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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

BIOLOGICAL STUDIES OF THIAZOLES OF NEW STRUCTURE

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Abstract.

Study objective: To test and evaluate a series of thiazoles of new structure, synthesized by us, for various biological activities and toxicity. During the work, a number of activities (anti-inflammatory, hypotensive, psychostimulant properties) were discovered among thiazole derivatives, which expands the scope of their application.

Materials: For the biological activity studies, we have taken the series of thiazole derivatives were synthesized by us, on the base of substituted glutaric acid. For the experiments, we took white mice of the same weight not more than 20 g and breed, adult rats 160-180 g. The experiments were carried out on 6 batches, 10 animals in each. Animals were kept in a barrier-type room under conditions corresponding to the standards.

Methods: Synthesis: On the base of diesters of (2-substituted-2-(2-bromacetyl) pentanedioic acid by the Hanch's method we obtained the corresponding thiazole derivatives. Through complete hydrazinolysis of the latter, we obtained the corresponding dihydrazide derivatives. **Anti-inflammatory activity** was determined using the formalin-induced inflammation method. **The hypotensive activity** of compounds 4d and 4e was studied in a generally accepted manner - on anesthetized (Nembutal *50 mg/kg*) rats and compare with known drug Bendazol (Dibazol). **Toxicity** parameters were calculated using the methods of Pershin, Miller and Teintner.

Results and conclusions. The synthesized compounds showed promising pharmacological effects such as anti-inflammatory, psychostimulant, and hypotensive activities. Locomotor and exploratory activity, body temperature, fear and aggression responses, seizure response to maximal electroshock (50 mA, 0.2 sec., 50 Hz), response to corazol. This study suggests that these thiazole derivatives may be of interest for further research due to their pharmacological properties, low toxicity (700 to 2200 mg/kg,) and diversity of biological activities.

Key words. Amino- and methylthiazoles, anti-inflammatory activity, psychostimulants, hypotensive activity.

Abbreviations.
SAP: Systemic Arterial Pressure
HR: Heart Rate
CO: Cardiac Output
TPR: Total Peripheral Resistance
SV: Stroke Volume
LVW: Left Ventricular Work

Introduction.

Among five-membered nitrogen-containing heterocyclic compounds, thiazoles held a prominent position due to their widespread application in generating free carbene species, serving as catalysts, and acting as ligands for the synthesis of coordination complexes with transition metals [1-2]. This class of compounds was first described by A.Hantzsch and A. Weber in the late 19th century [3] and the discovery of novel thiazole derivatives with potential relevance to pharmacology and medicine continued thereafter. Compounds bearing a thiazole fragment were detected in numerous natural products, particularly among secondary metabolites of marine organisms. Several such structures were characterized and subsequently served as templates for the synthesis of new pharmaceuticals [4-6]. For instance, derivatives of latrunculin A were applied as inhibitors of prostate tumor growth and as activators of HIF-1 in breast cancer therapy [7-8]. Many thiazole-based compounds were reported to exhibit significant antitumor [9-14], anticonvulsant [15-17], antibacterial, and antifungal activity [7,15,18]. A clear outcome of such work was the introduction of several representatives of this class into clinical practice (Figure1).

Epothilones are a class of potential cancer drugs. Like taxanes, they prevent cancer cells from dividing by interfering with tubulin, but in early trials, epothilones have better efficacy and milder adverse effects than taxanes [19-20].

Vitamin B1(or thiamine) is a biologically active substance that supports the functioning of the nervous system, heart and muscles, participates in glucose metabolism, improves blood circulation, participates in hematopoiesis, acts as an antioxidant - protects the body from the destructive effects of aging, alcohol and tobacco.

Tiazofurin is a drug, which acts as an inhibitor of the enzyme IMP dehydrogenase. Tiazofurin and its analogues were under investigation for potential use in the treatment of cancer [21] though side effects such as pleuropericarditis and a flu-like syndrome precluded further development. They also show antiviral effects and may be reevaluated as potential options in the treatment of newly emerging viral diseases [22].

Famotidine is a histamine-2 blocker that works by reducing the amount of acid produced by the stomach. Famotidine is used to treat and prevent stomach and intestinal ulcers, as well as conditions in which the stomach produces too much acid, such as Zollinger-Ellison syndrome [23,24].

Materials and Methods.

Materials: For the biological activity studies, we have taken the compounds synthesized by us, not described in the literature. All reagents were of analytical grade and were used as such or distilled prior to the use. For the experiments, we took white mice of the same weight not more than 20 g and breed, adult rats 160-180 g. The experiments were carried out on 6 batches, 10 animals in each. The animals were kept in a barrier-type room under conditions corresponding to the standards (The Guide for the care and use of laboratory animals, IRB Expert Conclusion 13-2/25).

