

контрольных вопросов и практических навыков по текущей теме занятия, которые должен знать каждый студент на кафедре физиологии.

Результаты. В результате самостоятельной работы у студента должны развиваться такие умения, как умение учиться самостоятельно, принимать решения, проводить исследования, осуществлять и организовывать коммуникацию, формулировать получаемые результаты, переопределять цели дальнейшей работы, корректировать свое образовательное направление.

На протяжении всей самостоятельной работы студентов в роли координатора действий и консультанта должен выступать педагог.

Заключение. Таким образом, организация самостоятельной подготовки является многоэтапной, которая включает в себя разнообразные методики преподавания, работа, направленная на повышение уровня знаний студентов.

Литература/References:

1. Насонова Н.А. [и др.]. Роль воспитательной работы в медицинском вузе в формировании нравственного облика врача//Инновационные обучающие технологии в медицине: сб. матер. Республиканской научно-практической конф. с международным участием. - 2017. - С. 356-357.

2. Козловский А.А., Козловская М.М., Мельник С.Н. «Организация внеаудиторной самостоятельной работы студентов в медицинских вузах» Учебно-методическое пособие для студентов медицинских вузов, клинических ординаторов, аспирантов, врачей-интернов. Гомель. ГомГМУ. 2014

3. Писарев Н.Н. [и др.]. Стиль педагогического общения преподавателя и студентов//Однораловские морфологические чтения: сб. научн. тр., посвящ. 120-летию со дня рождения проф. Н.И.Одноралова и 100-летию ВГМУ им. Н.Н.Бурденко. - 2018. - С. 210-212.

4. Фетисов С.О., Карандеева А.М., Соболева М.Ю. Проблемы формирования профессиональных компетенций в процессе самостоятельной работе студентов, обучающихся на иностранном языке//Медицинское образование XXI века: компетентностный подход и его реализация в системе непрерывного медицинского и фармацевтического образования: Сб. матер. Республиканской научно-практич. конф. с международн. участ. - Витебский гос. мед. ун-т, 2017. - С. 477-479.

5. Гладилина Г.А. Использование информационно-коммуникационных технологий в формировании профессиональных компетенций студентов при организации самостоятельной работы. <http://jdanova-ren.narod.ru/obob/gladilina.htm>

6. Ходжаева Д.Т., Хайдарова Д.К., Хайдарова Н.К. Рекомендации по снижению депрессивных и тревожных расстройств в условиях карантина по коронавирусной инфекции. Услуги – тавсиянома. Бухоро-2020.

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THE REACTION OF SUBSTITUTED BENZOYLISOTHIOCYANATES WITH METHIONINE AND STUDY OF THE ANTI-INFLAMMATORY ACTIVITY OF THE SYNTHESIZED COMPOUNDS

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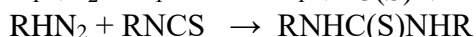
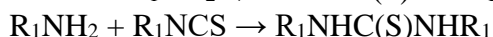
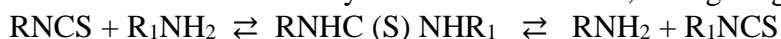
Abstract: The thiourea derivatives were synthesized by the reaction of substituted benzoyl isothiocyanates and α -amino acid – methionine in a dimethylformamide medium. The anti-inflammatory activity of the obtained compounds was studied. It has been established that N-(meta-iodobenzoyl) –NI–methionylthiourea has a much greater latitude of anti-inflammatory action and is of undoubted practical interest.

Keywords. thiourea; benzoyl isothiocyanate; α -Amino acids; methionine; methionylthiourea Inflammation; anti-inflammatory activities.

РЕАКЦИЯ ЗАМЕЩЕННЫХ БЕНЗОИЛИЗОТИОЦИАНАТОВ С МЕТИОНИНОМ И ИЗУЧЕНИЕ ПРОТИВОВОСПАЛИТЕЛЬНОЙ АКТИВНОСТИ СИНТЕЗИРОВАННЫХ СОЕДИНЕНИЙ.

