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RESEARCH ARTICLE

Directed Search of Anti-inflammatory Agents Among (3*H*-Quinazoline-4-ylidene)hydrazides of *N*-protected Amino acids and their Heterocyclization Products

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Abstract: ***Background*:** (Quinazoline-4-ylidene)hydrazides are valued intermediates in modern organic chemistry, as they are commonly used for the synthesis of substituted [1,2,4]triazolo[1,5-*c*]quinazolines.

***Objective*:** Unknown *N*-acyl-2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)-alkyl-(alkaryl-, aryl-)amines were synthesized and evaluated for anti-inflammatory potential.

***Methods*:** The peculiarities of the synthesized compounds structures were studied by IR-, NMR spectroscopy and chromatography-mass spectrometry and were discussed in detail. Probable molecular mechanisms of activity (inhibition of COX-1 and COX-2) were predicted due to molecular docking. Anti-inflammatory activity of synthesized compounds was determined by their ability to reduce the formalin-induced paw edema in rats. Diclofenac sodium was used as reference drug.

***Results*:** In this study, the synthesis of *N*-acetyl-(benzoyl)-2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)alkyl-(aralkyl-, aryl-)amines, using (3*H*-quinazoline-4-ylidene)hydrazides of *N*-protected amino acids or 4-hydrazinoquinazoline and *N*-prorotected amino acids as starting compounds was developed. It was established that the reaction of (3*H*-quinazoline-4-ylidene)hydrazides of *Boc*-amino acids occurred with the formation of *N*-acetyl-substituted triazoloquinazolines. High anti-inflammatory activity was detected for unknown (3*H*-quinazoline-4-ylidene)hydrazides *Boc*-amino acids (**1.13-1.15**) and *N*-acetyl-(benzoyl)-2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)aralkyl-(aryl-)amines (**3.2**, **3.3**, **3.11, 3.12)**, using the experimental formalin test.

***Conclusion*:** The conducted SAR-analysis allowed to detect critical fragments. Namely, the *Boc*-aminoaralkyl-(aryl-)acid residue in (3*H*-quinazoline-4-ylidene)hydrazides (**1.13-1.15**), benzyl and phenyl linker groups in *N*-acetyl-(benzoyl)-2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)aralkyl-(aryl-) amines (**3.2**, **3.3**, **3.11**, **3.12**) are believed to be substantial for anti-inflammatory activity.

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1. INTRODUCTION

(Quinazoline-4-ylidene)hydrazides have interesting properties, that let them be used as effective reagents for the construction of novel 2-aminoalkyl-(alkaryl-, aryl-)[1,2,4]triazolo[1,5-*c*]quinazolines. Heterocyclization of the corresponding hydrazides of aliphatic, aromatic and heterocyclic acids in high boiling solvents under catalysis or thermolysis [1-7] are examples of the above mentioned tricyclic system synthesis.

Due to the widespread using of modern *in silico* technologies and molecular biology methods, it was established that quinazolines and triazolo [*c*]quinazolines have an affinity to adenosine, benzodiazepine, NMDA, AMPA, KA, 5-HT3, tyrosinekinase, Syk-kinase and PARP-1 receptors. Also, they are inhibitors of phosphodiesterase 10A (PDE10A), EGF-induced ERK1/2 phosphorylation, P14KIIIα and HCV replication, dihydrophолate reductase, glucosidase, SUMO E1, topoisomerases, thymidylate syntase, *etc*. [8-24] and may exhibit a versatile biological activity. Thus, drugs and biologically active substances with anticancer, anti-hepatitis, antidepressant, anticonvulsant, anti-inflammatory, analgesic, antimicrobial, antiviral, anti-tubercular, antioxidant and antifungal activity [6-24] were found among these derivatives.

Despite the fact that a considerable number of works were devoted to the synthesis, properties and application of (quinazoline-4-ylidene)hydrazides of *N*-protected amino acids, till nowadays, the heterocyclization of the last ones has not been sufficiently studied [25]. As we consider, the presence of amino acid moieties in the mentioned hydrazides molecules will have a positive effect on their biological activity and extend the range of their application in the synthesis of unknown 2-alkyl-(alkaryl-, aryl-)amino-substituted triazolo [1,5-*c*]quinazolines. Moreover, the combination of heterocycles with amino acid residues resulted in the appearance of new pharmacological activity types or the enhanced known ones [26-30].

Thus, this work aims towards the directed search of anti-inflammatory agents among (quinazoline-4-ylidene)hydrazides of *N*-protected amino acids and products of their heterocyclization; as well as the establishment of structure-activity relationship for further optimization of the structure.

2. MATERIALS AND METHODS

2.1. Chemistry

Melting points were determined in open capillary tubes in a Stuart SMP30 apparatus and were uncorrected. The elemental analyses (C, H, N) were performed using the ELEMENTAR vario EL cube analyzer. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometer with TMS as internal standard in DMSO-d_6 solution. LC/MS spectra were recorded using chromatography-mass-spec-trometer, which consists of high-performed liquid chromatograph Agilent 1100 Series equipped with diode-matrix and mass-selective detector Agilent LC/MSD SL (atmospheric pressure chemical ionization - APCI). Ionization mode was a concurrent scanning of positive and negative ions in the mass range 80-1000 m/z.

Synthetic studies were conducted according to the general approach to the search of potential biologically active substances, using reagents of companies: Sigma-Aldrich (Missouri, USA) and Enamine Ltd (Kyiv, Ukraine).

2.2. General Method

(3*H*-Quinazoline-4-ylidene)hydrazides of *N*-protected aminoacids (**1.1**-**1.15**) were synthesized according to the known methods and their constants correspond to the literature [25]. Other starting materials and solvents were obtained from commercially available sources and were used without additional purification.