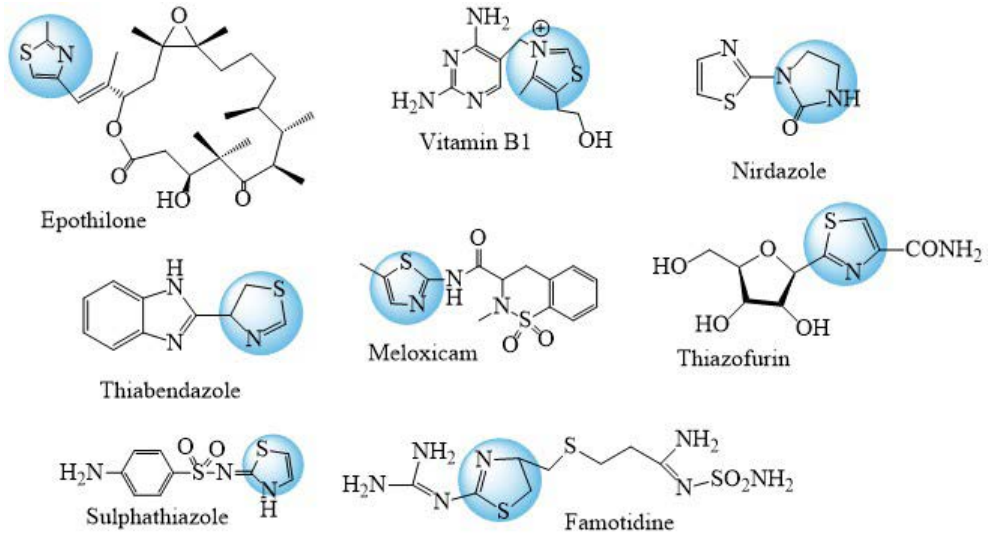

Figure 1. *Thiazole ring containing drugs.*

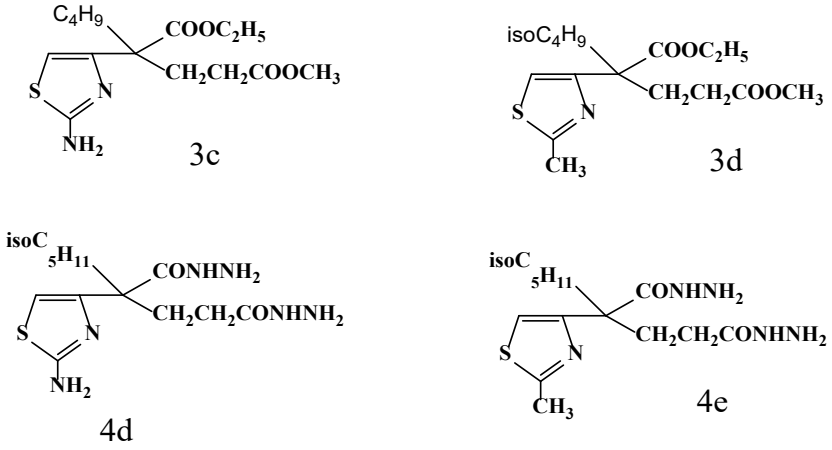

Figure 2. *The structure of bioactive - leader compounds.*

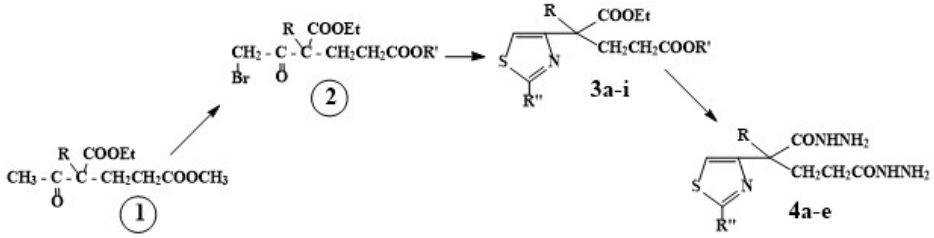

Figure 3. *Scheme of synthesized compounds 3a-i and 4a-e.*

Methods:

Toxicity to determine, 60 white mongrel mice with a live weight of 20 g were used, of which 5 experimental and one control groups were formed. The toxicity of the compounds was evaluated in white mice via a single intraperitoneal injection, followed by a 14-day observation period.

Anti-inflammatory activity studied on the white rats (Wistar strain). Assess its anti-inflammatory effect, a formalin-induced paw edema model was used: 0.1 mL of a 2.5% formalin solution was injected beneath the plantar aponeurosis of the rat's hind paw. The degree of edema was measured by plethysmometry at 3 and 6 hours after administration of the phlogogenic agent. The test compound was administered 30 minutes before and 3 hours after the formalin injection [25].

