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## THE SYNTHESIS, COMPUTER PREDICTION OF THE BIOLOGICAL ACTIVITY AND THE ACUTE TOXICITY OF 4-ARYL-5-OXO-4,5-DIHYDRO[1,2,4]TRIAZOLO[4,3-*a*]QUINAZOLINE-8-CARBOXAMIDES

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**Aim.** The aim of present study was to conduct modelling of the virtual library of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides, to determine the most probable biological activity spectrum and the acute toxicity of studied compounds by PASS and GUSAR software, sort out the most perspective substances and develop preparative protocols for their synthesis.

**Methods.** Using the PASS program computer prediction of the biological activity of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides has been performed. Prediction of the acute toxicity has been carried out by the GUSAR software. The structure of the compounds synthesized has been proven by elemental analysis and <sup>1</sup>H NMR spectroscopy data.

**Results.** The synthesis of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides has been conducted starting from corresponding methyl 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylates, which were converted into corresponding 3-aryl-2-hydrazino-4-oxo-3,4-dihydroquinazoline-7-carboxylic acid hydrazides by treatment with hydrazine hydrate. Heating of these 2-hydrazinoquinazolin-4(3H)-ones with acetylacetone was resulted in 4-aryl-8-[(3,5-dimethyl-1H-pyrazol-1-yl)carbonyl]-1-methyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4H)-ones formation. Following substitution of pyrazole moiety by interaction of these compounds with primary amines led to destined 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides. The PASS program computer prediction of the biological activity of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides has allowed identifying the types of activity of studied compounds and sorting out the leaders with potential antineurotic activity, which are perspective for male reproductive and erectile dysfunction treatment. Prediction of the acute toxicity has been carried out by the GUSAR software, which allowed to refer them to slightly toxic (class 4) or practically nontoxic (class 5) substances.

**Conclusions.** The obtained compounds are perspective objects for further investigations as slightly toxic (nontoxic) substances with potential antineurotic activity, which are perspective for male reproductive and erectile dysfunction treatment.

**Keywords:** synthesis, 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides, computer prediction, biological activity, acute toxicity

**Мета.** У даному дослідженні було поставлено за мету провести моделювання віртуальної бібліотеки 4-арил-5-оксо-4,5-дигідро[1,2,4]триазоло[4,3-*a*]хіназолін-8-карбоксамідів, за допомогою комп'ютерних програм PASS та GUSAR визначити найбільш ймовірний спектр біологічної активності та гостру токсичність досліджуваних сполук, а також виділити найбільш перспективні сполуки та розробити препаративні методи їх синтезу.

**Методи.** Комп'ютерне прогнозування біологічної активності 4-арил-5-оксо-4,5-дигідро[1,2,4]триазоло[4,3-*a*]хіназолін-8-карбоксамідів проведено за допомогою програми PASS. Комп'ютерне прогнозування гострої токсичності здійснено за програмним забезпеченням GUSAR. Будову синтезованих сполук доведено за допомогою елементного аналізу та даних <sup>1</sup>H ЯМР спектроскопії.

**Результати.** Синтез 4-арил-5-оксо-4,5-дигідро[1,2,4]триазоло[4,3-*a*]хіназолін-8-карбоксамідів був проведений виходячи з відповідних метил 3-арил-4-оксо-2-тіоксо-1,2,3,4-тетрагідрохіназолін-7-карбоксилатів, які були перетворені у відповідні 3-арил-2-гідразино-4-оксо-3,4-дигідрохіназолін-7-карбогідразиди під дією гідразин гідрату. Нагрівання цих 2-гідразинохіназолін-4(3*H*)-онів в ацетилацетоні привело до утворення 4-арил-8-[(3,5-диметил-1*H*-піразол-1-іл)карбоніл]-1-метил[1,2,4]триазоло[4,3-*a*]хіназолін-5(4*H*)-онів. Наступне заміщення залишку піразолу при взаємодії цих сполук з первинними амінами дало цільові 4-арил-5-оксо-4,5-дигідро[1,2,4]триазоло[4,3-*a*]хіназолін-8-карбоксаміди. Комп'ютерне прогнозування біологічної активності 4-арил-5-оксо-4,5-дигідро[1,2,4]триазоло[4,3-*a*]хіназолін-8-карбоксамідів за допомогою програми PASS дозволило визначити напрямки активності досліджуваних сполук та виділити серед них лідерів з потенційною антиневротичною активністю, які можуть бути перспективними для лікування чоловічих репродуктивних захворювань та еректильних дисфункцій. Комп'ютерне прогнозування гострої токсичності здійснено за програмним забезпеченням GUSAR, що дозволило віднести їх до малотоксичних (4 клас) або практично нетоксичних речовин (5 клас).

**Висновки.** Отримані сполуки є перспективними об'єктами для подальших досліджень як малотоксичні (нетоксичні) речовини з потенційною антиневротичною активністю, які можуть бути перспективними для лікування чоловічих репродуктивних захворювань та еректильних дисфункцій

**Ключові слова:** синтез, 4-арил-5-оксо-4,5-дигідро[1,2,4]триазоло[4,3-*a*]хіназолін-8-карбоксаміди, комп'ютерне прогнозування, біологічна активність, гостра токсичність

## 1. Introduction

Derivatives of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one, which are representatives of the important class of condensed heterocycles possessing wide range of the biological activity, attract particular interest in development of innovative drug substances.