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Introduction. The reaction of primary amines with isothiocyanates usually results in unsymmetrical 1,3-disubstituted thioureas. However, according to some data [1-3], the condensation of heterocyclic amines with AITC with longer heating is ambiguous: along with asymmetrically 1,3-disubstituted thioureas, symmetrically 1,3-disubstituted thioureas are formed. Symmetrical substituted thioureas, apparently, are products of secondary transformations of the formed asymmetric thioureas, the cleavage of which leads to the accumulation of two different amines and two different isothiocyanates in the mixture, then giving two symmetric thioureas:



The driving force behind this transformation is the difference in the basicity of the amines RNH_2 and R_1NH_2 , on the one hand, and the reactivity of amines and aryl isothiocyanates, on the other. The ratio of the reaction products depends on the stability of the initially formed thiourea derivative.

Considering that α -amino acids are non-toxic, have very interesting and diverse properties [4-6] and are, along with proteins, natural constituents of food products, we decided to carry out the synthesis of thiourea derivatives based on amino acids.

For the synthesis of thiourea derivatives, prolonged heating is often required, and the product yield is usually low [7-9]. One of the main tasks of our study is the development of new methods for the preparation of thiourea derivatives based on α -amino acids with a high yield of the target product while reducing the duration of the synthesis time and identifying new biological properties among them.

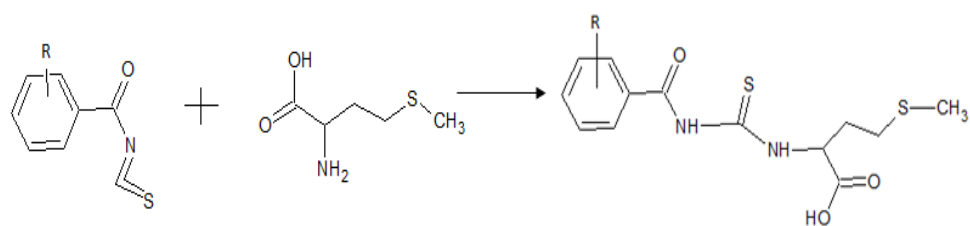
In the literature [10], methods for obtaining substituted thioureas based on various amino acids are given.

Synthesis processes involving substituted aryl isothiocyanates with α -amino acids have not been previously studied. This determined the need to develop new reaction methods in order to obtain thiourea derivatives and to increase the yield of products, to study the patterns of such reactions, to reveal the biological activity of the synthesized compounds, in order to increase the arsenal of biologically active substances, to make judgments about the reaction mechanism for the formation of substituted thioureas.

It is known that among thiourea derivatives there are physiologically active compounds that have antimicrobial, anti-tuberculosis, antiulcer and anti-inflammatory activity [11-20].

Materials and methods

In order to obtain compounds with anti-inflammatory properties, we synthesized thiourea derivatives by the reaction of substituted benzoyl isothiocyanates with an α -amino acid – methionine in dimethylformamide according to the scheme:



Experimental part. N- (para-bromobenzoyl) - N1 - methionylthiourea (VI). A solution consisting of 1.64 g (0.011 mol) of methionine in 20 ml of dimethylformamide is placed into a four-necked flask with a capacity of 250 ml, equipped with a reflux condenser with a calcium chloride tube, an auto-stirrer, a thermometer, and a dropping funnel, heated to a temperature of 55-60 ° C, and added dropwise 2.42 g (0.01 mol) of para-bromobenzoyl isothiocyanate in 20 ml of dimethylformamide. The reaction mixture is kept for 5 hours at a temperature of 85 ° C.

At the end of the reaction, the mixture is cooled and 150-200 ml of water is added. The formed precipitate is filtered off, washed with water and 10% hydrochloric acid solution. The resulting product is dried at a temperature of 40-50 ° C. N- (para - bromobenzoyl) -N1 - methionylthiourea recrystallized from benzene has a melting point of 214–215 ° C in 2.8 g yield (60% of theory). The completeness of the purification is controlled by TLC on alumina. The rest of the compounds (I – V, VII – XII) were obtained in a similar way.

Results and discussion. The obtained compounds I – XII (Table 1) are white crystals, soluble in most organic solvents and insoluble in water.

The structure of the synthesized compounds was confirmed by analytical data and IR spectroscopy.

The IR spectra have similar absorption bands characteristic of C = S, NH – CS, N – CS – N, CH = CH aryl, C = O, OH, NH and CH bonds. Thus, the IR spectrum of compound II has an absorption band at 1115 cm⁻¹, which is inherent in stretching vibrations of the C = S bond, an absorption band at 1330 cm⁻¹ indicates the presence of an N – CS – N bond, the band at 1480 cm⁻¹ corresponds to stretching vibrations of the NH – CS group. The CH = CH groups of phenyl are characterized by an absorption band at 1610 cm⁻¹. The absorption regions at 1710 cm⁻¹ and 1580 cm⁻¹ are characteristic of the C = O bond. For CH, OH and NH groups, absorption bands are characteristic in the region of 2930 cm⁻¹, 2610 cm⁻¹, 3400 cm⁻¹, respectively.