The hypotensive activity of compounds 4d and 4e was studied in a generally accepted manner - on anesthetized (Nembutal 50 mg/kg) rats and compare with known drug Bendazol (Dibazol).

Synthesis: We propose a new synthetic pathway for amino-substituted thiazole derivatives - as illustrated in Figure 3. The novel compounds were synthesized by two steps. At first to a mixture of thiourea or thioacetamide in absolute acetone, added dropwise the corresponding bromoacetyl derivative of pentanedioic acid dissolved in absolute acetone, (Hanch's method), and obtained the corresponding 1-ethyl-5-substituent-

2-(2-aminothiazol-4-yl)-2-butylpentanedioate derivatives (3a-3i). Through complete hydrazinolysis of the latters (used concentrated 98% hydrazine hydrate and solvent abs. ethanol) we obtained the dihydrazide derivatives (4a-4e). The reactions proceed rapidly and provide high yields of products. Radicals and yields of compounds are shown in Table 1.

Table 1. *Radicals and yields of compounds* ***3a-i*** *and* ***4a-e****.*

Comp.#	R	R'	R"	Yield, %
3a	C_2H_5	CH_3	NH_2	75
3b	C_3H_7	CH_3	NH_2	79
3c	C_4H_9	CH_3	NH_2	80
3d	iso-C_4H_9	CH_3	NH_2,	88
3e	iso-C_5H_{11}	CH_3	NH_2	86
3f	C_4H_9	C_2H_5	NH_2	80
3g	iso-C_5H_{11}	C_2H_5	NH_2	83
3h	C_4H_9	C_2H_5	CH_3	85
3i	iso-C_5H_{11},	C_2H_5	CH_3	85
4a	C_4H_9	-	NH_2	80
4b	C_4H_9,	-	CH_3	85
4c.	iso-C_4H_9	-	NH_2	82
4d	iso-C_5H_{11}	-	NH_2	80
4e.	iso-C_5H_{11}	-	CH_3	87

The Compounds identities were confirmed by standard chemical analysis.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-400 MHz in DMSO-CCl_4 mixture (1:3) The coupling constants (J) are given in Hertz. TLC analysis was performed on "Silufol UV-254" plates, eluent (ethanol: benzene: hexane-1:4:13). Melting points were determined on "Boetius" micro-heating stage

General procedure for the preparation of 4-(2-amino or methylthiazol-4-yl)-4-substituted-pentanedioates. To a mixture of 0.006 mol of thiourea or thioacetamide in 5 ml of absolute acetone, add dropwise 0.006 mol of the corresponding bromoacetyl derivative, dissolved in 5 ml of absolute acetone. Stir for 1 hour at room temperature and 1 hour with the mixture boiling, after removing the acetone, cool, add water and alkalize with dilute aqueous ammonia to pH 9-10. Filter off the precipitated crystals, wash with water to pH 7 and dry. Recrystallize from aqueous alcohol.

1-ethyl 5-methyl 2-(2-aminothiazol-4-yl)-2-butylpentanedioate (3c). Yield 1,52 g (80%), m.p. 116-117°C. R_f 0.49. Found, %: C 54.84; H 7.35; N 8.55. S 9.76, $C_{15}H_{24}N_2O_4S$. Calculated: C, 54.86; H, 7.37; N, 8.53; S 9.77.

IR, ν, cm^{-1}: 1720 (C=O сл.эфир); 1120, 1180 (C-O-C), 1560 (C=N), 3080 (=CH), 3190, 3250(NH).

^{1}H NMR (400 MHz, DMSO+CCl_4) δ 6.47 (s, 1H), 5.46 (s, 1H), 4.20 (q, J = 6.4 Hz, 2H), 3.74 (s, 2H), 3.40 (t, J = 9.8 Hz, 1H), 2.70 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 1.85 (dtd, J = 15.0, 7.6, 5.7 Hz, 1H), 1.80 – 1.68 (m, 1H), 1.23 (t, J = 6.4 Hz, 3H), 0.95 (t, J = 7.5,Hz, 3H). ^{13}C (101 MHz, DMSO+CCl_4) δ 175.85, 173.66, 166.11, 151.48, 101.07, 61.85, 53.39, 51.54, 30.43, 28.95, 26.11, 22.58, 14.08, 13.89.