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

The possibility to synthesize a large amount of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives leads to the necessity for the rational presynthetic selection the most perspective compounds from defined variety. One of the effective ways to solve this problem is computer prediction of various properties of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives, such as biological activity and acute toxicity, that enables to eliminate unpromising substances at the early stages of the research.

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

Among potential pharmacologically significant properties of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives the H1-antihistaminic [1–9], anticonvulsant [10], antiHIV [11], antibacterial [11–13], antifungal [11, 12], antitubercular [11, 13], anticancer [13], anti-asthmatic [8, 14], antiallergic [14], anti-inflammatory [14, 15] bioactivities should be mentioned. In the previous study [16] we predicted potential antiasthmatic and antiallergic activity of compounds of the specified class.

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

The presence of amide group may have a significant impact on biological behavior of compounds. Investigation of influence of amide moiety on the biological activity of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones is important for expansion of knowledge about pharmacological properties of this class of compounds.

## 5. Formulation of goals (tasks) of article

Taking into account actuality of searching biological active substances among [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives and modern advances in software for virtual screening the goal of present study was to conduct modelling of the virtual library of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-8-carboxamides, to determine the most probable biological activity spectrum and the acute toxicity of studied compounds by PASS and GUSAR software, sort out the most perspective substances and develop preparative protocols for their synthesis.

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

For design of the virtual library of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-8-carboxamides 2 randomization points (aryl substituent in position 4 and different amine residue) and fixed methyl substituent in position 1 of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one were chosen.

The synthesis of studied 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-8-carboxamides was carried out by scheme, which were based on previously founded the formation of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones by reaction of 2-hydrazinoquinazolin-4(3*H*)-ones with acetylacetone (Fig. 1) [17]. Starting methyl 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolin-7-carboxylates **1a, b** were converted into corresponding 2-hydrazinoquinazolin-4(3*H*)-ones **2a, b** by treatment with hydrazine hydrate according improved method [18]. Heating of hydrazines **2a, b** with acetylacetone was resulted in 4-aryl-8-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-1-methyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **3a, b** formation. Following substitution of pyrazole moiety by interaction of compounds **3a, b** with primary amines led to destined amides **4a-1**. This way allows obtaining the library of final products in good yields.

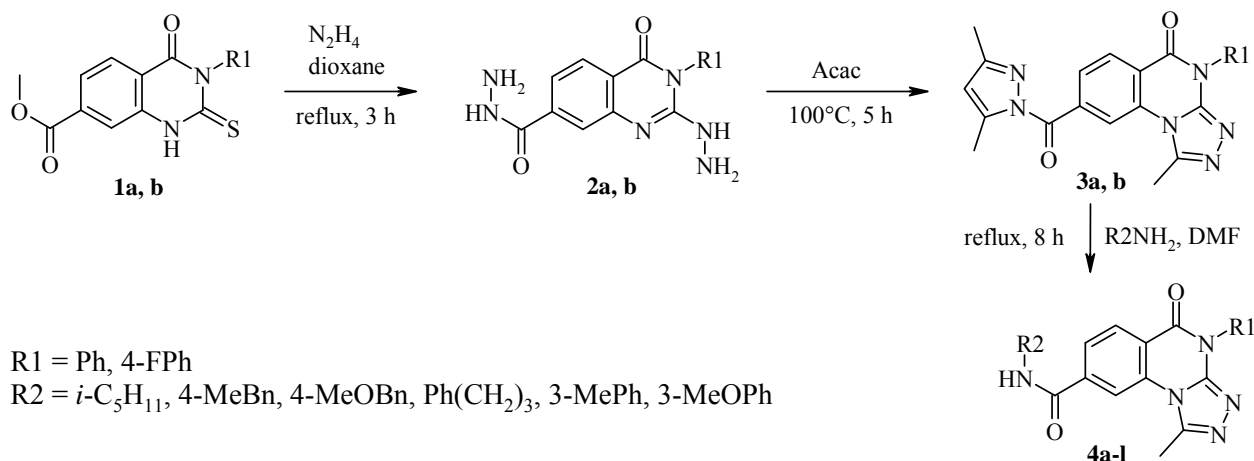


Fig. 1. The synthesis of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazoline-8-carboxamides

**The general procedure for the synthesis of 3-aryl-2-hydrazino-4-oxo-3,4-dihydroquinazolin-7-carbohydrazides (2a, b).** Add the corresponding methyl 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolin-7-carboxylate **1a, b** (0.05 mol) to stirred mixture of dioxane (100 ml) and hydrazine hydrate (40 ml). Reflux the obtained emulsion with stirring for 3 h. Separate the lower dioxane layer and dilute it with H<sub>2</sub>O (200 ml). Filter the precipitate, wash it with *i*-propanol (100 ml) and recrystallize from mixture of DMF (100 ml) and *i*-propanol (200 ml). Yields, melting points, elemental analysis and <sup>1</sup>H NMR data are given in Table 1.