2.2.1. The General Procedure for the Synthesis of N-substituted 2-([1,2,4]triazolo[1,5-c]quinazoline-2-yl-)-alkyl-(alkaryl-, aryl-)amines (3.1-3.20)

Method A: The suspension of 0.01 mole of the corresponding (3*H*-quinazoline-4-ylidene)hydrazides of *N*-acylamino acids (**1.1**-**1.12**) in 15 ml of acetic acid was refluxed for 3-4 h. The solvent was evaporated under vacuum. After that, 5 ml of methanol was added to the dry residue and was dispersed. The resulting precipitate was filtered. If it was necessary, the precipitate was crystallized

from methanol. Cyclization of compounds **1.13-1.15** yielded corresponding acetyl derivatives **3.1-3.3** as a result of re-acylation.

Method B: To the suspension of 0.01 mole of the corresponding acyl(*Boc*)amino acid in 30 ml of dioxane, 1.62 g (0.01 mole) of *N,N'*-carbonyldiimidazole was added. The mixture formed was kept at temperature 60-70°C for 60 min until the carbon dioxide was completely released. Then, 1.6 g (0.01 mole) of 4-hydrazinoquinazoline (**1.0**) was added and the mixture was kept at ambient temperature overnight or at 80°C for 1.5 h. Solvent was evaporated under vacuum, then 20 ml of acetic acid was added to form a solution, that was refluxed for 3-4 h. Acetic acid was evaporated under vacuum and the residue was dispersed with aqueous methanol. The resulting precipitate was filtered. If it was necessary, the precipitate was crystallized from methanol.

2.2.2. N-([1,2,4]Triazolo[1,5-c]quinazoline-2-ylmethyl)acetamide (3.1)

Yield- 45.6% (Method A), 81.9% (Method B); m.p. 211-213°C; IR (cm^{-1}): 3291, 1645, 1623, 1562, 1523, 1494, 1364, 1292, 1248, 1035, 900, 770, 687, 611; ^{1}H NMR, δ (ppm): 9.43 (s, 1H, H-5), 8.45 (d, *J* = 7.8 Hz, 1H, H-10), 8.40 (t, *J* = 5.7 Hz, 1H, NH), 8.03 (d, *J* = 8.1 Hz, 1H, H-7), 7.88 (t, *J* = 7.2 Hz, 1H, H-8), 7.78 (t, *J* = 7.3 Hz, 1H, H-9), 4.57 (d, *J* = 5.8 Hz, 2H, CH_2), 1.93 (s, 3H, CH_3); ^{13}C NMR, δ (ppm): 169.79 (CO), 165.41 (C-2), 150.78 (C-5), 142.71 (C-10b), 139.27 (C-6a), 132.69 (C-8), 129.53 (C-7), 128.94 (C-9), 123.61 (C-10), 117.84 (C-10a), 37.15 (-CH_2-), 22.95 (-CH_3); LC-MS, m/z = 241 [M+1]; Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03; Found: C, 59.79; H, 4.65; N, 29.09.

2.2.3. N-(3-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)benzyl)acetamide (3.2)

Yield- 51.5% (Method A), 84.5% (Method B); m.p. 277-280°C; IR (cm^{-1}): 3258, 1631, 1552, 1479, 1447, 1422, 1357, 1249, 1123, 898, 847, 777, 750, 727, 637; ^{1}H NMR, δ (ppm): 9.48 (s, 1H, H-5), 8.56 (d, *J* = 7.7 Hz, 1H, H-10), 8.31 - 8.18 (m, 3H, 2-Ar H-2,6, NH), 8.06 (d, *J* = 8.2 Hz, 1H, H-7), 7.90 (t, *J* = 7.8 Hz, 1H, H-8), 7.81 (t, *J* = 7.3 Hz, 1H, H-9), 7.44 (d, *J* = 8.0 Hz, 2H, 2-Ar H-3,5), 4.35 (d, *J* = 5.8 Hz, 2H, CH_2), 1.92 (s, 3H, CH_3); ^{13}C NMR, δ (ppm): 169.75 (CO), 163.93 (C-2), 151.20 (C-5), 142.90 (C-10b), 139.42 (C-6a), 137.00 (C-4, 2-Ar), 132.73 (C-8), 129.51 (C-1, 2-Ar), 128.99 (C-7), 128.75 (C-9), 128.29 (C-3,5, 2-Ar), 127.50 (C-2,6, 2-Ar), 123.81 (C-10), 117.99 (C-10a), 42.41 (-CH_2-), 23.06 (CH_3); LC-MS, m/z = 317 [M+1]; Anal. Calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07; Found: C, 68.21; H, 4.82; N, 22.13.

2.2.4. N-(3-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)phenyl)acetamide (3.3)

Yield- 51.9% (Method A), 63.5% (Method B); m.p. 290-292°C; IR (cm^{-1}): 3248, 1663, 1598, 1511, 1476, 1443, 1410, 1359, 1314, 1252, 899, 836, 772, 751, 714; ^{1}H NMR, δ (ppm): 9.98 (s, 1H, NH), 9.45 (s, 1H, H-5), 8.53 (d, *J* = 7.9 Hz, 1H, H-10), 8.20 (d, *J* = 8.4 Hz, 2H, 2-Ar H-2,6), 8.04 (d, *J* = 8.1 Hz, 1H, H-7), 7.89 (t, *J* = 7.3 Hz, 1H, H-8), 7.84-7.64 (m, 3H, H-9, 2-Ar H-3,5), 2.10 (s, 3H, CH_3); ^{13}C NMR, δ (ppm): 169.10 (CO), 159.32 (C-2), 151.15 (C-5), 142.88 (C-10b), 141.97 (C-4, 2-Ar), 139.37 (C-6a), 132.67 (C-8), 129.46 (C-7), 128.96 (C-9), 128.21 (C-2,3,5,6; 2-Ar), 123.78 (C-10), 119.49 (C-1, 2-Ar), 117.97 (C-10a), 24.58 (CH_3); LC-MS, m/z = 303 [M+1]; Anal. Calcd. for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09; Found: C, 67.38; H, 4.38; N, 23.13.

