the necessity of finding new organic substances with useful pharmacological properties, also establishing "structure of organic compounds - properties". In this respect, vinyl ethers substituted with various groups are unique starting materials for fine organic synthesis, not traditional products and advanced materials for new technologies.

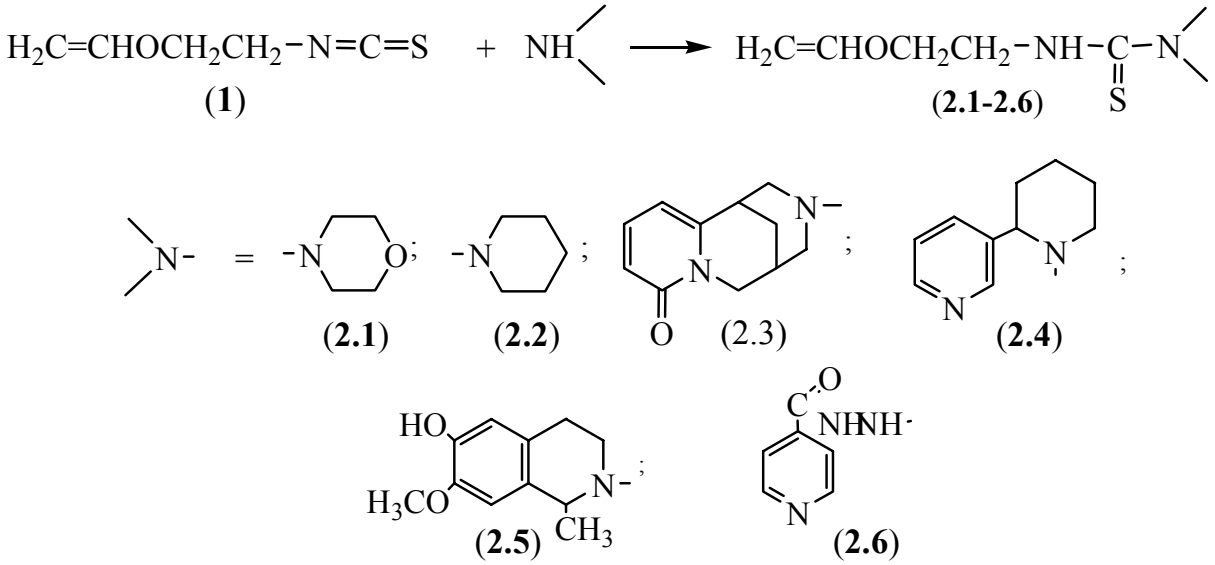
The derivatives of the vinyl ether mono ethanolamine is used as intermediate compounds in the synthesis of substances having analgesic, psychotropic and radio protective properties [1]. The study of

the physiological activity revealed that mono ethanolamine vinyl ether derivatives have a hypotensive and spasmodic effect [2, 3].

One of the representatives of the vinyl ether containing isothiocyanate group is 2- vinyl oxy ethyl isothio cyanate (**1),** that represents high functional monomer and a semi-product with unique synthetic capabilities of vinyl ethers and isotihocyanates [4]. Reacting vinyl oxy ethylisothiocyanate (**1**) with the aromatic diols of (pyrocatechol, resorcinol, hydroquinone, 2,3-dihydosnaphthaline, di-n-hydroxyl phenyl propane) in electrophilic conditions (0.25-0.5 mass% CF_3CO_2H, °C, 0.5 -2 h) leads to quantitative results in bis-acetol with isothiocyanate groups [5].

Interest in the selected object is that the chemistry compounds based on vinyl oxy ethyl isothio cyanate (**1**) in many ways is still relatively little-studied sphere and is of great interest in searching new biologically active substances.

To search new biologically active substances we carried out the condensation reaction of vinyl oxy ethyl isothio cyanate (**1**) with amines, alkaloid anabasine, cytisine and salsolin and also isonicotinic acid hydrozide, which exhibits a strong anti-tuberculosis effect and antagonizes nicotinamide - a factor of oxidizing restoring processes inside cells [6,7]. So we reasonably decided to combine thiourea fragments with the structure of the molecule amines (alkaloid, hydrozide). Highly reaction of NH-group in combination with carbomide (carbonate) urea function makes the N-vinyl oxy productive urea and thiourea valuable monomers [6-10].



The compounds (**2.1,2.3-2.6**) are well crystallized colorless compounds, and thiourea (**2.3**) is an oil well soluble substance in organic solvents.

The composition, structure and identity of the synthesized compounds are confirmed by elemental analysis, IR spectroscopy and thin-layer chromatography.

In IR spectrum of connection (**2.6**) there are characteristic strips of absorption answering to the fluctuations of functional groups NH-, NH-CS, CH2=CH and - C=S in areas of 3460-3440, 1510-1500, 1645-1621 of cm-1 and 1350-1300 cm-1 respectively.