For example, in the IR spectrum of N- (meta-bromobenzoyl) - N1 - methionylthiourea (V), there is an absorption band of stretching vibrations of the C-Br bond in the region of 532 cm⁻¹, there is an absorption band for the C = S group at 1069 cm⁻¹, there are absorption bands characteristic of C – N bonds in the region of 1302 cm⁻¹, for N-C (S) -N groups at 1181, 1287, 1302 cm⁻¹ for NH-CS group at 1489 cm⁻¹, for HC = CH groups of the phenyl radical in the region of 1610 cm⁻¹, for C = O bonds at 1570 cm⁻¹, for N – H groups at 3180, 3362 cm⁻¹.

It is known that thiourea derivatives, along with other types of pharmacological activity, exhibit an anti-inflammatory effect [12-14].

The study of the anti-inflammatory activity of compounds I – XII was carried out on white rats of both sexes weighing 140–180 g. Inflammation was caused by 1% formalin solution, which was injected under the aponeurosis of the ankle joint in an amount of 0.2 ml. The paw volume of rats was measured oncometrically 3 times before and 3, 6 hours after formalin administration.

The test compounds were administered orally using a metal probe in the form of a suspension in cottonseed oil at doses of 50, 100, and 200 mg / kg. The drugs were administered 1 before causing inflammation, that is, 2 hours before the introduction of formalin.

Physicochemical characteristics of thiourea derivatives of general formula

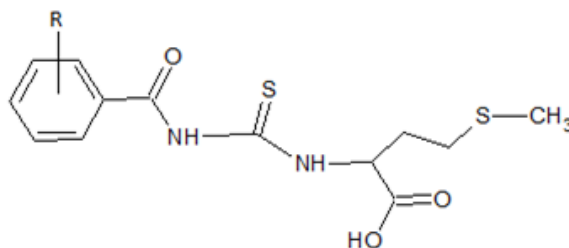


Table 1

№	-R	Output %	Melting temperature	R _f	Formula
I	2-Cl	72	148-9	0.75	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ Cl
II	3-Cl	75	153-4	0.62	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ Cl
III	4-Cl	82	161-2	0.83	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ Cl
IV	2-Br	69	133-4	0.69	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ Br
V	3-Br	72	174-5	0.64	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ Br
VI	4-Br	78	214-5	0.73	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ Br
VII	2-I	66	139-40	0.54	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ I
VIII	3-I	70	172-3	0.75	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ I
IX	4-I	74	185-6	0.68	C ₁₃ H ₁₅ N ₂ O ₃ S ₂ I
X	2-NO ₂	75	190-1	0.73	C ₁₃ H ₁₅ N ₂ O ₅ S ₂
XI	3-NO ₂	78	175-6	0.66	C ₁₃ H ₁₅ N ₂ O ₅ S ₂
XII	4-NO ₂	86	171-2	0.61	C ₁₃ H ₁₅ N ₂ O ₅ S ₂

For comparison, well-known anti-inflammatory drugs were taken - butadion (Butadion), indomethacin (Indometacin) and Voltaren (Voltaren). They have been used in doses that produce the most pronounced anti-inflammatory effect. (Table 2).

As a result of the studies carried out, it was found that all substances (I – XII) in certain doses exhibit a distinct anti-inflammatory activity. Among them, the compounds were comparatively less active, which, within the dose range of 50-200 mg / kg, reduce the intensity of the inflammatory process by about 17.5-25%. Compounds III, VII – XII have a stronger anti-inflammatory effect. In doses of 50-200 mg / kg, they suppress formalin edema by 27-45%. Compound VIII has a rather strong anti-inflammatory effect, so at doses of 50 and 100 mg / kg after 6 hours it suppresses inflammation by 71.6% and 79.1%, respectively. A further increase in the dose of the drug did not lead to a noticeable increase in the observed effect. While butadione at a dose of 100 mg / kg suppresses inflammation by 28.1%, indomethacin at a dose of 10 mg / kg by 36.4%, voltaren at a dose of 25 mg / kg by 43.2%.