1-ethyl 5-methyl 2-(2-aminothiazol-4-yl)-2-isobutylpentanedioate(3d). Yield 1,59g (88.8%), m.p. 109-110°C. R_f 0.53. Found, %: C 54.87; H 7.36; N 8.54. S 9.79. $C_{15}H_{24}N_2O_4S$. Calculated, %: C, 54.86; H, 7.37; N, 8.53; S 9.77. ^{1}H NMR (400 MHz, DMSO+CCl_4) δ 6.70 (s, 1H), 5.21 (s, 2H), 4.27 (q, *J* = 6.1, 6.1, 6.0 Hz, 2H), 3.64 (s, 2H), 2.62 – 2.53 (m, 1H), 2.56 – 2.50 (m, 1H), 2.53 – 2.43 (m, 1H), 2.43 – 2.33 (m, 1H), 2.12 – 2.04 (m, 1H), 2.04 – 1.91 (m, 2H), 1.22 (t, *J* = 6.0, 6.0 Hz, 3H), 0.94 (dd, *J* = 6.6, 1.3 Hz, 5H), 0.94 (s, 1H).. ^{13}C NMR (101 MHz, DMSO+CCl_4) δ 175.9, 173.7, 166.1, 151.5, 101.4, 61.8, 52.5, 51.5, 46.1, 29.0, 25.9, 24.7, 13.9.

1-ethyl 5-methyl 2-(2-aminothiazol-4-yl)-2-isopentylpentanedioate (3e). Yield 1,76 g (86%), m.p. 112-113°C. R_f 0.55. Found, %: C 56.14; H 7.66; N 8.19. S 9.35. $C_{16}H_{26}N_2O_4S$. Calculated, %: C 56.12; H 7.65; N 8.18; S 9.36. H NMR (400 MHz, DMSO+CCl_4) δ. 6.54 (s, 1H), 5.17 (s, 1H), 4.20 (q, *J* = 5.9, 6.0 Hz, 2H), 3.59 (s, 2H), 2.58 – 2.40 (m, 3H), 2.43 – 2.30 (m, 1H), 2.16 (dt, *J* = 15.4, 9.0 Hz, 1H), 2.06 (dt, *J* = 15.6, 9.2 Hz, 1H), 1.69 (dq, *J* = 12.5, 6.2 Hz, 1H), 1.42 – 1.30 (m, 2H), 1.22 (t, *J* = 6.0, Hz, 3H), 0.87 (dd, *J* = 15.6, 6.2 Hz, 6H). ^{13}C NMR (101 MHz DMSO+CCl_4) δ 176.0, 173.2, 165.9, 150.0, 101.0, 61.85, 52.0, 50.0, 32.6, 31.5, 30.6, 28.5, 28.2, 21.5, 12.9.

1-ethyl 5-methyl 2-isopentyl-2-(2-methylthiazol-4-yl) pentanedioate (3i). Yield 1,73 г (85%), m.p. 119-120°C. R_f 0.57. Found, %: C 59.82; H 8.00; N 4.12. S 9.37. $C_{16}H_{26}N_2O_4S$. Calculeted, %: C 59.80; H 7.97; N 4.10; S 9.39. ^{1}H NMR (400 MHz, DMSO+CCl_4) δ 7.23 (s, 1H), 4.22 (q, *J* = 6.1, 6.0 Hz, 2H), 3.61 (s, 2H), 2.71 (s, 2H), 2.62 – 2.44 (m, 3H), 2.44 – 2.33 (m, 1H), 2.16 (dt, *J* = 15.4, 9.0 Hz, 1H), 2.06 (dt, *J* = 15.6, 9.2,Hz, 1H), 1.69 (m 1H), 1.42 – 1.30 (m, 2H), 1.22 (t, *J* = 6.0 Hz, 3H), 0.87 (dd, *J* = 15.6, 6.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO+CCl_4) δ 174.8, 173.6, 164.7, 161.4, 106.7, 61.8, 52.6, 51.5, 28.9, 28.6, 22.5, 19.0, 13.9.

General procedure for obtaining 2-(2-amino- or methylthiazol-4-yl)-2-substituted pentanedihydrazides. Place 20 ml of 96% ethanol, 0.005 mol of the corresponding thiazole and concentrated hydrazine hydrate in a flask and heat for 2 hours at the boiling point of the mixture. Distil off the ethanol and cool after removing the ethanol, add water and leave for one hour. The resulting crystals are filtered, dried and pre-crystallized from aqueous alcohol.

