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THE SYNTHESIS, COMPUTER PREDICTION OF THE BIOLOGICAL ACTIVITY AND THE ACUTE TOXICITY OF 1-Ar-4-*R*-[1,2,4] TRIAZOLO[4,3-*a*] QUINAZOLIN-5(4*H*)-ONES

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Key words: computer prediction; biological activity; acute toxicity; synthesis; 2-hydrazinoquinazolin-4(3H)-ones; [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones

Using the PASS programme computer prediction of the biological activity of 1-Ar-4-R-[1,2,4]triazolo[4,3-a] quinazolin-5(4H)-ones has been performed; it has allowed to identify the types of the biological activity of the compounds studied and sort out the most promising compounds 5{1-20} with the potential anti-asthmatic and anti-allergic activity. Prediction of the acute toxicity of 1-Ar-4-R-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones 5{1-20} has been carried out by the GUSAR software, which allows to refer them to slightly toxic (toxicity class 4) or practically nontoxic (toxicity class 5) substances. The synthesis of the most promising compounds 5{1-20} studied in silico for the biological activity and the acute toxicity has been conducted by interaction of the corresponding 2-hydrazinoquinazolin-4(3H)-ones 1{1-5} with imidazolides 3{1, 2} of aromatic acids 2{1, 2}, or with aromatic aldehydes 4{1, 2} followed by oxidation in the presence of $FeCl_3$. The structure of the compounds 5{1-20} synthesized has been proven by the data of the elemental analysis and ^1H NMR spectroscopy. The compounds obtained are promising objects for further investigations as slightly toxic or nontoxic substances with the potential anti-asthmatic and anti-allergic activity.

СИНТЕЗ, КОМП'ЮТЕРНЕ ПРОГНОЗУВАННЯ БІОЛОГІЧНОЇ АКТИВНОСТІ ТА ГОСТРОЇ ТОКСИЧНОСТІ 1-Ar-4-R-[1,2,4]ТРИАЗОЛО[4,3-a]ХІНАЗОЛІН-5(4H)-ОНІВ
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Ключові слова: *комп'ютерне прогнозування; біологічна активність; гостра токсичність; синтез; 2-гідразинохіназолін-4(3H)-они; [1,2,4]триазоло-[4,3-a]хіназолін-5(4H)-они*
Проведено комп'ютерне прогнозування біологічної активності віртуальної бібліотеки 1-Ar-4-R-[1,2,4] триазоло[4,3-a]хіназолін-5(4H)-онів за допомогою комп'ютерної програми PASS, що дозволило визначити напрямок біологічної активності досліджуваних сполук та виділити серед них найбільш перспективні 5{1-20} з потенційною протиастматичною та антиалергічною активністю. Комп'ютерне прогнозування гострої токсичності 1-Ar-4-R-[1,2,4]триазоло[4,3-a]хіназолін-5(4H)-онів 5{1-20} здійснено за програмним забезпеченням GUSAR, що дозволило віднести їх до малотоксичних (4 клас токсичності) або практично нетоксичних речовин (5 клас токсичності). Синтез найбільш перспективних сполук 5{1-20}, досліджених методом in silico на біологічну активність та гостру токсичність, був проведений при взаємодії відповідних 2-гідразинохіназолін-4(3H)-онів 1{1-5} з імідазолідами 3{1, 2} ароматичних кислот 2{1, 2} або з ароматичними альдегідами 4{1, 2} з наступним окисненням у присутності $FeCl_3$. Будову синтезованих сполук 5{1-20} доведено за допомогою елементного аналізу та даних ^1H ЯМР спектроскопії. Отримані сполуки є перспективними об'єктами для подальших досліджень як малотоксичні або нетоксичні речовини з потенційною протиастматичною та антиалергічною активністю.