2.2.5. N-([1,2,4]Triazolo[1,5-c]quinazoline-2-ylmethyl)benzamide (3.4)

Yield- 41.2% (Method A), 50.3% (Method B); m.p. 215-216°C; IR (cm^{-1}): 3271, 1639, 1543, 1367, 1297, 1248, 902, 771, 717, 689; ^{1}H NMR, δ (ppm): 9.43 (s, 1H, H-5), 9.02 (t, *J* = 5.1 Hz, 1H, NH), 8.46 (d, *J* = 7.9 Hz, 1H, H-10), 8.03 (d, *J* = 8.1 Hz, 1H, H-7), 7.95 (d, *J* = 7.6 Hz, 2H, 2-Ar H-2,6), 7.87 (t, *J* = 7.8 Hz, 1H, H-8), 7.77 (t, *J* = 7.4 Hz, 1H, H-9), 7.55-7.32 (m, 3H, 2-Ar H-3,5), 4.81 (d, *J* = 5.4 Hz, 2H, CH_2); LC-MS, m/z = 303 [M+1]; Anal. Calcd. for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09; Found: C, 67.39; H, 4.37; N, 23.11.

2.2.6. N-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)ethyl)benzamide (3.5)

Yield- 75.6% (Method A), 69.4% (Method B); m.p. 227-229°C; IR (cm^{-1}): 3249, 1629, 1491, 1380, 1330, 1120, 777, 696; ^{1}H NMR, δ (ppm): 9.43 (s, 1H, H-5), 8.78 (d, *J* = 7.7 Hz, 1H, NH),

8.47 (d, *J* = 7.9 Hz, 1H, H-10), 8.03 (d, *J* = 8.2 Hz, 1H, H-7), 7.95 (d, *J* = 7.6 Hz, 2H, 2-Ar H-2,6), 7.87 (t, *J* = 7.6 Hz, 1H, H-8), 7.77 (t, *J* = 7.5 Hz, 1H, H-9), 7.55-7.32 (m, 3H, 2-Ar H-3,4,5), 5.53 (m, *J* = 7.4 Hz, 1H, -CHCH$_3$), 1.73 (d, *J* = 7.0 Hz, 3H, CH$_3$); LC-MS, m/z = 317 [M+1]; Anal. Calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07; Found: C, 68.18; H, 4.81; N, 22.12.

2.2.7. N-(2-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)ethyl)benzamide (3.6)

Yield- 82.1% (Method A), 74.6% (Method B); m.p. 137-140°C; IR (cm^{-1}): 1625, 1535, 1487, 1308, 901, 770, 692; ^{1}H NMR, δ (ppm): 9.39 (s, 1H, H-5), 8.62-8.52 (m, 1H, NH), 8.46 (d, *J* = 8.4 Hz, 1H, H-10), 8.03 (d, *J* = 8.2 Hz, 1H, H-7), 7.95-7.80 (m, 3H, 2-Ar H-2,6, H-8), 7.77 (t, *J* = 7.5 Hz, 1H, H-9), 7.54-7.35 (m, 3H, 2-Ar H-3,5,6), 3.80 (q, *J* = 7.0 Hz, 2H, NHCH$_2$CH$_2$), 3.21 (t, *J* = 7.2 Hz, 2H, NHCH$_2$CH$_2$); LC-MS, m/z = 317 [M+1]; Anal. Calcd. for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07; Found: C, 68.21; H, 4.83; N, 22.13.

2.2.8. N-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)-2-methylpropyl)benzamide (3.7)

Yield- 63.3% (Method A), 53.7% (Method B); m.p. 117-118°C; IR (cm^{-1}): 1642, 1519, 753, 691; ^{1}H NMR, δ (ppm): 9.44 (s, 1H, H-5), 8.67 (d, *J* = 8.6 Hz, 1H, NH), 8.57 (d, *J* = 8.6 Hz, 1H, H-10), 8.03 (d, *J* = 8.3 Hz, 1H, H-7), 7.92 (d, *J* = 6.9 Hz, 3H, 2-Ar H-2,6, H-8), 7.83-7.72 (t, *J* = 8.6 Hz, 1H, H-9), 7.63-7.36 (m, 3H, 3-Ar H-3,4,5), 5.25 (t, *J* = 8.4 Hz, 1H, CHCH(CH$_3$)$_2$), 2.46-2.24 (m, 1H, CHCH(CH$_3$)$_2$), 1.19-1.03 (m, 6H, CHCH(CH$_3$)$_2$); LC-MS, m/z = 345 [M+1]; Anal. Calcd. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28; Found: C, 69.62; H, 5.62; N, 20.32.