2-(2-aminothiazol-4-yl)-2-butylpentanedihydrazide(4a). Yield 1,73 г (80%), m.p. 91-92°C. R_f 0.54. Found, %: C 45.85; H 7.03; N 26.75. S 10.22. $C_{12}H_{22}N_6O_2S$. Calculated, %: C 45.84; H 7.05; N 26.73; S 10.20. ^{1}H NMR (400 MHz, DMSO+CCl_4) δ 7.75 (t, *J* = 4.1 Hz, 1H), 7.55 (t, *J* = 4.1 Hz, 1H), 6.69 (brs, 1H), 5.21 (brs, 2H), 4.42 (d, *J* = 4.0 Hz, 2H), 4.03 (d, *J* = 4.0 Hz, 2H), 2.40 (td, *J* = 9.0, 8.7, 2.9 Hz, 2H), 2.20 (m, 1H), 2.14 – 1.96 (m, 2H), 1.91 (dt, *J* = 16.1, 9.1, 9.1 Hz, 1H), 1.57 – 1.47 (m, 2H), 1.36 (p, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 2H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101MHz, DMSO+CCl_4) δ 181.1, 172.7, 166.1, 155.2, 101.3, 57.0, 26.0, 22.3, 14.0

2-(2-aminothiazol-4-yl)-2-isopentylpentanedihydrazide(4d). Yield 1,73 г (80%),m.p. 95-96°C. R_f 0.56. Found, %: C 47.55; H 7.40; N 25.60. S 9.78. $C_{13}H_{24}N_6O_2S$.Calculeted: C 47.54; H 7.37; N 25.59; S 9.76. ^{1}H NMR (400 MHz, DMSO+CCl_4) δ 7.85 (t, *J* = 4.1 Hz, 1H), 7.55 (t, *J* = 4.1 Hz, 1H), 6.51 (s, 1H), 5.00 (brs, 2H), 4.42 (d, *J* = 4.0 Hz, 2H), 4.03 (d, *J* = 4.0 Hz, 2H), 2.40 (td, *J* = 9.0, 8.7, 2.9 Hz, 2H), 2.26 – 2.15 (m, 1H), 2.15 –

1.96 (m, 2H), 1.91 (dt, *J* = 15.9, 8.9 Hz, 1H), 1.69 (dq, *J* = 12.5, 6.2, Hz, 1H), 1.40 – 1.27 (m, 2H), 0.87 (dd, *J* = 15.6, 6.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO+CCl_4) δ 182.1, 173.9, 166.0, 156.3, 100.8, 55.8, 33.3, 32.1, 30.4, 29.2, 27.0, 22.5.

2-isopentyl-2-(2-methylthiazol-4-yl) pentanedihydrazide(4e). Yield 1,42 г (87%), m.p. 106-107°C. R_f 0.63. Found, %: C 47.55; H 7.40; N 25.60. S 9.78. $C_{14}H_{25}N_5O_2S$. Calculated, %: C 47.54; H 7.37; N 25.59; S 9.76. ^{1}H NMR (400 MHz, DMSO+CCl_4) δ 7.75 (t, *J* = 4.1, Hz, 1H), 7.55 (t, *J* = 4.1, Hz, 1H), 4.42 (d, *J* = 4.0 Hz, 2H), 4.03 (d, *J* = 4.0 Hz, 2H), 2.72 (s, 2H), 2.40 (td, *J* = 9.0, 8.7, 2.9 Hz, 2H), 2.26 – 2.15 (m, 1H), 2.15 – 1.96 (m, 2H), 1.91 (dt, *J* = 15.9, Hz, 1H), 1.69 (m, 1H), 1.40 – 1.27 (m, 2H), 0.87 (dd, *J* = 15.6, 6.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO+CCl_4) δ 181.0, 172.5, 165.2, 161.4, 107.9, 56.4, 33.0, 32.8, 30.4, 29.8, 28.4, 22.5, 18.7.

Results and Discussion.

Among the synthesized compounds (3a–i, 4a–e), only 3c, 3d, 4d, and 4e are of particular interest due to their low toxicity and high biological efficacy.

Of these, 1-ethyl-5-methyl-2-(2-aminothiazol-4-yl)-2-butylpentanedioate (3c) belongs to the class of mixed esters of 2-alkyl-2-aminothiazolylglutaric acids. It was established that modifications of the radical at position 2 of the aminothiazolylglutaric acid core result in the manifestation of new biological properties within this series. Upon testing compounds 3a–i in white rats (Wistar strain) and outbred white mice, we compared anti-inflammatory effect with Amidopirin, the control system was starchy mucus – 2%. Among testing compounds, 2-ethyl-5-methyl-2-(2-aminothiazol-4-yl)-2-butyl-pentanedioate (3c) exhibits pronounced anti-inflammatory activity The toxicity of the compound was evaluated via a single intraperitoneal injection, followed by a 14-day observation period. Compound 3c was found to be low in toxicity, with an DL_{50} 700 mg/kg. Its biological activity was assessed at a dose of 100 mg/kg (equivalent to 1/7 of the DL_{50}). The results are given in Table 2.