**The general procedure for the synthesis of 4-aryl-8-[(3,5-dimethyl-1H-pyrazol-1-yl)carbonyl]-1-methyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-ones (3a, b).** Heat the suspension of corresponding 3-aryl-2-hydrazino-4-oxo-3,4-dihydroquinazolin-7-carbohydrazide **2a, b** (0.03 mol) in acetylacetone (100 ml) at 100 °C with stirring for 5 hours. After cooling dilute the reaction mixture with *i*-propanol (300 ml). Filter the precipitate, wash it with *i*-

propanol (50 ml) and recrystallize from mixture of DMF (50 ml) and *i*-propanol (100 ml). Yields, melting points, elemental analysis and <sup>1</sup>H NMR data are given in Table 1.

**The general procedure for the synthesis of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-8-carboxamides (4a-l).** Reflux the solution of corresponding 4-aryl-8-[(3,5-dimethyl-1H-pyrazol-1-yl)carbonyl]-1-methyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one **3a, b** (0.002 mol) in anhydrous DMF (10 ml) and corresponding amine (0.003 mol) during 8 hours. After cooling dilute the reaction mixture with H<sub>2</sub>O (30 ml). Filter the precipitate formed, wash it with *i*-propanol (10 ml) and recrystallize from mixture of DMF (5 ml) and *i*-propanol (10 ml). Yields, melting points, elemental analysis and <sup>1</sup>H NMR data are given in Table 1.

The structures of obtained compounds **4a-l** have been confirmed by the <sup>1</sup>H NMR spectroscopy data (Table 1). <sup>1</sup>H NMR-spectra were recorded on Varian WXR-400 (200 MHz) spectrometer in DMSO-d<sub>6</sub> solution with TMS as internal standard, chemical shifts are reported in ppm.

Table 1

Properties of the compounds **2a, b; 3a, b; 4a-l**

Comp. code	R	Yield, %	M.p., °C	Molecular formula, m.m	C, % Calc./found	H, % Calc./found	N, % Calc./found	<sup>1</sup> H NMR spectral data δ, ppm, J, hz
1	2	3	4	5	6	7	8	9
<b>2a</b>	R1=Ph	78	>300	C <sub>15</sub> H <sub>14</sub> N <sub>6</sub> O <sub>2</sub> 310.31	58.06/ 57.97	4.55/ 4.58	27.08/ 27.13	4.55 br.s, (2H, CONHNH <sub>2</sub> ); 5.70 s, (2H, NHNH <sub>2</sub> -2); 7.08 t, (J 7.8, 1H, H-4 Ph); 7.33 t, (J 7.8, 2H, H-3,5 Ph); 7.57 dd, (J <sub>5,6</sub> 7.8, J <sub>6,8</sub> 2.0, 1H, H-6); 7.75 d, (J <sub>6,8</sub> 2.0, 1H, H-8); 7.88 d, (J 7.8, 2H, 2,6 Ph); 8.00 d, (J <sub>5,6</sub> 7.8, 1H, H-5); 9.40 s, (1H, NHNH <sub>2</sub> -2); 10.02 s, (1H, CONHNH <sub>2</sub> )
<b>2b</b>	R1= =4-FPh	80	>300	C <sub>15</sub> H <sub>13</sub> FN <sub>6</sub> O <sub>2</sub> 328.30	54.88/ 54.92	3.99/ 4.01	25.60/ 25.57	4.55 br.s, (2H, CONHNH <sub>2</sub> ); 5.70 s, (2H, NHNH <sub>2</sub> -2); 7.20-7.41 m (4H, H Ar); 7.57 dd, (J <sub>5,6</sub> 7.8, J <sub>6,8</sub> 2.0, 1H, H-6); 7.75 d, (J <sub>6,8</sub> 2.0, 1H, H-8); 8.04 d, (J <sub>5,6</sub> 7.8, 1H, H-5); 9.40 s, (1H, NHNH <sub>2</sub> -2); 10.02 s, (1H, CONHNH <sub>2</sub> )
<b>3a</b>	R1=Ph	74	296- 298	C <sub>22</sub> H <sub>18</sub> N <sub>6</sub> O <sub>2</sub> 398.42	66.32/ 66.39	4.55/ 4.52	21.09/ 21.16	2.12 s, (3H, CH <sub>3</sub> Pyr-3); 2.36 s, (3H, CH <sub>3</sub> -1); 2.55 s, (3H, CH <sub>3</sub> Pyr-5); 6.26 s, (1H, H Pyr-4); 7.52-7.76 m, (6H, H-7, 5H Ph); 8.00 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.31 d, (1H, J <sub>6,7</sub> 7.8, 1H, H-6)