The acute toxicity of the test compounds was determined by calculating the LD₅₀ according to the Litchfield and Wilcoxon method. White mice weighing 18–25 g were injected with the study drug orally. Each dose was tested in 6 animals. The experimental animals were observed for 24 hours.

Tests have shown that the LD₅₀ of the compounds is outside 2000mg / kg, while the LD₅₀ of butadione is 430mg / kg, indomethacin –47mg / kg, voltaren 370mg / kg.

Comparison of these data shows that test compound VIII was less toxic than butadione by 4.6 times, indomethacin by 42.6 times, and voltaren by 5.4 times.

Thus, it has been established that of the tested new thiourea derivatives, only compound VIII, that is, N- (meta-iodobenzoyl) –NI – methionylthiourea, has a significantly greater breadth of anti-inflammatory action and is of undoubted practical interest.

Table 2.

Anti-inflammatory activity of thiourea derivatives

Compound	Anti-inflammatory activity%	Acute toxicity LD ₅₀ mg / kg
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I	21	>2000
II	17,5	>>
III	33,7	>>
IV	19,2	>>
V	25	>>
VI	28	>>
VII	38,5	>>
VIII	79,1	>>
IX	27	>>
X	36,1	>>
XI	39	>>
XII	45	>>
Butadion	28,1	430
Indometacin	36,4	47
Voltaren	43,2	370

Литература/References:

1. Galstukhova N.B., Shchukina M.N., Berzina I.M. Synthesis of thiourea derivatives V. Arylthiocarbanilides // *Journal of Organ Chemistry*. 1967. V.3. S.2134-2139.
2. Novikov E.G., Tugarinova I.N. Selective di (β -oxyethylation) of diamines at the less basic amino group // *Chemistry heterocycle. connect.* 1968. T. 4. S. 281-283.
3. A.S. 1391041. N- (Methancarboxy) -N1-p-chlorobenzoylthiourea as an accelerator for vulcanization of a rubber compound / Makhsumov A.G., Baltabaev U.A., Tukhtamuradov Z.T., Asatov Kh., Sadetova Zh.M. - *Applied*. 12/23/85; No. 3969133; publ. 12/22/87.
4. Pat. 3825560. USA. N-monoacyl derivatives of arginine / Tadaomi S., Masahiro T., Kazuhiko Y., Ryonosuke Y., Yukiko S. - *Appr.* 06/28/71; publ. 07/23/74. // *RZhKhim*. 1975.9 R 492 P.
5. Berezin B.D., Berezin D. B. Course in modern organic chemistry. - M.: Higher school. 1999. 768 p.
6. Application 55-620066. Japan. N- (2-substituted pyridyl-4) ureas and thioureas, a method for their preparation and growth regulators based on them / Toshi-hiko O., Haruka I., Koichi S., Sajiro T. [Sato Susumu]. - *Applied*. 3.11.78; No. 53-135236; publ. 10.05.80. // *RZhKhim*. 981.20 0 393 P.
7. Jirman J., Kavalek J., Machacek V. Priprava substituovanych 1-benzoyl-thiomocovin transacylaci 1-acetyl-thiomocovin // *Sb. ved. pr, VSCHT. Pardubice*. 1987. V. 50. P.101-110.
8. Saczewski F. 2-Chloro-4,5-dihydroimidazole. Part IV. Reaction with aroyl isothiocyanates // *Pol. J. Chem.* 1988. V. 62. no. 7-12. P. 891-893.
9. Cejpek K., Volusek J., Velisek J. Reactions of allylisothiocyanate with alanine, glycine and several peptides in model systems // *J. Agric Food Chem.* 2000. Vol. 48. No. 8. P. 3560-3565.
10. Gorak O., Gorak F., Antituberculous properties of some derivatives of p-ethoxyphenylthiourea // *Zhur. Honey. industry*. 1963, Issue 2. Pp. 11-12.
11. Pat. 367 (RUz) 1- (p-chlorobenzoyl) -3- (carboxyethyl) -thiourea exhibiting anti-inflammatory activity // Baltabaev U.A., Makhsumov A.G., Zokirov U.B. // *Official Bulletin*. 1993. No. 2.
12. Baltabaev U.A., Makhsumov A.G., Zokirov U.B. Babaev I.D., Shukurlaev K.Sh. Anti-inflammatory activity of new aryl and aroylthioureas // *Chem. pharmaceutical journal-Moscow*. 2002. T.36. No. 2. P.24-26.
13. Baltabaev U.A., Dzhuraev A.D., Makhsumov A.G. New derivatives of thiourea and their biological activity // *Zhur. Chemistry and chemical technology*. -2007. # 1. Pp. 23-26.
14. Baltabaev U.A., Abdullaeva U.M., Kadyrova M.N., Ergasheva N.Sh. Reactions of derivatives of benzoyl isothiocyanates with α -amino acids // V International youth competition of

scientific works "YOUTH IN SCIENCE: NEW ARGUMENTS" Russia, Lipetsk, November 10, 2016 pp. 82-85.