Table 2. *Anti-inflammatory and toxicity effect of compound* ***3c****.*

Compound	**Dose, mg/kg**	**Inflammation, increase in edema volume in % after**	
		3 h	**6 h**
3c	100 ($1/7DL_{50}$)	45,8±3,1; p<0,001 P_1>0,05	56,6±3,8 p< 0,001 P_1>0,1
Amidopyrine	100 ($1/3DL_{50}$)	37,0±2,7	45,0±4,5
Control (starchymucus – 2%)		77,5±4,2	110,5±4,9

P – calculated in comparison with control; P_1 - calculated in comparison with the standard.

The animals of the control group were intact. After a single administration, the physical condition of the experimental mice was observed for 14 days; body weight gain, suspected clinical symptoms of poisoning and possible death were assessed (no animal deaths were reported). Weight gain in the experimental and control mice was assessed before and on days 1, 3, 7, 11, and 14 of the experiment. Toxicity parameters were calculated using the methods of Pershin, Miller and Teintner.

The next example supporting the hypothesis regarding the influence of alkyl substituent structure on biological activity is 1-ethyl-5-methyl-2-(2-aminothiazol-4-yl)-2-isobutylpentanedioate (3d), which differs from compound **3c** by the substitution of a butyl radical with an isobutyl group at position 1.

Screening of compound 3d showed that, in contrast to 3c, it exhibited only a weak anti-inflammatory effect. However, further evaluation showed that it exhibits *psychostimulant properties.* To evaluate this effect, the following parameters were analyzed using standard methods [26].

–behavioral responses in mice.

– locomotor and exploratory activity (number of movements per 10 minutes).

–body temperature.

–fear and aggression responses.

– effects on hexanal (60 *mg/kg*), apomorphine (10 *mg/kg*), and arecoline (25 *mg/kg*).

seizure response to maximal electroshock (50 mA, 0.2 sec., 50 Hz).

– response to corazol (150 *mg/kg*, subcutaneous).

Compound 3d was found to be moderately toxic, with an DL_{50} of 700 *mg/kg* after a single intraperitoneal administration. At relatively low doses (4–205 *mg/kg*), the compound exerted weak to moderate stimulatory effects on behavior, including enhanced spontaneous locomotion and increased reactivity to stimuli. At higher doses (300–700 *mg/kg*), pronounced excitation, jumping behavior, and clinic seizures were observed. In doses ranging from 82 to 205 *mg/kg*, body temperature increased by 1.0–1.8 °C, and thresholds for fear and aggression decreased (Table 3). Compound 3d reduced and shortened the sedative effect of hexenal, potentiated the action of apomorphine and phenamine, and to a lesser extent arecoline. It also alleviated ptosis and hypothermia induced by reserpine. The compound did not affect seizure responses caused by corazolor electroshock.

The most promising compounds were studied in mice and rats. The hypotensive activity of compounds 4d and 4e was studied in a generally accepted manner - on anesthetized (Nembutal 50 mg/kg) rats (Figure 2). The effect on the level of systemic arterial pressure (SAP) and on central hemodynamics also was studied. The studied compounds were administered to rats intravenously, in the form of aqueous solutions, in doses of 10, 25 and 50 mg/kg. With the introduction of 10 and 25 mg/kg, a decrease in SAP by 10-15% was observed. Hypotension persists for 60 minutes, and at a dose of 50 mg/kg, the hypotensive effect increases by 20-25% (Table 4).

During the assessment of central hemodynamics, the following parameters were monitored: systemic arterial pressure (SAP), heart rate (HR), cardiac output (CO), total peripheral resistance (TPR), stroke volume (SV), and left ventricular work (LVW).

Compound 4dwas administered intravenously at doses of 10 and 25 *mg/kg*, corresponding to 1/50 and 1/25 of its LD_{50}. Experimental results indicated that compound 4d exerted a moderate hypotensive effect. At 10 *mg/kg*, SAP decreased by approximately 10%and returned to baseline by the 80th minute. At 25 *mg/kg*, SAP was reduced by 20–30%, and the hypotensive