1	2	3	4	5	6	7	8	9
3b	R1= =4-FPh	78	303- 304	C <sub>22</sub> H <sub>17</sub> FN <sub>6</sub> O <sub>2</sub> 416.41	63.46/ 63.51	4.11/ 4.09	20.18/ 20.22	2.12 s, (3H, CH <sub>3</sub> Pyr-3); 2.36 s, (3H, CH <sub>3</sub> -1); 2.55 s, (3H, CH <sub>3</sub> Pyr-5); 6.26 s, (1H, H Pyr-4); 7.50 t (J 7.6, 2H, H-3,5-Ar); 7.70-7.82 m, (3H, H 7, H-2,6-Ar); 8.04 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.30 d, (J <sub>6,7</sub> 7.8, 1H, H-6)
4a	R1=Ph R2= <i>i</i> -C <sub>5</sub> H <sub>11</sub>	84	>300	C <sub>22</sub> H <sub>23</sub> N <sub>5</sub> O <sub>2</sub> 389.45	67.85/ 67.78	5.95/ 5.99	17.98/ 18.03	0.88 d, (J 7.0, 6H, 2CH <sub>3</sub> ); 1.40 qr, (J 7.0, 2H, NHCH <sub>2</sub> CH <sub>2</sub> ); 1.52-1.72 m, (1H, CH(CH <sub>3</sub> ) <sub>2</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 3.25 qr, (J 7.0, 2H, NHCH <sub>2</sub> CH <sub>2</sub> ); 7.42-7.56 m, (5H, H Ph); 7.74 dd, (J <sub>6,7</sub> 7.8, J <sub>7,9</sub> 2.0, 1H, H-7); 8.00 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 8.55 t, (J 7.0, 1H, CONH)
4b	R1=Ph R2= =4-MeBn	86	>300	C <sub>25</sub> H <sub>21</sub> N <sub>5</sub> O <sub>2</sub> 423.47 <sub>2</sub>	70.91/ 70.86	5.00/ 4.97	16.54/ 16.58	2.24 s (3H, CH <sub>3</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 4.40 d (J 7.0, 2H, CH <sub>2</sub> ); 7.09 d, (J 7.8, 2H, 3,5 Bn); 7.19 d, (J 7.8, 2H, 2,6 Bn); 7.58-7.72 m, (5H, H Ph); 7.77 dd, (J <sub>6,7</sub> 7.8, J <sub>7,9</sub> 2.0, 1H, H-7); 8.04 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 9.18 t, (J 7.0, 1H, CONH)
4c	R1=Ph R2= =4-MeOBn	85	>300	C <sub>25</sub> H <sub>21</sub> N <sub>5</sub> O <sub>3</sub> 439.47	68.33/ 68.39	4.82/ 4.78/	15.94/ 15.89	2.36 s, (3H, CH <sub>3</sub> -1); 3.70 s (3H, OCH <sub>3</sub> ); 4.37 d (J 7.0, 2H, CH <sub>2</sub> ); 6.85 d, (J 7.8, 2H, 3,5 Bn); 7.22 d, (J 7.8, 2H, 2,6 Bn); 7.58-7.72 m, (5H, H Ph); 7.77 dd, (J <sub>6,7</sub> 7.8, J <sub>7,9</sub> 2.0, 1H, H-7); 8.04 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 9.18 t, (J 7.0, 1H, CONH)
4d	R1=Ph R2= =Ph-(CH <sub>2</sub> ) <sub>3</sub>	75	282- 284	C <sub>26</sub> H <sub>23</sub> N <sub>5</sub> O <sub>2</sub> 437.49	71.36/ 71.40	5.30/ 5.28	16.01/ 15.98	1.80 qn, (J 7.0, 2H, 2-CH <sub>2</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 2.59 t, (J 7.0, 2H, 3-CH <sub>2</sub> ); 3.25 qr, (J 7.0, 2H, 1-CH <sub>2</sub> ); 7.15-7.30 m, (5H, H Ph-3); 7.42-7.56 m, (5H, H Ph); 7.74 dd, (J <sub>6,7</sub> 7.8, J <sub>7,9</sub> 2.0, 1H, H-7); 8.00 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 8.66 t, (J 7.0, 1H, CONH)
4e	R1=Ph R2=3-MePh	74	>300	C <sub>24</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> 409.44	70.40/ 70.35	4.68/ 4.71	17.10 17.05	2.24 s (3H, CH <sub>3</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 6.90 d, (J 7.8, 1H, H-4 Ar'); 7.20 t, (J 7.8, 1H, H-5 Ar'); 7.60-7.72 m, (7H, H Ph, 2,6-Ar'); 7.83 dd, (J <sub>6,7</sub> 7.8, J <sub>7,9</sub> 2.0, 1H, H-7); 8.14 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.32 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 10.28 s, (1H, CONH)
4f	R1=Ph R2= =3-MeOPh	73	>300	C <sub>24</sub> H <sub>19</sub> N <sub>5</sub> O <sub>3</sub> 425.44	67.76/ 67.80	4.50/ 4.49	16.46/ 16.42	2.36 s, (3H, CH <sub>3</sub> -1); 3.70 s (3H, OCH <sub>3</sub> ); 6.60 d, (J 7.8, 1H, H-4 Ar'); 7.08-7.22 m, (2H, H-5,6-Ar'); 7.35 s, (1H, H-2 Ar'); 7.42-7.56 m, (5H, H Ph); 7.74 dd, (J <sub>6,7</sub> 7.8, J <sub>7,9</sub> 2.0, 1H, H-7); 8.14 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.32 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 10.10 s, (1H, CONH)
4g	R1=4-FPh R2= <i>i</i> -C <sub>5</sub> H <sub>11</sub>	86	>300	C <sub>22</sub> H <sub>22</sub> FN <sub>5</sub> O <sub>2</sub> 407.44	64.85/ 64.81	5.44/ 5.46	17.19/ 17.22	0.88 d, (J 7.0, 6H, 2CH <sub>3</sub> ); 1.40 qr, (J 7.0, 2H, NHCH <sub>2</sub> CH <sub>2</sub> ); 1.52-1.72 m, (1H, CH(CH <sub>3</sub> ) <sub>2</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 3.25 qr, (J 7.0, 2H, NHCH <sub>2</sub> CH <sub>2</sub> ); 7.50 t (J 7.6, 2H, H-3,5-Ar); 7.70-7.82 m, (3H, H 7, H-2,6-Ar); 8.00 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 8.55 t, (J 7.0, 1H, CONH)
4h	R1=4-FPh R2=4-MeBn	85	>300	C <sub>25</sub> H <sub>20</sub> FN <sub>5</sub> O <sub>2</sub> 441.46	68.02/ 67.97	4.57/ 4.60	15.86/ 15.88	2.24 s (3H, CH <sub>3</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 4.40 d (J 7.0, 2H, CH <sub>2</sub> ); 7.09 d, (J 7.8, 2H, 3,5 Bn); 7.19 d, (J 7.8, 2H, 2,6 Bn); 7.50 t (J 7.6, 2H, H-3,5-Ar); 7.70-7.82 m, (3H, H 7, H-2,6-Ar); 8.04 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 9.20 t, (J 7.0, 1H, CONH)