СИНТЕЗ, КОМПЬЮТЕРНОЕ ПРОГНОЗИРОВАНИЕ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ И ОСТРОЙ ТОКСИЧНОСТИ 1-Ar-4-R-[1,2,4]ТРИАЗОЛО[4,3-a]ХИНАЗОЛИН-5(4H)-ОНОВ
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Ключевые слова: *компьютерное прогнозирование; биологическая активность; острая токсичность, синтез; 2-гидразинохиназолин-4(3H)-оны; [1,2,4]триазоло[4,3-a]хиназолин-5(4H)-оны*
Проведено компьютерное прогнозирование биологической активности виртуальной библиотеки 1-Ar-4-R-[1,2,4]триазоло[4,3-a]хиназолин-5(4H)-онов с помощью компьютерной программы PASS, что позволило определить направление биологической активности исследуемых соединений и выделить из них наиболее перспективные 5{1-20} с потенциальной противоастматической и антиаллергической активностью. Компьютерное прогнозирование острой токсичности 1-Ar-4-R-[1,2,4]триазоло[4,3-a] хиназолин-5(4H)-онов 5{1-20} проведено за счет использования программного обеспечения GUSAR, что позволило отнести их к малотоксичным (4 класс токсичности) или практически нетоксичным веществам (5 класс токсичности). Синтез наиболее перспективних соединений 5{1-20}, исследованных методом in silico на биологическую активность и острую токсичность, был проведен при взаимодействии соответствующих 2-гидразинохиназолин-4(3H)-онов 1{1-5} с имидазолидами 3{1, 2} ароматических кислот 2{1, 2} или с ароматическими альдегидами 4{1, 2} с последующим окислением в присутствии $FeCl_3$. Строение синтезированных соединений 5{1-20} доказано при помощи элементного анализа и данных ^1H ЯМР-спектроскопии. Полученные соединения являются перспективными объектами для дальнейших исследований как малотоксичные или нетоксичные вещества с потенциальной противоастматической и антиаллергической активностью.

In recent years domestic and foreign researchers pay much attention to the targeted synthesis of low toxic compounds with the expressed biological properties, and it is an important stage in development of innovative drug substances. 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 a wide range of the biological activity, attract particular interest in this direction. Among their potential pharmacologically significant properties the H1-antihistaminic [1-11], anticonvulsant [12], antibacterial [13-15], antitubercular [13, 15], antifungal [13, 14], anticancer [15], anti-asthmatic [10, 16], antiHIV [13], anti-allergic [16], anti-inflammatory [16, 17] bioactivities should be mentioned. It determines the prospects for developing synthetic approaches to fundamentally new compounds of the specified class.

The possibility to synthesize a large amount of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives leads to understanding of the necessity for the rational presynthetic selection of the most promising compounds of this class. 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 the biological activity [18] and the acute toxicity [19]; it allows to eliminate unpromising substances at the early stages of the research.

Taking into account the 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 was to conduct modelling of the virtual library of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones, to determine the most probable biological activity spectrum and the acute toxicity of the compounds studied using the PASS and GUSAR software, sort out the most promising substances and develop preparative methods for their synthesis.

Results and Discussion

For design of the virual library of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones two randomization points in position 1 and 4 of [1,2,4]triazolo-[4,3-*a*]quinazolin-5(4*H*)-one were chosen.

Analysis of the computer prediction results for the virual library of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones by the PASS software showed the possibility of searching substances possessing the anti-asthmatic and anti-allergic activity among these compounds and allowed to generate the library of the most promising compounds **5***{1-20}* for further research (Table 1) [18].

The data of computer prediction of the biological activity obtained are fully consistent with the fact that [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives are similar in their chemical structure to the chemical structures described as promising non-sedative H1-antihistaminic drugs [1-11].

The research results *in silico* by the GUSAR software gave the possbility to predict the acute toxicity values for different routes of administration of 1-Ar-4-*R*-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5***{1-20}* (Table 2). The values of LD_{50} in the intraperitoneal administration were between 391 to 960 mg/kg, when introducing intravenously they were between 91 to 251 mg/kg. The values of LD_{50} in the oral administration were between 556 to 1891 mg/kg, and when introducing subcutaneously – 405 to 2934 mg/kg [19]. The data obtained indicate that compounds **5***{1-20}* are slightly toxic (toxicity class 4) or practically non-toxic (toxicity class 5) [19, 20].

The synthesis of 1-Ar-4-*R*-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones without hydroxyls **5***{1, 4, 5, 8, 9, 12, 13, 16, 17, 20}* was carried out by interaction of the corresponding 2-hydrazinoquinazolin-4(3*H*)-ones **1***{1-5}* previously synthesized according to the improved method [21] with imidazolides **3***{1, 2}* of aromatic acids **2***{1, 2}* preliminary obtained via carbonyldiimidazole (CDI). This way allows obtaining the final products in good yields, but is not suitable for hydroxyl-containing compounds due to adverse reactions. Hydroxyl-containing compounds **5***{2, 3, 6, 7, 10, 11, 14, 15, 18, 19}* were synthesized by the reaction of 2-hydrazinoquinazolin-4(3*H*)-ones **1***{1-5}* with aromatic aldehydes **4***{1, 2}* followed by oxidation in the presense of $FeCl_3$ (Scheme).

