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ANTIPYRETIC ACTIVITY OF THE NEW 2-(((3-MERCAPTO-5-METHYL-4*H*-1,2,4-TRIAZOL-4-YL)IMINO)METHYL)-5-R-BENZOATES

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Підвищення температури тіла є необхідною захисною реакцією організму, що активує імунну систему та підсилює фагоцитоз, це призводить до пригнічення розмноження вірусів та бактерій. Жарознижувальна дія, що супроводжується збільшенням тепловіддачі через розширення судин шкіри та посилене потовиділення, пов'язана значною мірою із заспокійливим впливом на збудливість теплорегулюючих центрів проміжного мозку, яка змінюється під впливом патологічного процесу.

Підвищення температури вище за 39 °С є небезпечним фактором для дорослих і дітей різних вікових категорій.

Незважаючи на високу ефективність анальгетиків, їх використання не завжди безпечне. Застосування аспірину підвищує ризик розвитку запальних змін з боку шлунково-кишкового тракту, підвищує ламкість судин, порушує згортання крові.Пошук нових високоефективних лікарських засобів із жарознижувальною дією є актуальною проблемою сьогодення.

***Метою** нашої роботи є фармакологічний скринінг антипіретиків серед вперше синтезованих 2-(((3-меркапто-5-метил-4Н-1,2,4-тріазол-4-іл)іміно)метил)-5-R-бензоатів.*

***Матеріали та методи дослідження.** Об'єктами дослідження стали нові 2-(((3-меркапто-5-метил-4Н-1,2,4-тріазол-4-іл)-іміно)-метил)-5-R-бензоати.*

Експериментальну лихоманку проводили на білих нелінійних щурах шляхом введення 2,4-динітрофенолу (2,4-ДНФ) (роз'єднувач окисного фосфорилювання) в дозі 20 мг/кг. В якості референс-препарату використовували ацетилсаліцилову кислоту в дозі 100 мг/кг.

Досліджувані речовини вводили через пів години ($T_{0,5}$) після введення 2,4-ДНФ, фіксували ректальну температуру тіла протягом 1 години (T_1). Початкову ректальну температуру (T_0) реєстрували до внутрішньочеревної ін'єкції 2,4-ДНФ. В якості препарату порівняння використовували ацетилсаліцилову кислоту в дозі 100 мг/кг.

***Результати дослідження та обговорення.** За даними серії досліджень було встановлено, що внутрішньочеревинне введення 2,4-ДНФ через 30 хвилин викликало підвищення температури тіла щурів (n=133)в середньому з 37,36 °С до 38,37 °С ($_{\Delta}T$=0,88 °С).*

Щодо референтного препарату ацетилсаліцилової кислоти, встановлено, що при її застосуванні за модельованої патології значення температури тіла щурів знижувались на 3 % ($_{\Delta}T$=-1,2 °С, p≤0,05) по відношенню до контрольної групи.

Згідно отриманим результатам в ході експерименту було виявлено сполуки, які за своїм ефектом перевищували референс-препарат. Так, сполуки IV, V та VIII знижували показники температури тіла щурів більш ніж на 0,39 %.

Серед досліджуваних речовин привертають на себе увагу сполуки IV та V, які знижували показники температури тіла щурів в інтервалі 4,66-4,95 % і при цьому знижували температуру від 1,19 до 2,10 °С.

***Висновки.** Синтезовано нові 2-(((3-меркапто-5-метил-4Н-1,2,4-тріазол-4-іл)іміно)метил)-5-R-бензоати. Найбільш активною серед досліджуваних сполук є амоній 2-(((3-меркапто-5-метил-4Н-1,2,4-тріазол-4-іл)-іміно)-метил)бензоат. Перехід до солей із неорганічними катіонами призводить до втрати активності. Так, заміна катіонів на піперидиній дещо підвищує показники активності, проте сполука поступається за силою ефекту референс-препарату*

***Ключові слова:** похідні 1,2,4-тріазолу, органічний синтез, біологічна активність, жарознижуюча дія, антипіретики, гіпертермія*

1. Introduction

Thermoregulation of the body relies on the balance of physiological processes of thermogenesis and thermolysis, which are controlled by neural and hormonal mechanisms. Antipyretic activity, which involves the increase of thermolysis through angiectasis

of skin vessels and heightened sweat production, is largely connected with a relaxing effect on the diencephalon's thermoregulation centers' irritation that may be altered due to disease [1].