2.2.9. N-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)-3-methylbutyl)benzamide (3.8)

Yield- 66.4% (Method A); m.p. 167-169; IR (cm^{-1}): 1633, 1547, 1486, 1363, 899, 769, 692; ^{1}H NMR, δ (ppm): 9.42 (s, 1H, H-5), 8.73 (d, *J* = 8.4 Hz, 1H, NH), 8.46 (d, *J* = 8.0 Hz, 1H, H-10), 8.02 (d, *J* = 8.2 Hz, 1H, H-7), 7.95 (d, *J* = 7.5 Hz, 2H, 2-Ar H-2,6), 7.87 (t, *J* = 7.6 Hz, 1H, H-8), 7.76 (t, *J* = 7.6 Hz, 1H, H-9), 7.52-7.32 (m, 3H, 2-Ar H-3,4,5), 5.52 (dq, *J* = 9.3, 5.6 Hz, 1H, CHCH$_2$ CH(CH$_3$)$_2$), 2.13-1.55 (m, 3H, CHCH$_2$CH(CH$_3$)$_2$), 1.04 (d, *J* = 6.3 Hz, 6H, CHCH$_2$CH(CH$_3$)$_2$); ^{13}C NMR, δ (ppm): 168.92 (CO), 166.57 (C-2), 150.70 (C-5), 142.71 (C-10b), 139.36 (C-6a), 134.61 (C-1; 2-Ar), 132.64 (C-8), 131.75 (C-1; 2-Ar), 129.48 (C-7), 128.95 (C-9), 128.67 (C-3,5; 2-Ar), 127.99 (C-2,6; 2-Ar), 123.65 (C-10), 117.91 (C-10a), 46.80 (-CHCH$_2$CH(CH$_3$)$_2$), 42.91 (CHCH$_2$CH (CH$_3$)$_2$), 24.98 (CHCH$_2$CH(CH$_3$)$_2$), 23.35/22.08 (CHCH$_2$CH(CH$_3$)$_2$); LC-MS, m/z = 359 [M+1]; Anal. Calcd. for $C_{21}H_{21}N_5O$: C, 70.17; H, 5.89; N, 19.48; Found: C, 70.21; H, 5.92; N, 19.51.

2.2.10. N-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)-2-phenylethyl)benzamide (3.9)

Yield- 43.2% (Method A); m.p. 218-220°C; IR (cm^{-1}): 1631, 1545, 1488, 899, 773, 748, 689; ^{1}H NMR, δ (ppm): 9.45 (s, 1H, H-5), 8.89 (d, *J* = 8.4 Hz, 1H, NH), 8.49 (d, *J* = 7.9 Hz, 1H, H-10), 8.04 (d, *J* = 8.2 Hz, 1H, H-7), 7.93-7.82 (m, 3H, H-8 COAr H-2,6), 7.78 (t, *J* = 7.7 Hz, 1H, H-9), 7.56-7.03 (m, 8H, COAr H-3,4,5, CH$_2$Ar H-2,3,4,5,6), 5.66 (td, *J* = 9.2, 5.3 Hz, 1H, -CHCH$_2$), 3.65-3.30 (m, 2H, -CHCH$_2$); LC-MS, m/z = 393 [M+1]; Anal. Calcd. for $C_{24}H_{19}N_5O$: C, 73.27; H, 4.87; N, 17.80; Found: C, 73.33; H, 4.90; N, 17.86.

2.2.11. N-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)-3-(methylthio)propyl)benzamide (3.10)

Yield- 58.9% (Method A); m.p. 148-150°C; IR (cm^{-1}): 1637, 1522, 1486, 1364, 900, 776, 724, 693; ^{1}H NMR, δ (ppm): 9.44 (s, 1H, H-5), 8.84 (d, *J* = 8.1 Hz, 1H, NH), 8.47 (d, *J* = 7.8 Hz, 1H, H-10), 8.03 (d, *J* = 8.3 Hz, 1H, H-7), 7.96 (d, *J* = 7.2 Hz, 2H, 2-Ar H-2,6), 7.87 (t, *J* = 7.7 Hz, 1H, H-8), 7.77 (t, *J* = 7.7 Hz, 1H, H-9), 7.61-7.34 (m, 3H, 2-Ar H-3,4,5), 5.56 (q, *J* = 7.8 Hz, 1H, CHCH$_2$ CH$_2$S), 2.65 (dt, *J* = 13.7, 6.5 Hz, 2H, CHCH$_2$ CH$_2$S), 2.41-2.28 (m, 2H, CHCH$_2$CH$_2$S), 2.13 (s, 3H, CH$_3$); LC-MS, m/z = 377 [M+1]; Anal. Calcd. for $C_{20}H_{19}N_5OS$: C, 63.64; H, 5.07; N, 18.55; Found: C, 63.67; H, 5.12; N, 18.63.

2.2.12. N-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)benzyl)benzamide (3.11)

Yield- 59.1% (Method A); m.p. 193-194°C; IR (cm^{-1}): 1614, 1536, 1475, 1388, 1310, 753, 686; ^{1}H NMR, δ (ppm): 9.45 (s, 1H, H-5), 8.51 (d, *J* = 7.7 Hz, 1H, H-10), 8.31-8.18 (m, 3H, 2-Ar H-2,6, NH), 8.14 (d, *J* = 8.2 Hz, 1H, H-7), 7.84 (t, *J* = 7.8 Hz, 1H, H-8), 7.76 (t, *J* = 7.3 Hz, 1H, H-9), 7.56-7.32 (m, 7H, 2-Ar H-3,5, PhC(O)-), 4.35 (m, 2H, -

CH_2-); LC-MS, m/z = 379 [M+1]; Anal. Calcd. for $C_{23}H_{17}N_5O$: C, 72.81; H, 4.52; N, 18.46; Found: C, 72.87; H, 4.58; N, 18.52.

2.2.13. N-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)phenyl)benzamide (3.12)

Yield- 72.3% (Method A); m.p. 281-283°C; IR (cm^{-1}): 1661, 1512, 771, 749; ^{1}H NMR, δ (ppm): 9.99 (s, 1H, NH), 9.47 (s, 1H, H-5), 8.53 (d, *J* = 7.0 Hz, 1H, H-10), 8.20 (d, *J* = 6.8 Hz, 2H, 2-Ar H-2,6), 8.04 (d, *J* = 8.8 Hz, 1H, H-7), 7.90 (t, *J* = 8.8 Hz, 1H, H-8), 7.85-7.56 (m, 8H, H-9, 2-Ar H-3,5, PhC(O)-); LC-MS, m/z = 365 [M+1]; Anal. Calcd. for $C_{22}H_{15}N_5O$: C, 72.32; H, 4.14; N, 19.17; Found: C, 72.39; H, 4.19; N, 19.21.