1	2	3	4	5	6	7	8	9
<b>4i</b>	R1=4-FPh R2= =4-MeOBn	88	>300	C <sub>25</sub> H <sub>20</sub> FN <sub>5</sub> O <sub>3</sub> 457.47	65.64/ 65.59	4.41/ 4.39	15.31/ 15.34	2.36 s, (3H, CH <sub>3</sub> -1); 3.70 s (3H, OCH <sub>3</sub> ); 4.37 d (J 7.0, 2H, CH <sub>2</sub> ); 6.85 d, (J 7.8, 2H, 3,5 Bn); 7.22 d, (J 7.8, 2H, 2,6 Bn); 7.50 t (J 7.6, 2H, H-3,5-Ar); 7.70-7.82 m, (3H, H 7, H-2,6-Ar); 8.03 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 9.18 t, (J 7.0, 1H, CONH)
<b>4j</b>	R1=4-FPh R2= =Ph-(CH <sub>2</sub> ) <sub>3</sub>	77	294- 296	C <sub>26</sub> H <sub>22</sub> FN <sub>5</sub> O <sub>2</sub> 455.49	68.56/ 68.52	4.87/ 4.90	15.38/ 15.40	1.80 qn, (J 7.0, 2H, 2-CH <sub>2</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 2.59 t, (J 7.0, 2H, 3-CH <sub>2</sub> ); 3.25 qr, (J 7.0, 2H, 1-CH <sub>2</sub> ); 7.15-7.30 m, (5H, H Ph-3); 7.50 t (J 7.6, 2H, H-3,5-Ar); 7.70-7.82 m, (3H, H 7, H-2,6-Ar); 8.00 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.26 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 8.64 t, (J 7.0, 1H, CONH)
<b>4k</b>	R1=4-FPh R2=3-MePh	70	>300	C <sub>24</sub> H <sub>18</sub> FN <sub>5</sub> O <sub>2</sub> 427.43	67.44/ 67.39	4.24/ 4.26	16.38/ 16.35	2.24 s (3H, CH <sub>3</sub> ); 2.36 s, (3H, CH <sub>3</sub> -1); 6.90 d, (J 7.8, 1H, H-4 Ar'); 7.20 t, (J 7.8, 1H, H-5 Ar'); 7.44-7.70 m, (4H, H-3,5-Ar, 2,6-Ar'); 7.70-7.82 m, (3H, H 7, H-2,6-Ar); 8.14 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.32 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 10.30 s, (1H, CONH)
<b>4l</b>	R1=4-FPh R2= =3-MeOPh	72	>300	C <sub>24</sub> H <sub>18</sub> FN <sub>5</sub> O <sub>3</sub> 443.43	65.01/ 64.97	4.09/ 4.11	15.79/ 15.81	2.36 s, (3H, CH <sub>3</sub> -1); 3.70 s (3H, OCH <sub>3</sub> ); 6.60 d, (J 7.8, 1H, H-4 Ar'); 7.08-7.22 m, (2H, H-5,6-Ar'); 7.35 s, (1H, H-2 Ar'); 7.50 t (J 7.6, 2H, H-3,5-Ar); 7.70-7.82 m, (3H, H 7, H-2,6-Ar); 8.14 d, (J <sub>7,9</sub> 2.0, 1H, H-9); 8.32 d, (J <sub>6,7</sub> 7.8, 1H, H-6); 10.10 s, (1H, CONH)

Formation of the [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones condensed system led to shift of H-6 protons signals to 8.26–8.32 ppm, that is in good correlation with the known data [19]. Melting points were measured with a Buchi B-520 melting point apparatus. Elemental analysis was performed on Euro EA-3000 apparatus. Starting methyl 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylates **1a, b** have been obtained from commercial producer.