The structures of the compounds **5***{1-20}* obtained were confirmed by the ^{1}H NMR spectroscopy data (Table 3). Formation of the [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones condenced system leads to shift of H-6 protons signals to 8.22-8.26 ppm, and it is in good correlation with the known data [22].

Experimental Part

The virtual screening for the biological activity of the virtual library of the substances studied was performed by the PASS Online web-resource. It enables to predict more than 4000 types of the biological activity with the average accuracy of more than 95% based on the analysis of the structure – activity relationships in a training set (drug substances, drug candidates being at various stages of clinical or preclinical trials, pharmacological substances and biochemical reagents, substances with the known specific toxicity data), which contains information about the structure and the biological activity of more than 300000 organic compounds [23-25].

Computer prediction of the biological activity spectrum of the virtual library of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives was performed with probability of demonstration of the specific type of the therapeutic action exceeding 50% (Pa>0.500). It al-

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Table 1

Prediction of the biological activity spectrum of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5***{1-10}* [18]

Biological activity	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
	5*{1}*		**5***{2}*		**5***{3}*		**5***{4}*		**5***{5}*		**5***{6}*		**5***{7}*		**5***{8}*		**5***{9}*		**5***{10}*	
Anti-asthmatic	0.639	0.012	0.573	0.018	0.599	0.016	0.651	0.011	0.698	0.009	0.617	0.014	0.643	0.012	0.696	0.009	0.640	0.012	0.573	0.018
Anti-allergic	0.629	0.013	0.590	0.016	0.615	0.014	0.644	0.012	0.662	0.011	0.609	0.015	0.636	0.013	0.662	0.011	0.613	0.014	0.577	0.018
Tumour necrosis factor alpha release inhibitor	–	–	–	–	–	–	0.517	0.008	0.579	0.005	–	–	0.532	0.007	0.626	0.005	0.528	0.007	–	–
CYP2A8 substrate	–	–	–	–	–	–	–	–	0.523	0.029	–	–	–	–	–	–	–	–	–	–
Tetrahydroxynaphthalene reductase inhibitor	–	–	–	–	–	–	–	–	–	–	0.589	0.009	–	–	–	–	–	–	0.522	0.013
5-O-(4-coumaroyl)-D-quinate 3′-monooxygenase inhibitor	–	–	–	–	–	–	–	–	0.527	0.073	–	–	–	–	–	–	–	–	–	–
Glycosylphosphatidylinositol phospholipase D inhibitor	–	–	–	–	–	–	–	–	0.512	0.095	–	–	–	–	–	–	–	–	–	–
Hepatic function stimulant	–	–	–	–	–	–	–	–	0.500	0.097	–	–	–	–	–	–	–	–	–	–
Phobic disorders treatment	0.681	0.085	–	–	–	–	–	–	0.516	0.165	–	–	–	–	–	–	–	–	–	–
Phosphodiesterase inhibitor	–	–	–	–	–	–	0.523	0.004	–	–	–	–	–	–	–	–	–	–	–	–
Acetylcholine neuromuscular blocking agent	–	–	–	–	–	–	0.505	0.071	–	–	–	–	–	–	–	–	–	–	–	–
Interferon alpha agonist	0.566	0.005	0.507	0.009	–	–	0.533	0.007	–	–	–	–	–	–	–	–	–	–	–	–
Histidine kinase inhibitor	–	–	0.594	0.016	0.545	0.022	–	–	–	–	0.631	0.013	0.580	0.018					0.584	0.017
Gluconate 2-dehydrogenase (acceptor) inhibitor	–	–	0.505	0.197	0.576	0.140	0.610	0.115	–	–	–	–	0.541	0.167	0.576	0.140	–	–	–	–
Aspulvinone dimethylallyl-transferase inhibitor	–	–	–	–	–	–	–	–	–	–	–	–	0.566	0.110	0.540	0.120	–	–	–	–
Chlordecone reductase inhibitor	–	–	–	–	–	–	–	–	–	–	–	–	0.502	0.083	–	–	–	–	–	–
Antineurotic	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Prediction of the biological activity spectrum of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5***{11-20}* [18]