Antipyretic drugs represent the type of medicines capable of decreasing body temperature during fever and belong to the group of non-steroidal anti-inflammatory drugs (NSAIDs) [2, 3]. Despite analgesics' high effectiveness, their use is not entirely safe. The use of aspirin impairs blood coagulation and increases the risk of inflammatory processes in gastroenteric tract [4].

As for the drug paracetamol, it is worth noting that its side effects are very rare. However, once manifested, they are of a rather high severity. Paracetamol administration increases the risk of myocardial infarction, premature death, gastrorrhagia, and acute liver or kidney diseases [5].

Literary sources indicate that both ibuprofen and analgin (dipyrone) are well-tolerated and safe during short-term administration to kids affected by fever.

However, the review of antipyretic activity showed that ibuprofen causes higher antipyretic effect than analgin during oral administration of one dose. This effect is more noticeable in kids with high temperature [6].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

The search and study of the new highly effective antipyretic medicines is of a great significance nowadays.The sources [7, 8] report that the derivatives of 1,2,4-triazol-3-thione possess a wide range of biological activity.

3. Analysis of recent studies and publications in which a solution of the problem and which draws on the author

Several articles describe the results of the study of antipyretic activity of 1,2,4-triazole derivatives. That said, the study [9] provides information on the antipyretic activity of new 2-(5-(adamantan-1-yl)-4-R-1,2,4-triazol-3-ylthio)acetate hydrazides. Another scholarly source [10] also describes new S-derivatives of 1,2,4-triazole that contain morpholinomethylene substituent in their structures, which makes them promising as antipyretic drugs.

4. Allocation of unsolved parts of the general problem, which is dedicated to the article

The heterocyclic nature of 1,2,4-triazole makes it a promising fragment for synthesis of new biologically active compounds, and antipyretics in particular. The search for the new highly effective antipyretic medicines is of a great relevance nowadays.

5. Formulation of goals (tasks) of the article

The aim of this work is to conduct a pharmacological screening over the new antipyretic drugs, specifically the derivatives of 2-(((3-mercapto-5-methyl-4*H*-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate that were obtained for the first time.

6. Statement of the basic material of the study (methods and objects) with the justification of the results

Materials and methods.

The objects of the research were the new 2-(((3-mercapto-5-methyl-4*H*-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate derivatives obtained in the Laboratory of organic synthesis at the Department of toxicological and inorganic chemistry of Zaporizhzhia State Medical University under the supervision of professor Panasenko O. I. and professor Knysh Ye. H.

In our opinion, the model of hyperthermia caused by 2,4-dinitrophenyl is the most convenient for screening.

The experimental fever was caused in white nonlinear rats by administrating 2,4-dinitrophenol (2,4-DNP), a dividing agent in oxidative phosphorylation, at the dose of 20 mg/kg [11].

The substances of research were administrated abdominally at the dose of 1/10 LD_{50}, substances were stabilized with Twin-80. The doses were determined by Prozorovskyi method prior the preparation [12].

According to the mentioned model, body temperature rises during 15–20 minutes after the injection of 2,4-DNP, while the temperature maximum is reached during 1 hour. Therefore, it was reasonable to inject the substances of research in 30 minutes ($T_{0,5}$) after the administration of 2,4-DNP and to record rectal temperature during 1 hour (T_1).

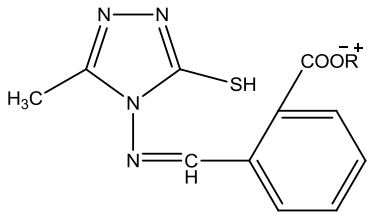
The initial rectal temperature (T_0) was recorded prior the abdominal injection of 2,4-DNP. Acetylsalicylic acid was used as a reference substance at the dose of 100 mg/kg.

The results were processed with modern methods of statistical analysis, including Microsoft Office 2010 (Microsoft Excel) and STATISTICA® for Windows 6.0. Mean values (M) and standard errors of the average (±m) were calculated. Data validity of intergroup variances as per experimental data were evaluated using Student's t-test. Three levels of statistical significance were applied in the processing, specifically $p<0.05$; $p<0.01$; and $p<0.001$ [13, 14].

Results and discussion

The obtained data (Table 1) demonstrates that the study substance and the reference substance affected rats' body temperatures in a different manner.

2-(((3-mercapto-5-methyl-4I-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoates



where R = morpholinium (I), piperidinium (II), diethylammonium (III), ethylammonium (IV), ammonium (V), K^+ (VI), Na^+ (VII), tert-butylammonium (VIII), monoethanolammonium (IX), methylammonium (X).