X-ray diffraction study of anabazino vinyl oxy ethyl amino thiourea molecule (**2.4**) is held to determine the spatial structure of the synthesized thiourea derivatives of mono ethanol amine vinyl ether (**2.1-2.6**). The general form of the molecule (**2.4**) is shown in Figure 1.

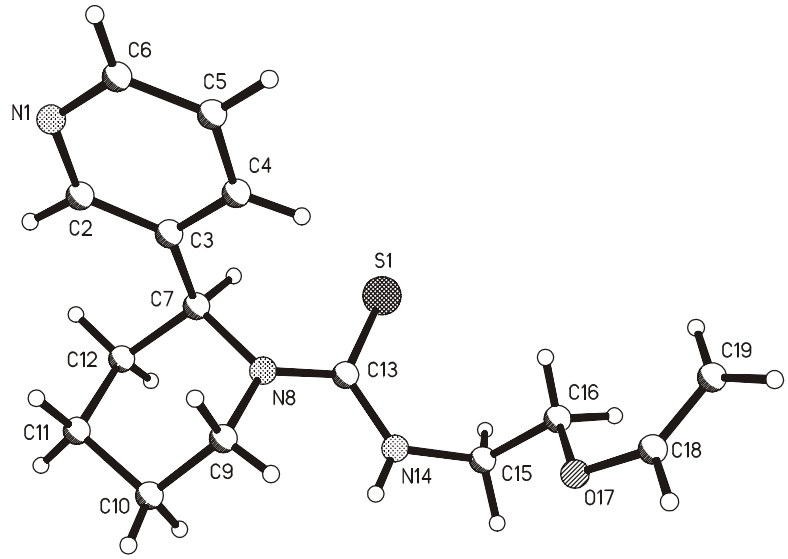


Figure 1 - The structure of the molecule anabazino vinyloxyethylaminothiourea (**2.4**)

The synthesized compounds (**2.3, 2.4** and **2.6**) have been tested for hepatoprotective activity in South Kazakhstan State Medical Academy under the guidance of the head of department of pharmacology, pharmacotherapy with a course of clinical pharmacology by the following scientists as MD, professor Ormanova N.J (Shymkent); on aphicidal, the fungicidal activity in the biotechnology lab of Kazakhstan scientific institute of healthcare (Almaty) D. Geshtovta N.Y and Ph.D. Temresheva I.I; for antimicrobial activity in the Karaganda State Medical University, associate professor of Immunology, allergy from microbiology Abdulina G.A.

Hepatoprotective activity

The object of the study was a thiourea derivative of mono ethanol amine vinyl ether N-(N'-vinyloxyethyl thiocarbamoil) cytosine (**2.3**).

The experiment was carried out on white mongrel rats of both sexes, and laboratory mice. A single intraperitonal injection of a 50% oil solution of carbon tetrachloride in a dose of 0.6 ml / 100 g of body weight induced acute toxic hepatitis in rats. Drugs were made one hour before intoxication and the 4th day. Slaughtered animals were studied on the 5th day. Hepatoprotective activity of the compound was evaluated by cytolytic activity of the products of hepatocytes – AT, AST, LAP.

The functional activity of the liver was determined by thymol. Detoxication activity of hepatocytes was evaluated by hexenal sample. At the same time the morphological changes of hepatocytes (histology) were studied.

Experiment results show that the content of ATL, AST, LAP is increased to 90%, 50% and 82% in acute toxic hepatitis induced by carbon tetrachloride, and respectively, indicators of thymol test are increased more than 3 times. It was found out that the compound (**2.3**) has not shown hepatoprotective activity in health care cases.

Aphicidal activity

The object of the study was a compound (**2.4**).

Initial assessment of aphicidal activity of the tested compound (**2.4**) was conducted on melon aphids in the laboratory. Amount of 30-50 insects were placed in petri dishes (4 times of repetition) on a filter paper and sprayed (concentration of 0.02 %) from the spray liquid at a rate of 1.5 ml per dish. Water is served as a control liquid. Registration of the insects death was carried out in 24 hours after processing, and the mortality rate of the pest was determined by variants. Compounds providing the highest level of destruction of insects were tested by further object SK50.

Evaluation of aphicidal action of the compound (**2.4**) had been carried out in laboratory on melon and peach aphids. The leaves of cucumber plants and peas, respectively populated with pest were sprayed from a spray in certain concentrations of tested compound (**2.4**), at the rate of the working fluid was 1 ml.

Pests were replaced in a petri dish on filter paper moistened with water. The insects' death was recorded in 24 hours after the processing, the calculation of biological effectiveness had been conducted by Abbott formula [11] with the correction of death of insects in control. Water is served as a control liquid.