The virtual screening for biological activity of virtual library of studied substances was performed by the PASS Online web-resource, which contains information about structure and biological activity more than 300000 organic compounds [20–22]. Computer prediction of the biological activity spectrum of virtual library of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides **4a-l** was performed with probability of demonstration of specific type of therapeutic action exceeding 50 % (Pa > 0,500).

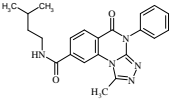
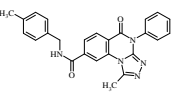
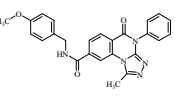
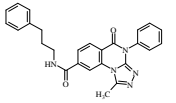
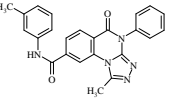
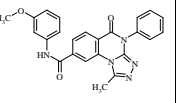
Analysis of the computer prediction results for the virtual library of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides by PASS software

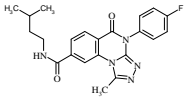
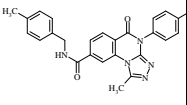
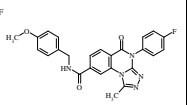
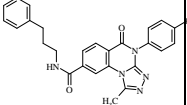
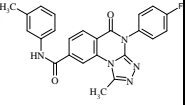
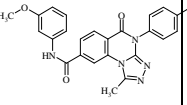
showed the possibility of searching substances possessing potential antineurotic activity, and perspective for male reproductive and erectile dysfunction treatment among these compounds and allowed to generate the library of the most perspective compounds **4a-l** for further investigations (Table 2). However, the probability of antiasthmatic and antiallergic activity is diminished compared to previously described library of having no amide group compounds [23].

Prediction of acute toxicity of compounds **4a-l** for different routes of administration (oral, subcutaneous, intravenous, intraperitoneal) has been carried out by GUSAR software [24, 25]. The training set of program was developed based on SYMYX MDL Toxicity Database, which contains information about acute toxicity more than 10000 chemical structures. Obtained data of acute toxicity of the studied compounds are presented by LD<sub>50</sub> value (log 10 (mmol/kg) and mg/kg) and the toxicity class according to the OECD classification project of chemical substance by acute toxicity values [24, 26].

Table 2

Prediction of the biological activity spectrum of  
4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides **4a-f** [23]

Biological activity	<b>4a</b> 		<b>4b</b> 		<b>4c</b> 		<b>4d</b> 		<b>4e</b> 		<b>4f</b> 	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
1	2	3	4	5	6	7	8	9	10	11	12	13
Antineurotic	0.569	0.083	0.534	0.096	0.605	0.070	0.730	0.032	0.306	0.241	0.456	0.131
Erectile dysfunction treatment	0.786	0.003	0.802	0.003	0.774	0.003	0.770	0.004	0.775	0.003	0.748	0.004
Male reproductive dysfunction treatment	0.733	0.004	0.746	0.004	0.722	0.004	0.736	0.004	0.742	0.004	0.715	0.004
Phobic disorders treatment	0.660	0.095	–	–	–	–	0.346	0.279	–	–	–	–
Fibrinogen receptor antagonist	0.533	0.033	0.424	0.073	0.380	0.092	0.499	0.044	–	–	–	–
Tumour necrosis factor alpha release inhibitor	0.493	0.009	0.469	0.009	0.477	0.009	0.456	0.010	0.540	0.007	0.524	0.007
Thiol protease inhibitor	0.451	0.016	–	–	–	–	–	–	–	–	–	–
Anticonvulsant	0.440	0.050	0.345	0.092	–	–	0.314	0.112	–	–	–	–
Dysmenorrhea treatment	0.392	0.002	0.445	0.002	0.392	0.002	0.410	0.002	0.480	0.002	0.410	0.002
Antiasthmatic	0.426	0.041	0.567	0.019	0.579	0.018	0.541	0.022	0.611	0.014	0.615	0.014
Interleukin 2 antagonist	0.377	0.004	0.416	0.004	0.361	0.004	0.383	0.004	0.566	0.003	0.488	0.003
Platelet aggregation inhibitor	0.370	0.027	0.388	0.023	0.399	0.021	0.416	0.018	0.434	0.015	0.442	0.014
Antiallergic	0.390	0.056	0.501	0.028	0.528	0.024	0.495	0.029	0.581	0.017	0.591	0.016
HIV attachment inhibitor	0.321	0.034	0.387	0.014	0.375	0.017	0.305	0.042	0.320	0.035	0.315	0.037
Interferon alpha agonist	0.335	0.049	–	–	–	–	–	–	–	–	–	–
CYP2C8 inhibitor	0.382	0.138	–	–	–	–	–	–	0.312	0.214	–	–
Kidney function stimulant	–	–	0.382	0.182	–	–	0.321	0.232	–	–	–	–
Gluconate 2-dehydrogenase (acceptor) inhibitor	–	–	–	–	0.398	0.300	–	–	–	–	–	–