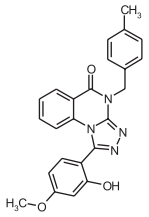
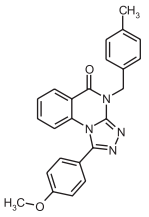
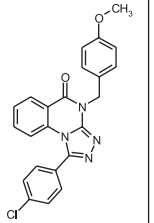
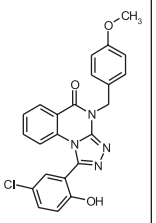
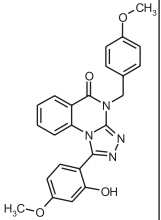
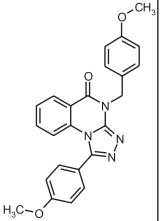
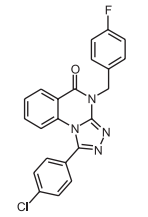
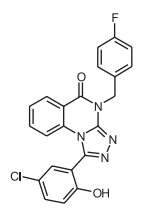
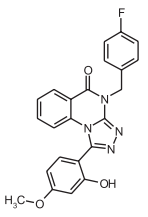
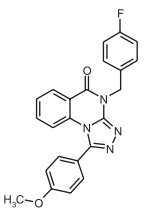
Biological activity	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
	5*{11}*		**5***{12}*		**5***{13}*		**5***{14}*		**5***{15}*		**5***{16}*		**5***{17}*		**5***{18}*		**5***{19}*		**5***{20}*	
																				
Anti-asthmatic	0.599	0.016	0.652	0.011	0.663	0.011	0.606	0.015	0.643	0.012	0.696	0.009	0.647	0.012	0.581	0.017	0.607	0.015	0.658	0.011
Anti-allergic	0.603	0.015	0.632	0.013	0.641	0.012	0.608	0.015	0.636	0.013	0.662	0.011	0.616	0.014	0.580	0.017	0.605	0.015	0.634	0.013
Tumour necrosis factor alpha release inhibitor	–	–	0.572	0.005	0.548	0.006	–	–	0.532	0.532	0.626	0.005	0.576	0.005	–	–	0.534	0.007	0.619	0.005
CYP2A8 substrate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Tetrahydroxynaphthalene reductase inhibitor	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
5-O-(4-coumaroyl)-D-quinate 3′-monooxygenase inhibitor	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Glycosylphosphatidylinositol phospholipase D inhibitor	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hepatic function stimulant	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Phobic disorders treatment	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Phosphodiesterase inhibitor	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Acetylcholine neuromuscular blocking agent	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Interferon alpha agonist	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Histidine kinase inhibitor	0.533	0.023	–	–	–	–	0.563	0.020	0.580	0.018	–	–	–	–	0.577	0.018	0.526	0.024	–	–
Gluconate 2-dehydrogenase (acceptor) inhibitor	–	–	0.522	0.182	0.661	0.080	0.630	0.101	0.541	0.167	0.576	0.140	–	–	–	–	–	–	–	–
Aspulvinone dimethylallyl-transferase inhibitor	–	–	–	–	–	–	–	–	0.566	0.110	0.540	0.120	–	–	–	–	–	–	–	–
Chlordecone reductase inhibitor	–	–	–	–	–	–	0.534	0.076	0.502	0.083	–	–	–	–	–	–	–	–	–	–
Antineurotic	–	–	–	–	0.511	0.106	–	–	–	–	–	–	0.551	0.089	–	–	–	–	0.551	0.089

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Table 2

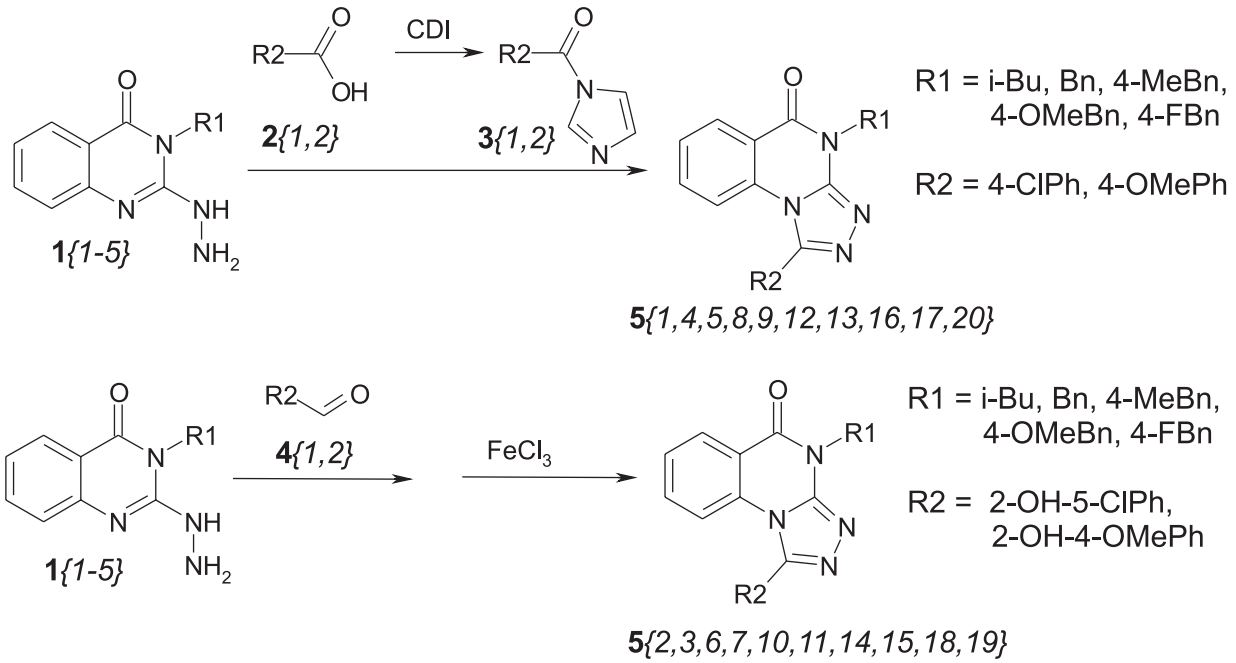
The values of acute toxicity of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5***{1-20}* according to the research results **in silico** studied by the GUSAR software [19]