2.2.14. N-(3-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)propyl)acetamide (3.13) (Obtained Without the Isolation of Intermediate Hydrazide)

Yield- 61.9% (Method B); m.p. 148-152°C; IR (cm^{-1}): 3263, 1623, 1553, 1520, 1494, 1363, 1290, 1103, 900, 707; ^{1}H NMR, δ (ppm): 9.35 (s, 1H, H-5), 8.42 (d, *J* = 7.8 Hz, 1H, H-10), 8.01 (d, *J* = 8.2 Hz, 1H, H-7), 7.86 (t, *J* = 7.5 Hz, 1H, H-8), 7.75 (t, *J* = 7.5 Hz, 1H, H-9), 7.72 (t, 1H, NH), 3.20 (q, *J* = 6.4 Hz, 2H, $CH_2CH_2\underline{CH_2}NH$), 2.94 (t, *J* = 7.6 Hz, 2H, $\underline{CH_2}CH_2CH_2NH$), 2.00 (q, *J* = 7.0 Hz, 2H, $CH_2\underline{CH_2}CH_2NH$), 1.82 (s, 3H, CH_3); LC-MS, m/z = 269 [M+1]; Anal. Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01; Found: C, 62.51; H, 5.67; N, 26.09.

2.3. Molecular Docking

The research was conducted by flexible molecular docking, as an approach of finding molecules with affinity to a specific biological target. Macromolecules from Protein Data Bank (PDB) were used as biological targets, namely COX-1 enzyme (PDB ID - 3N8Y) and COX-2 (PDB ID - 3LN1) [31]. The choice of biological targets was due to the literature on the mechanism of action of anti-inflammatory drugs [32].

2.3.1. Ligand Preparation

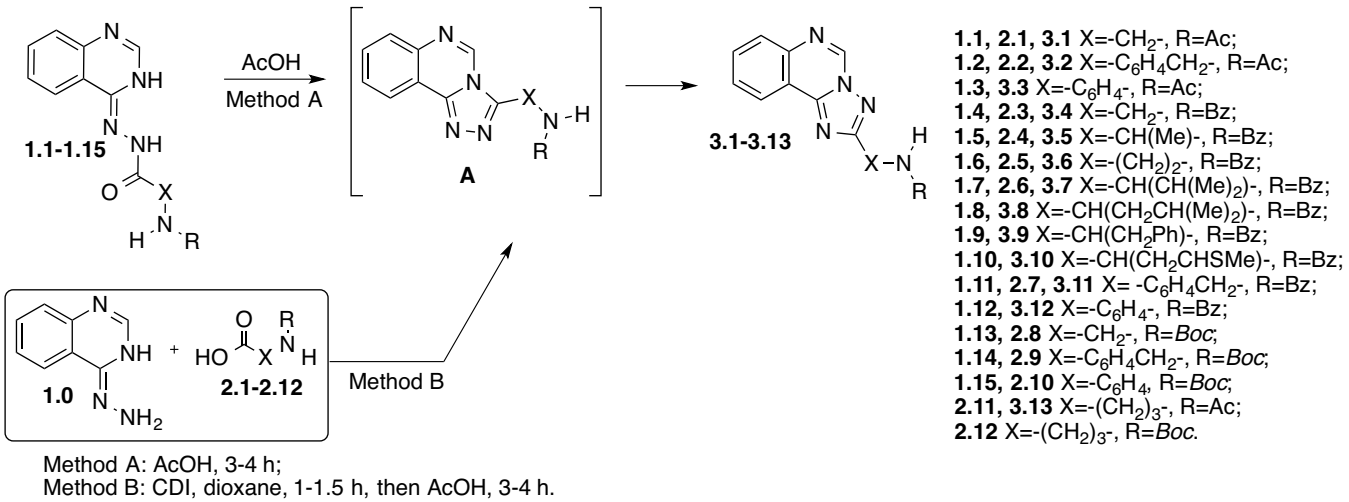
Substances were drawn using MarvinSketch 18.23 and saved in mol format [33]. After that, they were optimized by program Chem3D, using molecular mechanical MM2 algorithm and saved as pdb-files. Molecular mechanics was used to produce more realistic geometry values for the majority of organic molecules, owing to the fact of being highly parameterized. Using AutoDock-Tools-1.5.6, pdb-files were converted into PDBQT, and the number of active torsions was set as default [34].

2.3.2. Protein Preparation

PDB files were downloaded from the protein data bank. Discovery Studio V17.2.0.16349 was used to delete water molecules and ligand from the crystal. Structures of proteins were saved as pdb-files. In AutoDockTools-1.5.6, polar hydrogens were added and saved as PDBQT. Grid box was set as following: center_x = 18.37, center_y = -52.296, center_z = 53.949, size_x = 18, size_y = 16, size_z = 16 for COX-2 (3LN1); center_x = 32.978, center_y = -44.488, center_z = -3.76, size_x = 16, size_y = 16, size_z = 16 for COX-1 (3N8Y). Vina was used to carry out docking [34]. For visualization, Discovery Studio V17.2.0.16349 was used.

2.4. Anti-inflammatory Activity

Evaluation of anti-inflammatory activity of the synthesized compounds was conducted on 192 Wistar white rats (weight 150-160 g), obtained from the nursery Institute of Pharmacology and Toxicology of Ukraine, Kyiv. All experimental procedures and treatment were carried out according to the European Convention and Regulations on the use of animals in biomedical research [35]. Screening of synthesized compounds with estimated anti-inflammatory activity began with the study of their effect on the exudative phase of acute aseptic inflammation (formalin test). Phlogogen (1% aqueous solution of formaldehyde) [36] was subplantally injected in a dose of 0.1 ml in the rats' back right paw. The left paw was used as a control. Intragastric administration of studied compounds was conducted using atraumatic probe 1 h before the injection of phlogogen as a water solution or finely dispersed suspension stabilized by Tween - 80 in a dose of 10 mg/kg. The reference drug Diclofenac sodium was administered intragastrically in a recommended for pre-clinical studies dose of 8 mg/kg. Measurement of the paws' volume was conducted before the experiment and in 3 h after injection of phlogogen using the described methods.