15. Mavlyanov I.R. Non-steroidal anti-inflammatory drugs: mechanism of action, the search for new effective and safe drugs.

Medical journal of Uzbekistan. -2002.№1. S.94-97.

16. . Nasonov E.L Stomach damage associated with the use of non-steroidal anti-inflammatory drugs//Clin.Med. 2000. T.78. №3. S. 4-10.

17. Devineni, S.R., Golla, M., Chamarthi, N.R., Meriga, B., Saddala, M.S., Asupathri, U.R. 2-Amino-2,3-dihydro-1H-2λ5-[1,3,2]diazaphospholo[4,5-b]pyridin-2-one-based urea and thiourea derivatives: Synthesis, molecular docking study and evaluation of anti-inflammatory and antimicrobial activities //(2016) Medicinal Chemistry Research, 25 (4), pp. 751-768. <https://www.scopus.com/inward/record.uri?id=2-s2.0-84959549710&doi=10.1>

18. 007%2fs00044-016-1518-x&partnerID=40&md5=DOI: 10.1007/s00044-016-1518-x

19. Moneer, A.A., Mohammed, K.O., El-Nassan, H.B. Synthesis of Novel Substituted Thiourea and Benzimidazole Derivatives Containing a Pyrazolone Ring as Anti-Inflammatory Agents. (2016) Chemical Biology and Drug Design, 87 (5), pp. 784-793.

20. Khodjieva D. T., Khaydarova D. K., Khaydarov N. K. Clinical and neuroimaging diagnostics of syringomyelia associated with Chiari malformation. International Journal of Pharmaceutical Research. 2021. P. 2418-2415

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ЮҚОРИ ЛАБ ВА ТАНГЛАЙИ ТУҒМА КЕМТИКЛИ БОЛАЛАРДА БУРУН БЎШЛИҒИ ВА БУРУН ЁНДОШ БЎШЛИҚЛАРИ ПАТОЛОГИЯСИНИ ЭНДОСКОПИК ТАШХИСЛАШ

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Мазкур ишда юқори лаб ва танглайи туғма кемтикли болаларда бурун ва бурун ёндош бўшлиқларини туғма нуқсонни жарроҳлик йўли билан даволаш босқичларида эндоскопик текшируви ўтказилган ва ҳар бир босқичдаги ҳолати батафсил ўрганилган. Бу ўз ўрнида бурун ва бурун ёндош бўшлиқларидаги патологик жараёнларни эрта босқичларда аниқлаш ва реабилитация муваффақиятни оширади.

Калит сўзлар: бурун ва бурун ёндош бўшлиқлари, эндоскопия, юқори лаб ва танглайи туғма кемтиги, болалар

В данной работе было проведено подробное эндоскопическое исследование полости носа и придаточных пазух носа у детей с врожденной расщелиной верхней губы и неба на этапах хирургического лечения врожденных пороков для определения влияния, данного аномалия на развития патологии в этих органах. Это, в свою очередь, увеличивает успешность раннего выявления и реабилитации патологических процессов в полости носа и придаточных пазух носа.

Ключевые слова: носовая полость, придаточный пазухи носа, эндоскопия, врожденная расщелина верхней губы и неба, дети.

Туғма юқори лаб ва танглай кемтикли (ТЛТК) болалар сонининг ўсиб бораётганини ҳисобга олиб, турли ихтисосликдаги шифокорларнинг ушбу контингентни даволаш ва реабилитация қилишга қизиқиши йилдан-йилга ортиб бормоқда. Ҳозирги вақтда бундай аномалияли болаларни олиб бориш алгоритмлари асосан юз-жағ жарроҳлари учун ишлаб чиқилган ва ЛОР аъзоларининг патологиясига эса эътибор кам. ТЛТКли болаларнинг