Table 1

Results for the study of antipyretic activity of the new 2-(((3-mercapto-5-methyl-4*H*-1,2,4-triazol-4-yl)-imino)-methyl)-5-R-benzoates

Group	Temperature, °C (M±m)			Temperature alteration, ^{0}C	Temperature alteration with relation to the reference, Δ %
	T_0	$T_{0.5}$	T_1	$\Delta T=T_1-T_{0.5}$	
Reference pathology (2,4-DNP + saline)	37.83±0.286	38.83±0.146	38.36±0.173	–0.47	100
2,4-Dinitrophenol + acetylsalicylic acid	37.69±0.282	39.09±0.183	37.89±0.144*	–1.20	–3.00*
2,4-Dinitrophenol + substance I	36.27±0.350	37.93±0.132	39.23±0.406	1.30	2.27
2,4-Dinitrophenol + substance II	36.27±0.704	38.46±0.136	37.36±0.109	–1.10	–2.61
2,4-Dinitrophenol + substance III	37.21±0.134	38.37±0.314	37.93±0.296	–0.44	–1.12
2,4-Dinitrophenol + substance IV	37.23±0.099	38.56±0.117	36.46±0.532*	–2.10	–4.95*
2,4-Dinitrophenol + substance V	37.43±0.123	37.76±0.320	36.57±0.462*	–1.19	–4.66*
2,4-Dinitrophenol + substance VI	37.44±0.242	37.91±0.432	38.26±0.206	0.35	–0.26
2,4-Dinitrophenol + substance VII	37.59±0.307	38.11±0.181	38.23±0.251	0.12	–0.34
2,4-Dinitrophenol + substance VIII	37.90±0.298	39.03±0.222	37.06±0.217*	–1.97	–3.39*
2,4-Dinitrophenol + substance IX	37.81±0.353	38.07±0.369	38.14±0.222	0.07	–0.56
2,4-Dinitrophenol + substance X	37.60±0.295	38.33±0.178	38.14±0.344	–0.19	–0.56

*Note * – the results are statistically significant with relation to the reference group ($p<0.05$)*

The results of the experiment established that in 30 minutes after the abdominal injection of 2,4-DNP body temperature in the population of rats (n=133) was in range from 37.36 °C to 38.37 °C on average ($_{\Delta}T=0.88$ °C).

As for the reference substance acetylsalicylic acid, it caused a 3 % decrease of body temperature in rats with a modeled pathology ($_{\Delta}T=-1.2^{o}$C, $p\leq0.05$) with relation to the reference group.

The results clearly illustrate that antipyretic activity of some of the substances was better than that of the reference substance. That said, substances IV, V, and VIII decreased body temperature in rats by more than 0.39 %.

Therefore, substances IV and V deserve the most of attention; they decreased body temperature in rats by 4.66–4.95 %, or by 1.19–2.10 °C, with relation to the reference group.

The connection between the structure and activities has been established. That said, the most significant temperature decrease was observed during the administration of ammonium 2-(((3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate (V); replacement of ammonium with ethylammonium ion (IV) slightly decreases body temperature in rats, more specifically by ΔT=0,91 °C (Δ %=0,29 %). Introduction of inorganic cations leads to the loss of activity. If piperidinium forms the salt (II), the activity increases slightly, but the compound demonstrates weaker effect than the reference substance.

7. Findings from the research and prospects of further development of this area

1. Ammonium 2-(((3-mercapto-5-methyl-4*H*-1,2,4-triazol-4-yl)imino)methyl)-5-R-benzoate (V) is the most active substance among the studied entities; its properties for hyperthermia slowing exceed the activity of acetylsalicylic acid and decreases body temperatures in rats by 1.19 °C ($p\leq0.05$).

2. Introduction of inorganic cations leads to the loss of activity.

3. If piperidinium forms the salt (II), the activity increases slightly, but the compound demonstrates weaker effect than the reference substance.

4. The possible mechanism of antipyretic activity of the new compounds is the inhibition of cyclooxygenase [15, 16].

5. The problem of finding new highly effective antipyretics is of a great importance nowadays. That is why 1,2,4-triazole derivatives merit further pharmacological research.

Having conducted a literature review and the study, we found that the newly synthesized compounds merit further research of their antipyretic activity with aim to find the new highly effective drugs with biological activity that have a potential to appear as active pharmaceutical ingredients of commercial antipyretic medicines.

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