Table 3. *Selected pharmacological effects of compound* ***3d****.*

Dose (mg/kg)	Change in locomotor activity (%).	Body temp. change (°C)	Thre-Shold of fear and aggression (V)	Hexenal induced sleep duration change, %	Arecoline tremor		Stereotypy duration (min)		Stereotypy intensity (scores)		Lifespan after corazol 150mg/kg (min)	Reserpine	
					Duration (min)	intensity (scores)	apomorphine	phenamine	apomorphine	phenamine		Ptosis from (scores	Hyperthermia (°C)
Cont.	100% ,300 (183-385	0	30±0.5	100 (156) ± 11/min	16±0.25	2±0.05	32±0.08	91±1.8	2±0.05	2±0.05	20±1.5	3.8±0/05	2.8±0.4
4.1	-5	0	30±0.05	-25	14±0.2	2±0.05	34±0.06	94±1.8	2±0.05	2±0.05	14±1.2	3.5±0.05	2.9±0.5
41	0	+0,2±0.01	24±0.1	-30	16±0.2	2.5±0.05	36±0.2	99±1.2	2.5±0.05*	2.8±0.05*	10±1.1	3.8±0.05	2.2±0.4
82	+25	+1,0±0,04	25±0.1	-48	17±0.4	2,8±0.05	39±0.09	111*±2.4	3,1±0.05*	3±0.03*	6±0.8*	2.2±0.05*	2.0±0.2*
164	+45	+1,5±0.08	20±0.4	-51	19±0.2	2.8±0.06	42±0.2*	115*±1.9	3.8±0.05*	4*	8±0.4*	1.5±0.05*	1.5±0.04*
205	+60	+1.8±0.12	20±0.4	-60	19±0.3	3±0.05	44±0.6*	122*±1.8	4*	4*	6±0.8*	1.5±0.05*	1.0±0.05*

*The difference with the control is statistically significant.

Table 4. *Effect of compounds* ***4d*** *and* ***4e*** *on systemic arterial pressure (SAP) in rats.*

Compound	Dose (mg/kg)	Solvent	SAP change after administration of compounds 4d and 4e relative to the initial values (%) at time (minutes)				
			5	15	30	45	60
4d	10	water	-6.3±4.1	-5.8±3.6	-8.2±7.0	-10.3±3.5	-10.3±3.5
	25	water	-17.0±3.5	-21.7±5.6	-21.7±5.6	-21.7±5.6	-21.7±5.6
	50	water	0	12.4±3.1	-20.0±3.3	-22.0±1.5	-22.0±1.5
4e	10	water	-16.7±3.31	-10.8±6.7	-10.8±6.7	-13.7±6.7	-13.7±6.7
	25	water	-9.1±5.0	-13,7±6.7	-10.4±6.7	-7.2±5.0	-7.2±5.0
	50	water	-13.3±7.2	-13.7±3.3	-20.0±3.3	-18.4±1.3	-22.0±1.3

effect persisted for up to one hour. The observed decrease in SAP was attributed to reductions in CO and TPR. A slight reduction in cardiac contractility was also noted (Table 5). In comparison, compound 4e induced hypotension lasting 20–30 minutes, followed by an increase in SAP above baseline by 7–10% after one hour (Table 5A and Table 5B).

The data on the effect of compounds 4d and 4e on central hemodynamics were compared with the data on the widely used drug Bendazol, for which a separate group of rats anesthetized (nembutal) were given Bendazol at doses of 10 and 20 *mg/kg*. The data obtained indicate that at a dose of 10 *mg/kg* (1/20 of LD50), the effect of Bendazol on central hemodynamics is very insignificant (Table 5). At a dose of 20 *mg/kg* Bendazol, hypotension increases, but after 30 minutes it returns to the initial value.

Thus, the results of the present study confirmed that compounds 4d and 4e exhibit hypotensive activity. A comparative analysis of the data indicated that this effect was more pronounced for compound 4d. In addition, both compounds 4d and 4ewere characterized by low toxicity: DL_{50} values were 880 *mg/kg* and 2200 *mg/kg*, respectively, while that of the reference drug Bendazol was 200 *mg/kg.* Acute toxicity of compounds 4d and 4e was determined by intraperitoneal administration on white mice.

Conclusion.

– The nature of biological activity was found to depend on the structure of the alkyl substituent. In particular, with an equal number of carbon atoms in the side chain, branched (isobutyl) and unbranched (butyl) derivatives displayed markedly different biological properties.

– The substitution of ester groups with amide groups resulted in substantial changes in biological activity.

– The newly proposed compounds demonstrated significantly higher DL_{50} values compared to widely used pharmaceutical agents, indicating a favorable safety profile.

Thus, the synthesized compounds may be of great importance in the field of medicine due to their wide spectrum of activity and low toxicity.

Conflict of Interest.

The authors declare no conflict of interest.

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Table 5. *Effect of compounds 4d and 4e on central hemodynamics in rats.*