1	2	3	4	5	6	7	8	9	10	11	12	13
CYP2H substrate	-	-	-	-	0.360	0.270	-	-	-	-	-	-
Platelet derived growth factor receptor kinase inhibitor	-	-	-	-	-	-	-	-	0.480	0.036	0.389	0.079
GABA receptor agonist	-	-	-	-	-	-	-	-	-	-	-	-
Antiinflammatory	-	-	-	-	-	-	-	-	-	-	-	-
Biological activity	<b>4g</b>		<b>4h</b>		<b>4i</b>		<b>4j</b>		<b>4k</b>		<b>4l</b>	
												
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Antineurotic	0.690	0.043	0.662	0.052	0.716	0.036	0.803	0.016	0.419	0.151	0.592	0.074
Erectile dysfunction treatment	0.763	0.004	0.777	0.003	0.751	0.004	0.736	0.004	0.740	0.004	0.713	0.004
Male reproductive dysfunction treatment	0.713	0.004	0.726	0.004	0.703	0.004	0.706	0.004	0.710	0.004	0.687	0.004
Phobic disorders treatment	0.476	0.187	-	-	-	-	-	-	-	-	-	-
Fibrinogen receptor antagonist	0.353	0.106	-	-	-	-	-	-	-	-	-	-
Tumour necrosis factor alpha release inhibitor	0.512	0.008	0.493	0.009	0.497	0.008	0.468	0.010	0.542	0.006	0.527	0.007
Thiol protease inhibitor	0.393	0.024	-	-	-	-	0.316	0.111	-	-	-	-
Anti-convulsant	0.431	0.053	0.338	0.097	-	-	-	-	-	-	-	-
Dysmenorrhea treatment	0.375	0.002	0.414	0.002	0.376	0.002	0.385	0.002	0.432	0.002	0.385	0.002
Antiasthmatic	0.409	0.045	0.541	0.022	0.557	0.020	0.510	0.026	0.575	0.018	0.583	0.017
Interleukin 2 antagonist	0.362	0.004	0.392	0.004	0.347	0.004	0.361	0.004	0.522	0.003	0.448	0.003
Platelet aggregation inhibitor	0.332	0.038	0.343	0.034	0.359	0.029	0.369	0.027	0.383	0.024	0.396	0.021
Antiallergic	0.383	0.058	0.487	0.030	0.513	0.026	0.477	0.033	0.554	0.020	0.566	0.019
HIV attachment inhibitor	0.337	0.028	0.397	0.012	0.385	0.014	0.325	0.033	0.339	0.027	0.333	0.029

1	2	3	4	5	6	7	8	9	10	11	12	13
Interferon alpha agonist	-	-	-	-	-	-	-	-	-	-	-	-
CYP2C8 inhibitor	0.331	0.192	-	-	-	-	-	-	-	-	-	-
Kidney function stimulant	-	-	-	-	-	-	-	-	-	-	-	-
Gluconate 2-dehydrogenase (acceptor) inhibitor	-	-	-	-	-	-	-	-	-	-	-	-
CYP2H substrate	-	-	-	-	-	-	-	-	-	-	-	-
Platelet derived growth factor receptor kinase inhibitor	-	-	0.348	0.112	0.321	0.139	0.345	0.114	0.510	0.028	0.426	0.058
GABA receptor agonist	0.317	0.025	0.313	0.026	-	-	-	-	-	-	-	-
Antiinflammatory	-	-	-	-	0.301	0.159	-	-	0.306	0.155	0.308	0.153

Results of investigation *in silico* by GUSAR software gave the possibility to predict acute toxicity values for different routes of administration of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides **4a-l** (Table 3). The values LD<sub>50</sub> by oral administration were between 511 to 1795 mg/kg, by

subcutaneous – 1057 to 3045 mg/kg. The values LD<sub>50</sub> by intravenous administration were between 94 to 215 mg/kg, and by intraperitoneal – were between 315 to 769 mg/kg. The data obtained indicate that compounds **4a-l** are slightly toxic (class 4) or practically nontoxic (class 5) [24, 26].