Scheme 1. Synthetic approaches for *N*-protected-2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)alkyl-(alkaryl-, aryl-) amines.

The activity of studied substances was determined by their ability to reduce the paw edema compared with the control group and was expressed in percentage. It showed how the substance inhibited formalin-induced paw edema compared to the control group, where the swelling value was taken as 100%. The activity of the studied compounds was calculated as follows:

$$A = 100\% - \frac{Vpe - Vhe}{Vpc - Vhc},$$

where A - anti exudative activity, %; V_{pe} - the volume of paw edema in the experiment; V_{he} - the volume of healthy paw in the experiment; V_{pc} - the volume of paw edema in control; V_{hc} - the volume of healthy paw in control.

Statistical data processing was performed using a license program STATISTICA® for Windows 6.0 (StatSoftInc., No. AXXR712D833214FAN5) and SPSS 16.0, Microsoft Office Excell 2003. The results were presented as mean ± standard error of the mean. Arithmetic mean and standard error of the mean were calculated for each of the studied parameters. During verification of statistical hypothesis, null hypothesis was declined if the statistical criterion was $p<0.05$ [37].

3. RESULTS AND DISCUSSION

3.1. Chemistry

As it was mentioned, [1,2,4]triazolo[*c*]quinazolines may be prepared from the corresponding hydrazides (**1**) by cyclocondensation under acidic catalysis. Thus, refluxing of (3*H*-quinazoline-4-ylidene)hydrazides of *N*-protected amino acids (**1.1**-**1.15**) in acetic acid for 3 h yielded heterocyclic derivatives **3.1-3.12** (method A). It was found, that cyclisation of *Boc*-amino acids hydrazides (**1.13-1.15**) in abovementioned conditions resulted in corresponding acetyl-contained triazolo[*c*] quinazolines (**3.1**-**3.3**, method A) as a result of reacylation process.

The attempt to synthesize compounds **3** *via* condensation of 4-hydrazinoquinazoline (**1.0**) generated *in situ* imidazolides of *N*-protected amino acids (**2.1**-**2.12**) without isolation of intermediate hydrazides (**1**, method B) which proved successful. It was shown, that cyclization occurred easily in acetic acid with prior evaporation of dioxane. It should be noted that in the above mentioned method, *Boc*-substituted derivatives (**2.8**-**2.10**, **2.12**) were also converted into the corresponding acetyl-containing compounds (**3.1**-**3.3**, **3.13**). It should also be noted that the formation of a heterocyclic system **3** was accompanied by the re-cyclic isomerization (Dimrot's rearrangement) of corresponding 2-substituted [1,2,4]triazolo[4,3-*c*]quinazolines (intermediate A) (Scheme **1**) [1-3, 6].

Structure and purity of obtained compounds were proven by a complex of appropriate physicochemical methods. The corresponding low-field singlet of H-5 at the 9.48-9.35 ppm in ^{1}H NMR spectra indicated the formation of compounds **3.1**-**3.13**. Signals of triazolo[1,5-*c*]quinazoline cycle were characteristic for **3.1**-**3.13** compounds and

were registered as: doublets at 8.57-8.42 ppm (H-10), at 8.14-8.01 ppm (H-7) and triplets at 7.92-7.84 ppm (H-8) and at 7.83-7.72 ppm (H-9). The proposed structures of compounds **3.1**-**3.3**, **3.8** were also confirmed by the ^{13}C NMR spectroscopy. The signals of sp^2-hybridized C-5 and C-2 atoms at 151.2-150.7 ppm and at 166.5-159.3 ppm were characteristic, respectively. The spectral data indicated the formation of substituted triazolo[1,5-*c*]quinazoline system [1-3, 6].

Besides, the ^1H NMR spectra of compounds **3.1**-**3.13** were characterized by signals of the amide group at 9.99-7.72 ppm. These signals were observed as a multiplet (**3.2**, **3.6**, **3.11**), triplet (**3.1**, **3.4**, **3.13**), doublet (**3.5**, **3.7**-**3.10**) and singlet (**3.3**, **3.12**), depending on the nature of the linker group with the corresponding chemical shifts. Also, there were signals of linker alkyl-, aralkyl- and aryl-groups in the ^1H NMR spectra for which the corresponding multiplicity and chemical shifts of protons are characteristic [38].

The IR-spectra of compounds **3.1**-**3.13** were characterized by absorption bands caused by -C(O)NH groups valence vibrations (amide-I) at 1663-1614 cm^{-1}, valence-deformation vibrations of the N-H and C-N (amide-II) bonds at 1598-1491 cm^{-1} as well as the band of *NH*-groups valence vibrations in the range of 3291-3248 cm^{-1}.

3.2. Molecular Docking and Biological Assay

The role of cyclooxygenases (COX-1 and COX-2) as an important molecular target is determinative for anti-inflammatory drugs development [32]. The synthetized compounds were analyzed using molecular docking in the first stage of the study. Complexes of COX-1 and COX-2 were downloaded from the Protein Data Bank, to evaluate the affinity of the studied compounds (Table **1**) [31]. Diclofenac sodium and Celecoxib were used as known reference inhibitors of COX-1 and COX-2. The results of molecular docking and anti-inflammatory activity are shown in Table **1**.