Compound code	LD_{50}, mg/kg			
	Intraperitoneal administration	Intravenous administration	Oral administration	Subcutaneous administration
5*{1}*	493	130	634	1305
5*{2}*	631	112	956	1330
5*{3}*	524	125	1560	935
5*{4}*	391	91	1891	405
5*{5}*	424	181	1227	2595
5*{6}*	790	194	1155	2934
5*{7}*	614	251	1655	2314
5*{8}*	548	182	1124	1284
5*{9}*	633	164	556	2373
5*{10}*	960	165	1024	2335
5*{11}*	564	183	1189	2146
5*{12}*	643	159	1538	1111
5*{13}*	607	165	597	713.7
5*{14}*	679	190	734	1109
5*{15}*	643	222	1172	2354
5*{16}*	410	150	1010	1515
5*{17}*	609	161	976.4	1736
5*{18}*	694	194	851	2225
5*{19}*	450	239	702	707
5*{20}*	482	158	972	560

lowed to eliminate unpromising substances at the early stages of the research.

Prediction of the acute toxicity of compounds **5**{1-20} for different routes of administration (intraperitoneal, intravenous, oral, subcutaneous) was carried out by the GUSAR software [19, 26].

The training set of the programme was developed based on SYMYX MDL Toxicity Database contai-



Scheme

Table 3

Properties of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4H)-ones **5***{1-20}*