As a result of laboratory biological evaluation it has been found out that the compound (**2.4**) at a concentration of 0.01% provides suppression of aphid to 84.2%. in laboratory vegetation tests.

The fungicidal activity

Sterilized by filtration on a machine of Nolgene system and aseptically injected into Chapek agar medium at various concentrations new thiourea derivative mono ethanolamine vinyl ether - 2 vinyl oxy ethyl thiosemicarbazid isonicotinic acid (**2.6**) received study. Phytopathogenic fungi: Fusarium oxysporum and Botrytis cinerea were used as test cultures. The fungicidal activity was evaluated by the intensity of the development of microorganisms on the medium in comparison with the control options without introducing the test compounds.

The analysis found out that the tested in vitro compound (**2.6**) has a pronounced fungicidal activity against the growth of a plant pathogenic fungus Botrytis cinerea (growth inhibition is of 69-73% percent), in an embodiment of Fusarium oxysporum (growth inhibition is of 58-65% percent).

Antimicrobial activity

The object of the study was a compound (**2.6**).

The antimicrobial activity of (**2.6**) was studied by the procedure described in generally accepted method [12] for antibiotics. The sensitivity of microorganisms to the compound was determined by the method of serial dilutions in a liquid nutrient medium. The following strains of microorganisms as S.aureus 505, P.vulgaris 1, P.aeruginosa ATC 464, E.coli *M- 17*, B.subtilis *ACCC-6633*, and also clynical strains S.agalactae, C.albicans were used for investigation.

The antimicrobial activity was studied in a number of divisible concentration tests of (**2.6**) 8.0; 4.0; 20; 10; 0.5; 0.25 and 0.125 mg/ ml within known limits.

In parallel the nutrient medium (**2.6**) for sterility and control of the preparation is tested. For the cultivation of S.aureus, P.vulgaris, E.coli, B.subtilis the peptone meat agar; for that of S.*agalactae* 1% of glucose broth; for C.albican Saburo liquid medium are used.

The minimal bactericidal concentration was evaluated visually in the lack of growth of microorganisms in liquid nutrient medium. For the evaluation of minimal bactericidal concentration transplantation was produced from tubes where there was no visual growth on dense nutrient medium: S.aureus for yolk-salt agar; E.coli the Endo medium; P.vulgaris, P.aeruginosa, B.subtilis the peptone meat agar; S.agalactae the blood-sugar agar. Candida albicans Saburo liquid medium.

The minimal bacteriostatic concentration was estimated turbidimetrically, by comparing the intensities of the microorganism growth on liquid nutrient media. Research analysis were stated by spectrometer, nutrient medium in accordance with the concentration served as a control.

So 2-vinyl oxy ethyl thiosemicarbazid isonicotinic acid has antifungal effect against Candida albicans. The minimal bacteriostatic concentration of the compound to the tested strain was 0.125 mg/ ml and the minimal germicidal concentration was 0. 25 mg/ $ml^{-1.}$

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N-2-ВИНИЛОКСИЭТИЛ-N`-АМИНОТИОМОЧЕВИНА МОНОЭТАНОЛАМИННІҢ ВИНИЛДІ ЭФИР ТУЫНДЫСЫНЫҢ СИНТЕЗІ ЖӘНЕ БИОЛОГИЯЛЫҚ БЕЛСЕНДІЛІГІ

А. М. Газалиев, А. Т. Такибаева, С. К. Кабиева, А.А. Дудкина, Ж.Б. Рахимберлинова

Түйінді сөздер: винилоксиэтилизотиоцианат, анабазин, N-2-винилоксиэтил-N`- аминотиомочевина, моноэтаноламиннің винилді эфирі

Мақалада N-2-винилоксиэтил-N`-аминотиомочевина (**2.1-2.6**) толықтай сипатталған және оны зерттеу бойынша мәліметтер келтірілген. Қосылыстар (**2.3, 2.4** және **2.6**) микробқа қарсы гепатопротекторлы, фунгицидті және афицидті белсенділікке зерттелді. Изоникотин қышқылының 2(винилокси)этилтиосемиркарбазиді (**2.6**) Candida albicans зендеріне қатысты микробқа қарсы және фунгицидті белсенділікке ие болатыны анықталды. Botrytis cinerea зендерінің өсуін 69-73% тоқтатады. 2-(Винилокси)этиланабазинотиомочевина (**2.4**) бақша және шабдалы битінің өсуін 84,2% тоқтатуын есепке алғанда, афицидті белсенділікті көрсетті. Қосылыстар (**2.1, 2.3-2.6**) оңай кристалданатын түссіз қосылыстар болып табылады, ал тиомочевина (**2.2**) – органикалық еріткіштерде жақсы еритын май тәрізді – зат.

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