Results of docking study showed that analyzed compounds have the higher affinity to COX-2, than to COX-1. High affinity to this enzyme is not always a determinative factor for revealing of anti-inflammatory activity. This is possible due to the influence of additional factors such as the features of distribution and metabolism in the body. Thus, in spite of significant affinity according to the docking studies, (3*H*-quinazoline-4-ylidene)hydrazides of *N*-benzoylamino acids with aliphatic linker groups (**1.4**-**1.10**) additionally induced the inflammation process. Whereas, hydrazides of *N*-benzoylamino acids with benzyl (**1.11**) and phenyl (**1.12**) linker groups inhibit the inflammation on 67.68% and 69.70%. A similar situation was observed for the corresponding *N*-acetylamino acid hydrazides (**1.1**-**1.3**). Thus, the introduction of benzyl (**1.2**) and phenyl (**1.3**) moiety into their molecules led to the significant anti-inflammatory activity, which competed with Diclofenac sodium.

Modification of *N*-acetylamino acid hydrazides (**1.1**-**1.3**) *via* replacing the acetyl by the *Boc*-moiety (compounds **1.13**-**1.15**) led to a significant increase in activity. Compounds **1.13**-**1.15** exceeded the activity of Diclofenac sodium on 31-46%. This fact and structural features of the compounds **1.13**-**1.15** motivated to conduct a detailed study of the main types of interactions between the above mentioned structures and the amino acid residues of COX-1 and COX-2. In the analysis of the compounds **1.13**-**1.15** and standard drugs, main types of interactions with amino acid residues of enzymes have been shown, highlighting the fact that they are characterized by a significant amount of hydrogen bonds and hydrophobic interactions (Table **2**).

Visualization of the most active agent`s **1.13** structure with the active site of COX-2 (Fig. **1**) allowed to establish, that it had two hydrogen bonds with the following amino acid residues: ARG106 (3.11Å) and TYR341 (3.18Å), and, in Addition, eleven hydrophobic interactions: PHE504 (5.68Å), GLY512 (3.94Å, 4.03Å), ALA513 (4.67Å), VAL102 (3.93Å, 4.52Å), VAL335 (5.13Å, 5.15Å), LEU345 (4.34Å), LEU517 (4.16Å) and LEU517 (4.44Å).

N-acetyl-(benzoyl)-2-([1,2,4]triazolo[1,5-*c*]quinazoli-ne-2-yl)-alkyl-(aralkyl-, aryl-) amines (**3.1**-**3.13**, Table **1**) also showed high affinity to COX-2 and significant anti-inflammatory activity. Inhibition of the inflammatory process on 56.34-62.63% was characteristic for compounds **3.2**, **3.3**, **3.11** and **3.12**. The mentioned compounds, as well

Table 1. Results of molecular docking and anti-inflammatory activity of synthesized compounds.

Compound	Affinity (kcal/mol) to COX-1 (PDB ID - 3N8Y)	Affinity (kcal/mol) to COX-2 (PDB ID - 3LN1)	Anti-inflammatory Activity, %
1.1	-7.7	-8.7	12.34
1.2	-6.9	-7.5	43.28
1.3	-8.1	-9.9	49.72
1.4	-9.2	-9.8	-23.64
1.5	-7.7	-9.7	-12.03
1.6	-7.6	-9.6	-5.09
1.7	-7.6	-9.3	-6.06
1.8	-8.9	-9.3	-29.29
1.9	-6.5	-9.7	-0.98
1.10	-6.8	-7.2	-4.60
1.11	-8.5	-8.2	67.68
1.12	-6.2	-8.1	69.70
1.13	-7.3	-8.2	91.92
1.14	-7.4	-9.4	79.80
1.15	-7.4	-9.3	76.77
3.1	-8.5	-9.0	32.83
3.2	-6.2	-8.5	62.63
3.3	-3.8	-7.3	59.74
3.4	-9.0	-10.5	55.56
3.5	-8.5	-9.2	46.44
3.6	-8.6	-9.6	45.23
3.7	-6.3	-10.0	44.95
3.8	-4.8	-8.5	46.32
3.9	-3.1	-9.7	58.93
3.10	-5.5	-9.1	47.22
3.11	-7.7	-8.5	56.34
3.12	-5.9	-7.4	58.32
3.13	-7.8	-8.9	45.21
Diclofenac sodium	-8.4	-	45.45
Celecoxib	**-**	**-12.1**	**-**