Compound code	R	Yield, %	M.p., °C	Molecular formula, m.m	N, % Calc./ found	^{1}H NMR spectral data δ, ppm, J, hz
1	2	3	4	5	6	7
5*{1}*	R1 = i-Bu R2 = 4-ClPh	87	246-248	$C_{19}H_{17}ClN_4O$ 352.82	15.88/ 15.90	0.96 d (J 7.0, 6H, $2CH_3$); 2.25-2.40 m (1H, CH); 4.08 d (J 7.0, 2H, CH_2); 7.07 d (J 7.8, 1H, H-9); 7.50 t (J 7.8, 1H, H-7); 7.58-7.78 m (5H, H-8, 2,3,5,6 Ar); 8.23 d (J 7.8, 1H, H-6)
5*{2}*	R1 = i-Bu R2 = 2-OH-5-ClPh	68	227-229	$C_{19}H_{17}ClN_4O_2$ 368.82	15.19/ 15.17	0.96 d (J 7.0, 6H, $2CH_3$); 2.25-2.40 m (1H, CH); 4.08 d (J 7.0, 2H, CH_2); 7.06 d (J 7.8, 1H, H-9); 7.18 d (J 7.8, 1H, H-3 Ar); 7.44-7.60 m (3H, H-7, 4,6 Ar); 7.72 t (J 7.8, 1H, H-8); 8.22 d (J 7.8, 1H, H-6); 10.50 c (1H, OH)
5*{3}*	R1 = i-Bu R2 = 2-OH-4-OMePh	64	214-215	$C_{20}H_{20}N_4O_3$ 364.40	15.38/ 15.40	0.96 d (J 7.0, 6H, $2CH_3$); 2.25-2.40 m (1H, CH); 3.80 c (3H, OCH_3); 4.08 d (J 7.0, 2H, CH_2); 6.54-6.68 m (2H, H-3,5 Ar); 7.22 d (J 7.8, 1H, H-9); 7.36 d (J 7.8, 1H, H-6 Ar); 7.50 t (J 7.8, 1H, H-7); 7.70 t (J 7.8, 1H, H-8); 8.22 d (J 7.8, 1H, H-6); 10.15 c (1H, OH)
5*{4}*	R1 = i-Bu R2 = 4-OMePh	81	233-234	$C_{20}H_{20}N_4O_2$ 348.40	16.08/ 16.05	0.96 d (J 7.0, 6H, $2CH_3$); 2.25-2.40 m (1H, CH); 3.86 c (3H, OCH_3); 4.08 d (J 7.0, 2H, CH_2); 7.05-7.26 m (3H, H-9, 3,5 Ar); 7.44-7.76 m (4H, H-7,8, 2,6 Ar); 8.22 d (J 7.8, 1H, H-6)
5*{5}*	R1 = Bn R2 = 4-ClPh	88	296-298	$C_{22}H_{15}ClN_4O$ 386.83	14.48/ 14.45	5.43 c (2H, CH_2); 7.07 d (J 7.8, 1H, H-9); 7.22-7.36 m (3H, H-3,4,5 Bn); 7.44-7.56 m (3H, H-7, 2,6 Bn); 7.60-7.78 m (5H, H-8, 2,3,5,6 Ar); 8.25 d (J 7.8, 1H, H-6)
5*{6}*	R1 = Bn R2 = 2-OH-5-ClPh	66	278-280	$C_{22}H_{15}ClN_4O_2$ 412.83	13.91/ 13.88	5.43 c (2H, CH_2); 7.11 d (J 7.8, 1H, H-9); 7.17 d (J 7.8, 1H, H-3 Ar); 7.24-7.36 m (3H, H-3,4,5 Bn); 7.44-7.58 m (5H, H-7, 4,6 Ar, 2,6 Bn); 7,81 t (J 7.8, 1H, H-8); 8.26 d (J 7.8, 1H, H-6); 10.50 c (1H, OH)
5*{7}*	R1 = Bn R2 = 2-OH-4-OMePh	62	269-271	$C_{23}H_{18}N_4O_3$ 398.41	14.06/ 14.03	3.80 c (3H, OCH_3); 5.43 c (2H, CH_2); 6,54-6,68 m (2H, H-3,5 Ar); 7.20-7.38 m (5H, H-9, 6 Ar, 3,4,5 Bn); 7.44-7.56 m (3H, H-7, 2,6 Bn); 7.72 t (J 7.8, 1H, H-8); 8.25 d (J 7.8, 1H, H-6); 10.17 c (1H, OH)
5*{8}*	R1 = Bn R2 = 4-OMePh	85	282-284	$C_{23}H_{18}N_4O_2$ 382.41	14.65/ 14.68	3.86 c (3H, OCH_3); 5.43 c (2H, CH_2); 7.07-7.21 m (3H, H-9, 3,5 Ar); 7.24-7.38 m (3H, H-3,4,5 Bn); 7.43-7.56 m (3H, H-7, 2,6 Bn); 7.56-7.72 m (3H, H-8, 2,6 Ar); 8.25 d (J 7.8, 1H, H-6)