Table 3

The values of acute toxicity of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides **4a-l** [26]

Compound code	R	LD <sub>50</sub> , mg/kg			
		Oral administration	Subcutaneous administration	Intravenous administration	Intraperitoneal administration
4a	R1=Ph; R2= <i>i</i> -C <sub>5</sub> H <sub>11</sub>	633	1361	94	425
4b	R1=Ph; R2=4-MeBn	1795	1798	143	497
4c	R1=Ph; R2=4-MeOBn	512	1057	177	654
4d	R1=Ph; R2=Ph(CH <sub>2</sub> ) <sub>3</sub>	998	1469	121	456.
4e	R1=Ph; R2=3-MePh	995	1695	210	507
4f	R1=Ph; R2=3-MeOPh	970	1840	202	672
4g	R1=4-FPh; R2= <i>i</i> -C <sub>5</sub> H <sub>11</sub>	693	1393	115	455
4h	R1=4-FPh; R2=4-MeBn	1119	1686	216	651
4i	R1=4-FPh; R2=4-MeOBn	603	3543	148	341
4j	R1=4-FPh; R2=Ph(CH <sub>2</sub> ) <sub>3</sub>	805	1760	189	316
4k	R1=4-FPh; R2=3-MePh	1668	2045	186	769
4l	R1=4-FPh; R2=3-MeOPh	589	1763	187	353

**7. Conclusions**

According to the result of computer prediction of the biological activity spectrum and acute toxicity of 4-aryl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamides the selection of slightly toxic or nontoxic substances with the potential antineurotic activi-

ty, and perspective for male reproductive and erectile dysfunction treatment has been performed.

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## SYNTHESIS OF THE ROW OF NEW FUNCTIONAL DERIVATIVES OF 7-ARYLALKYL -8-HYDRAZINE THEOPHYLLINES

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*Hydrazine functional derivatives are widely used in medical practice as remedies applied for pharmacotherapy of depression, infection diseases, hypertension, diabetes, etc. It is worth mentioning that among obtained 7-R-8-hydrazine derivatives of 1,3-dimethylxantine promising substances have been identified. Due to the fact that literature sources display only results of occasional studies of the reactions between 7-R-8-hydrazine theophyllines and mono- or dicarbonyl substances, the use of other keto reagents for xanthine bicycle at 8<sup>th</sup> position functionalization will allow to explore synthetic potential of the last one, and with high probability may lead to obtaining original biologically active substances.*

**Aim.** To study types of reaction between 8- hydrazinyl-1,3-dimethyl-7-aryl alkyl-1H-purine-2,6(3H,7H)-diones and a number of carbonyl containing reagents.

**Methods.** A nucleophilic addition reaction followed by dehydration or ethanol splitting was used, as well as the complex of the modern analysis methods to confirm the structure and individuality of the synthesized substances.

**Results.** Different directions of 8-hydrazinyl-1,3,-dimethyl-7(fenetyl-, 3-phenylpropyl-, 3-phenylalyl)- 1H-purine-2,6(3H,7H)-diones chemical transformations in reactions with the appropriate carbonyl containing compounds have been studied experimentally. The structure of synthesized substances was confirmed by chromatography/mass and <sup>1</sup>H NMR spectroscopy.

**Conclusion.** The group of 7-arylalkyl-8-(3,5-R,R<sub>1</sub>-pyrazole-1-yl)theophyllines, consisting of two functionally substituted bioactive heterocycles, has been synthesized by reaction between initial substances and selected mono- and dicarbonyl compounds

**Keywords:** synthesis, 7,8-disubstituted of 1,3-dimethylxantine, hydrazine derivatives, spectral analysis methods

Функціональні похідні гідразину набули широкого застосування в медичній практиці як лікарські засоби для фармакокорекції депресії, інфекційних уражень, запальних процесів, гіпертензивних станів, цукрового діабету тощо. Варто зазначити, що серед вже одержаних 7-R-8-гідразинопохідних 1,3-диметилксантину також ідентифіковані перспективні у фармакологічному відношенні субстанції. Оскільки з літератури відомо лише про спорадичні дослідження взаємодії 7-R-8-гідразинотеофілінів з моно- та дикарбонільними сполуками, використання інших кетовмісних реагентів з метою функціоналізації 8 положення ксантинного біциклу дозволить не тільки вивчити синтетичний потенціал останнього, але може з високою вірогідністю призвести до одержання нових біологічно активних речовин.

**Мета.** Дослідити напрямки взаємодії 8-гідразиніл-1,3-диметил-7-арилалкіл-1H-пурін-2,6(3H,7H)-діонів з рядом карбонільвмісних реагентів.

**Методи.** Використано реакцію нуклеофільного приєднання з наступною дегідратацією чи відщепленням етанолу, а також комплекс сучасних спектральних методів аналізу для підтвердження структури й індивідуальності синтезованих речовин.

**Результати.** Експериментально встановлені окремі напрямки хімічних перетворень 8-гідразиніл-1,3-диметил-7-(фенетил-, 3-фенілпропіл-, 3-фенілаліл)-1H-пурін-2,6(3H,7H)-діонів в реакціях з відповідними карбонільвмісними сполуками. Структуру синтезованих речовин підтверджено даними хромато-мас-та <sup>1</sup>H ЯМР-спектрів.

**Висновки.** Ряд 7-арилалкіл-8-(3,5-R,R<sub>1</sub>-піразол-1-іл)теофілінів, що складаються з двох функціонально-заміщених біоактивних гетероциклів, синтезовані шляхом взаємодії вихідних речовин з окремими представниками моно- та дикарбонільних сполук

**Ключові слова:** синтез, 7,8-дизаміщені 1,3-диметилксантину, похідні гідразину, спектральні методи аналізу