Compound	Dose (mg/kg)	Time after (min)	Shift in central hemodynamic parameters under the influence of compounds 4d, 4e and Bendazol					
			SAP	HR	CO	TPR	SV	LVW
4d	10	St.dose	149±20.3	200±13.8	248±42.6	50353±1380	1.15±0.8	2159±420
		5	-2.4±0.6	-1.7±0.9	-13.8±7.2	+14.8±12.8	-5.0±0.7	-5.0±3.5
		15	-3.6±1.8	-3.4±1.2	-8.2±4.1	-14.7±12.8	0	+4.0±3.3
		30	-5.8±2.7	-3.2±2.5	-23.8±3.8	+5.8±1.7	-15.4±0.3	-15.4±4.8
		45	-6.3±0.9	-5.0±1.8	-17.0±3.2	+14.05±2.4	-10.0±0.5	-1.3±4.8
		60	-8.3±1.2	-6.5±3.7	-43.0±6.6	+28.9±2.9	-10.0±0.5	+1.7±5.6
		90	-16.6±0.9	-6.5±3.7	-10.5±4.1	+29.8±3.7	-10.05±0.5	-4.6±3.8
	25		135±19.5	179.5±22.5	219±71	61647.5±1780	1.2±0.4	5480±250
		5	-5.3±4.2	-3.5±1.8	-28.9±4.1	+30.6±16.3	-27.5±13	-21.5±6.8
		15	-16.5±8.3	-2,4±0.9	-35.7±8.6	-28.3±12.1	-28.4±7.5	-21.0±3.4
		30	-16.5±8.3	-3.2±2.5	-23.8±3.8	+5.8±1.7	-15.4±0.3	-21.0±3.4
		45	-18.2±4.7	-4.0±1.6	-46.6±8.4	-13.7±7.1	-24..3±5.2	-17.8±8.7
		60	-8.6±3.2	-6.3±3.3	-34.5±3.7	7.5±3.8	-24..3±5.2	-17.8±8.7
		90	-3.1±1.8	-6.2±3.3	-22.8±4.1	-12.6±5.7	-14.3±3.6	-8.4±3.1
4e	25	St.dose	133.3±18.5	156.0±2.0	301.6±2,8	34519±1201	1.5±0.3	3359±186
		5	-4.0±1.3	-6.2±2.0	-25.6±6.0	+28.7±6.3	-60.6±1.8	-30±12
		15	-1.8±0.6	-3.9±0.9	-18.5±6.7	+7.9±5.1	-26.4±4.8	-28.4±14
		30	-2.0±3.4	-2.6±1.8	-12.5±4.2	+5.7±3.9	-18.3±3.6	-16.3±17
		45	-0.7±1.3	+1.2±1.0	-8.3±4.2	-12.6±4.0	-6.7±3.6	-8.7±4.2
		60	+7.1±4.2	0	-1.3±3.1	16.2±8.4	-1.8±0.9	-4.3±1.8
	50	St.dose	146.2±3.2	162.5±8.5	287.5±48	38060±5948	1.75±0.25	3213±536
		5	-6.2±0.9	-8.7±4.0	-58±13.0	+44.7±8.1	-54.3±0.2	-50.8±13
		15	-4.7±1.8	-4.7±3.2	-40.5±19.0	+39.7±12.8	-48.2±0.1	-32.6±15
		30	-5.7±4.5	-2.8±4.0	-27.8±48.0	+124.3±8.7	-26.8±0.1	-16.3±8.7
		45	+1.8±2.6	+5.3±0.8	-19.9±16.0	+18.2±0.3	-18.2±0.3	-16.3±8.7
		60	+6.4±4.3	-2.8±4.0	-0.7±41.0	+7.6±1.8	0	-3.7±4.1
Bendazol	10	St.dose	133±6.4	181±19.4	345±22.4	37644±1026	1.9±0.08	0.62±0.3
		5	-16.1±4.2	-8.8±9.4	-6.7±4.1	-12.4±11.2	-13.3±5.4	-18.3±6.6
		15	-6.2±4.8	-3.3±7.3	-19.6±9	+16.6±7.0	-6.3±6.9	-6.4±6
		30	-3.1±5.9	0±8.8	-26.0±10	+22.2±8.8	-26.2±9.4	-9.6±9.1
		45	-6.5±9.4	+2.2±5.8	-28±8.2	+42.3±8.2	-31.9±7.0	+6.0±9.1
		60	-2.3±4.4	+2.2±6.5	-13.2±7	+24.2±6.1	-15.1±8.3	+7.8±6.4
	20	St.dose	140±4.6	200±18.5	328±12.6	32012±160	2.4±0.7	0.7±0.1
		5	-21.4±6.8	-10.6±8	-15.2±4.1	-27.3±6.2	-21.9±3.6	-30.9±5.6
		15	-7.8±2.4	-7.1±8.1	-23.8±1.6	+13.8±3.2	-29.8±5.3	-10.4±8.7
		30	-6.2±3.8	1.3±0.9	-34.3±0.9	+1.9±1.8	-59.6±8.7	-12.1±8.7
		45	-1.5±2.1	-0.7±1.2	-19.4±5.4	+136.7±6.4	-27.6±11	-4.3±3.2
		60	+5.1±4.3	+2.4±1.3	-17.4±3.6	+63.5±9.8	-21.3±9.7	+9.9±7.8

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