5*{9}*	R1 = 4-MeBn R2 = 4-ClPh	84	288-290	$C_{23}H_{17}ClN_4O$ 400.86	13.98/ 14.01	2.24 c (3H, CH_3); 5.38 c (2H, CH_2); 7.03-7.17 m (3H, H-9, 3,5 Bn); 7.38 d (J 7.8, 2H, H-2,6 Bn); 7.52 t (J 7.8, 1H, H-7); 7.62-7.78 m (5H, H-8, 2,3,5,6 Ar); 8.25 d (J 7.8, 1H, H-6)
5*{10}*	R1 = 4-MeBn R2 = 2-OH-5-ClPh	63	268-270	$C_{23}H_{17}ClN_4O_2$ 416.86	13.44/ 13.47	2.24 c (3H, CH_3); 5.38 c (2H, CH_2); 7.00-7.22 m (4H, H-9, 3 Ar, 3,5 Bn); 7.38 d (J 7.8, 2H, H-2,6 Bn); 7.47-7.62 m (3H, H-7, 4,6 Ar); 7.72 t (J 7.8, 1H, H-8); 8.26 d (J 7.8, 1H, H-6); 10.50 c (1H, OH)
5*{11}*	R1 = 4-MeBn R2 = 2-OH-4-OMePh	62	262-264	$C_{24}H_{20}N_4O_3$ 412.44	13.58/ 13.60	2.24 c (3H, CH_3); 3.80 c (3H, OCH_3); 5.38 c (2H, CH_2); 6,54-6,68 m (2H, H-3,5 Ar); 7.12 d (J 7.8, 2H, H-3,5 Bn); 7.22 d (J 7.8, 1H, H-9); 7.32-7.45 m (3H, H-6 Ar, 2,6 Bn); 7.50 t (J 7.8, 1H, H-7); 7.72 t (J 7.8, 1H, H-8); 8.25 d (J 7.8, 1H, H-6); 10.17 c (1H, OH)
5*{12}*	R1 = 4-MeBn R2 = 4-OMePh	85	282-283	$C_{24}H_{20}N_4O_2$ 396.44	14.13/ 14.16	2.24 c (3H, CH_3); 3.86 c (3H, OCH_3); 5.38 c (2H, CH_2); 7.07-7.21 m (5H, H-9, 3,5 Ar, 3,5 Bn); 7.38 d (J 7.8, 2H, H-2,6 Bn); 7.50 t (J 7.8, 1H, H-7); 7.56-7.70 m (3H, H-8, 2,6 Ar); 8.25 d (J 7.8, 1H, H-6)
5*{13}*	R1 = 4-OMeBn R2 = 4-ClPh	88	>300	$C_{23}H_{17}ClN_4O_2$ 416.86	13.44/ 13.42	3.70 c (3H, OCH_3); 5.34 c (2H, CH_2); 6.87 d (J 7.8, 2H, H-3,5 Bn); 7.06 d (J 7.8, 1H, H-9); 7.42-7.54 m (3H, H-7, 2,6 Bn); 7.58-7.78 m (5H, H-8, 2,3,5,6 Ar); 8.24 d (J 7.8, 1H, H-6)
5*{14}*	R1 = 4-OMeBn R2 = 2-OH-5-ClPh	72	294-296	$C_{23}H_{17}ClN_4O_3$ 432.86	12.94/ 12.93	3.70 c (3H, OCH_3); 5.35 c (2H, CH_2); 6.87 d (J 7.8, 2H, H-3,5 Bn); 7.05 d (J 7.8, 1H, H-9); 7.16 d (J 7.8, 1H, H-3 Ar); 7.42-7.58 m (5H, H-7, 4,6 Ar, 2,6 Bn); 7.72 t (J 7.8, 1H, H-8); 8.24 d (J 7.8, 1H, H-6); 10.50 c (1H, OH)
5*{15}*	R1 = 4-OMeBn R2 = 2-OH-4-OMePh	70	288-289	$C_{24}H_{20}N_4O_4$ 428.44	13.08/ 13.11	3.70 c (3H, OCH_3-Bn); 3.80 c (3H, OCH_3-Ar); 5.33 c (2H, CH_2); 6.54-6.68 m (2H, H-3,5 Ar); 6.87 d (J 7.8, 2H, H-3,5 Bn); 7.22 d (J 7.8, 1H, H-9); 7.34 d (J 7.8, 1H, H-6 Ar); 7.42-7.58 m (3H, H-7, 2,6 Bn); 7.72 t (J 7.8, 1H, H-8); 8.24 d (J 7.8, 1H, H-6); 10.48 c (1H, OH)
5*{16}*	R1 = 4-OMeBn R2 = 4-OMePh	86	>300	$C_{24}H_{20}N_4O_3$ 412.44	13.58/ 13.61	3.70 c (3H, OCH_3-Bn); 3.88 c (3H, OCH_3-Ar); 5.37 c (2H, CH_2); 6.87 d (J 7.8, 2H, H-3,5 Bn); 7.15-7.26 m (3H, H-9, 3,5 Ar); 7.44-7.54 m (3H, H-7, 2,6 Bn); 7.58-7.76 m (3H, H-8, 2,6 Ar); 8.24 d (J 7.8, 1H, H-6)

Continuation of the Table 3

1	2	3	4	5	6	7
5*{17}*	R1 = 4-FBn R2 = 4-ClPh	91	>300	$C_{22}H_{14}ClFN_4O$ 404.82	13.84/ 13.82	5.43 c (2H, CH_2); 7.04-7.22 m (3H, H-9, 3,5 Bn); 7.48-7.60 m (3H, H-7, 2,6 Bn); 7.62-7.78 m (5H, H-8, 2,3,5,6 Ar); 8.25 d (J 7.8, 1H, H-6)
5*{18}*	R1 = 4-FBn R2 = 2-OH-5-ClPh	70	>300	$C_{22}H_{14}ClFN_4O_2$ 420.82	13.31/ 13.28	5.43 c (2H, CH_2); 7.08 d (J 7.8, 1H, H-9); 7.14-7.21 m (3H, H-3 Ar, 3,5 Bn); 7.44-7.62 m (5H, H-7, 4,6 Ar, 2,6 Bn); 7.73 t (J 7.8, 1H, H-8); 8.26 d (J 7.8, 1H, H-6); 10.44 c (1H, OH)
5*{19}*	R1 = 4-FBn R2 = 2-OH-4-OMePh	66	296-298	$C_{23}H_{17}FN_4O_3$ 416.41	13.45/ 13.48	3.80 c (3H, OCH_3); 5.40 c (2H, CH_2); 6.52-6.68 m (2H, H-3,5 Ar); 7.07-7.26 m (3H, H-9, 3,5 Bn); 7.35 d (J 7.8, 1H, H-6 Ar); 7.48-7.62 m (3H, H-7, 2,6 Bn); 7.72 t (J 7.8, 1H, H-8); 8.24 d (J 7.8, 1H, H-6); 10.17 c (1H, OH)
5*{20}*	R1 = 4-FBn R2 = 4-OMePh	88	>300	$C_{23}H_{17}FN_4O_2$ 400.41	13.99/ 14.02	3.86 c (3H, OCH_3); 5.38 c (2H, CH_2); 7.07-7.22 m (5H, H-9, 3,5 Ar, 3,5 Bn); 7.45-7.74 m (6H, H-7,8, 2,6 Ar, 2,6 Bn); 8.24 d (J 7.8, 1H, H-6)

ning information about the acute toxicity of more than 10000 chemical structures. The baseline information regarding the acute toxicity of the compounds under study are presented by LD_{50} values (log 10 (mmol/kg) and mg/kg) and the toxicity class according to the OECD classification project of chemical substances by acute toxicity values [19, 20].

The ^{1}H NMR-spectra of compounds **5***{1-20}* were recorded on a Varian WXR-400 (200 MHz) spectrometer in DMSO-d6 solution with TMS as an internal standard, chemical shifts were reported in ppm. Melting points were measured with a Buchi B-520 melting point apparatus. Elemental analysis was performed on an Euro EA-3000 apparatus. Starting 2-hydrazinoquinazolin-4(3*H*)-ones **1***{1-5}* were obtained according to the method [21].

The general procedure for the synthesis of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones 5*{1, 4, 5, 8, 9, 12, 13, 16, 17, 20}*. Dissolve the mixture of 1.5 mmol of the corresponding acid **2***{1, 2}* and 0.24 g (1.5 mmol) of carbonyldiimidazole (CDI) in 5 ml of anhydrous DMFA. Heat the solution at 100°C for 1 h, then add 1 mmol of the corresponding 2-hydrazinoquinazolin-4(3*H*)-one **1***{1-5}*. Reflux the reaction mixture for 24 h. After cooling dilute the reaction mixture with 10 ml of water. The next day filter the precipitate formed, wash with 20 ml of *i*-propanol and recrystallize from the mixture of 5 ml of DMFA and 10 ml of *i*-propanol. Yields and ^{1}H NMR data are given in Table 3.

The general procedure for the synthesis of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones 5*{2, 3, 6, 7, 10, 11, 14, 15, 18, 19}*. Heat the solution of 1 mmol of the corresponding 2-hydrazinoquinazolin-4(3*H*)-one **1***{1-5}* and 1 mmol of the corresponding salicylic aldehyde **4***{1, 2}* in 5 ml of anhydrous DMFA at 100°C for 2 h, then add the solution of 0.54 g (2 mmol) $FeCl_3 \cdot 6\ H_2O$ in 5 ml of DMFA. Heat the reaction mixture at 130°C for 4 hs. After cooling dilute the reaction mixture with 10 ml of water. The next day filter the precipitate formed, wash with 20 ml of *i*-propanol and recrystallize from the mixture of 5 ml of DMFA and 10 ml of *i*-propanol. Yields and ^{1}H NMR data are given in Table 3.

Conclusions

According to the result of computer prediction of the biological activity spectrum and the acute toxicity of 1-Ar-4-R-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones the selection of slightly toxic or nontoxic substances with the potential anti-asthmatic and anti-allergic activity has been performed.

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