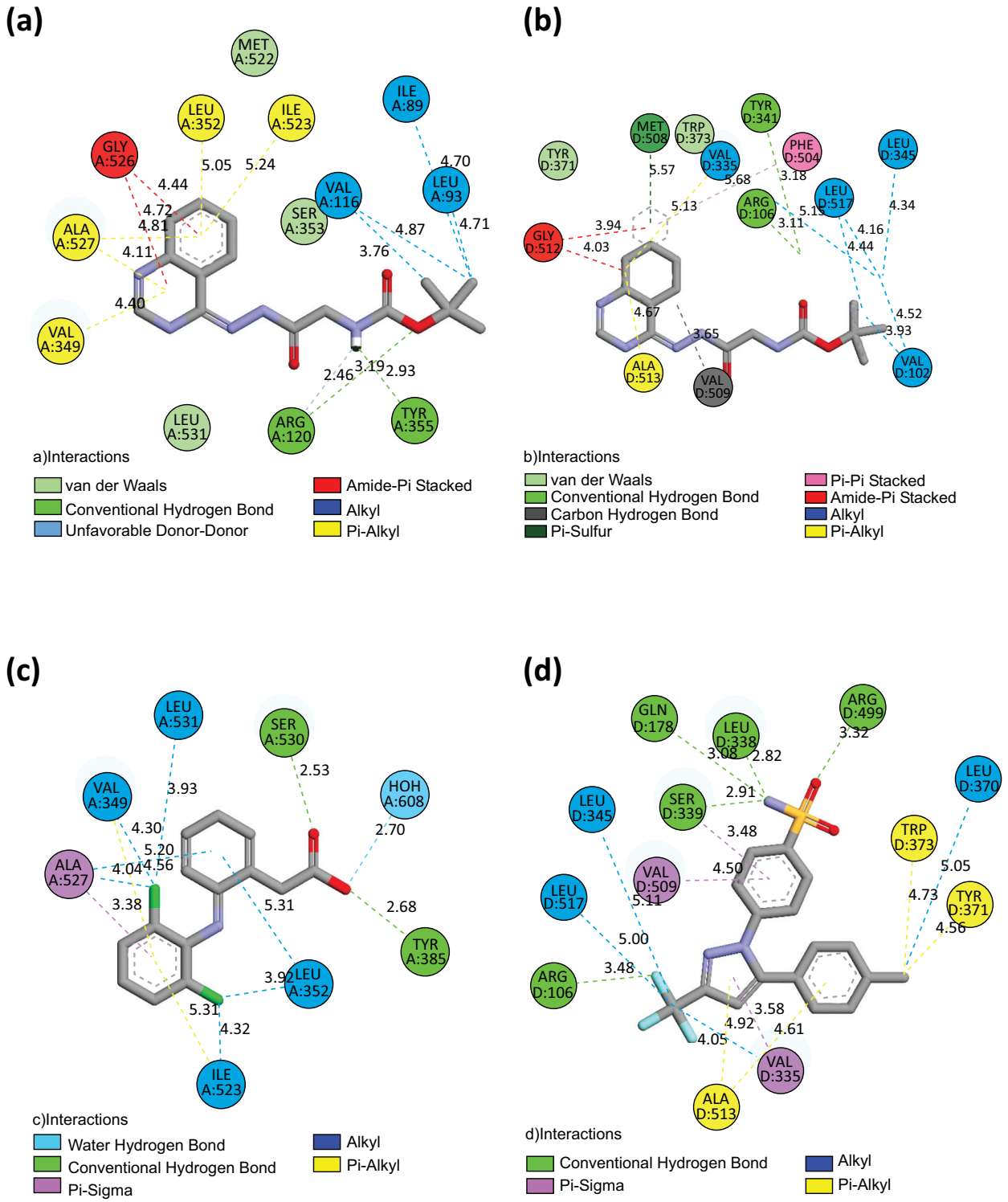


Fig. (1). Visualization of affinity according to the docking **a**) compound **1.13** with COX-1; **b**) compound **1.13** with COX-2; **c**) Diclofenac with COX-1; **d**) Celecoxib with COX-2.

as hydrazides **1.2**, **1.3**, **1.11** and **1.12** contain benzyl (**3.2**, **3.11**) and phenyl (**3.3**, **3.12**) linker groups, that join ([1,2,4]triazolo[1,5-*c*]quinazoline fragment with the acetyl-(benzoyl) amino group.

CONCLUSION

The approaches for the synthesis of *N*-acetyl-(benzoyl)-2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl) alkyl-(aralkyl-, aryl-)amines, using (3*H*-quinazo-

Table 2. The main types of interactions of the most active compounds and pharmacological standards with amino acid residues of enzymes, according to the docking studies.

Compound	COX-1, PDB ID - 3N8Y	COX-2, PDB ID - 3LN1
1.13	ARG120[a], TYR355[a], GLY526[b], ALA527[b], GLY526[b], ALA527[b], VAL116[b], ILE89[b], LEU93[b], VAL116[b], LEU352[b], ILE523[b], ALA527[b], VAL349[b], ALA527[b].	ARG106[a], TYR341[a], MET508[c], PHE504[b], GLY512[b], ALA513[b], VAL102[b], VAL335[b], LEU345[b], LEU517[b], VAL102[b], LEU517[b], VAL335[b], ALA513[b].
1.14	ARG120[a], TYR355[a], SER530[a], SER530[a], SER530[a], TYR355[a], TYR385[a], LEU352[b], LEU531[b], MET522[c], GLY526[b], ALA527[b], GLY526[b], ALA527[b], ILE89[b], LEU93[b], VAL116[b], VAL116[b], LEU352[b], ILE523[b], VAL116[b], VAL349[b], ALA527[b].	ARG499[a], SER516[a], LEU338[b], ALA513[b], ALA502[b], ALA502[b], ARG499[b], ILE503[b], VAL509[b], HIS75[b], PHE504[b], VAL102[b], VAL335[b], VAL335[b], LEU345[b], ALA513[b], LEU517[b], VAL335[b], VAL509[b].
1.15	TYR355[a], ALA527[d], GLY526[b], ALA527[b], LEU384[b], ILE89[b], VAL116[b], PHE381[b], TYR385[b], TRP387[b], LEU352[b], ILE523[b], ALA527[b], VAL116[b], ARG120[b], LEU531[b].	SER516[a], TYR341[a], ALA513[a], TYR371[a], ALA502[b], ALA502[b], VAL509[b], ALA513[b], VAL509[b], HIS75[b], PHE504[b], PHE504[b], VAL335[b], LEU338[b], VAL335[b], VAL509[b], ALA513[b].
Diclofenac sodium	TYR385[a], SER530[a], ALA527[b], LEU352[b], ALA527[b], ALA527[b], LEU352[b], ILE523[b], VAL349[b], LEU531[b], VAL349[b], ILE523[b].	-
Celecoxib	-	ARG106[a], ARG499[a], GLN178[a], LEU338[a], SER339[a], VAL335[b], SER339[b], VAL509[b], VAL509[b], LEU370[b], VAL335[b], LEU345[b], LEU517[b], TYR371[b], TRP373[b], ALA513[b], ALA513[b].

[a] - hydrogen, [b] - hydrophobic, [c] - others.

line-4-ylidene)hydrazides of *N*-protected amino acids or 4-hydrazinoquinazoline and *N*-protected amino acids as starting compounds were developed. It was established that cyclization of (3*H*-quinazoline-4-ylidene)hydrazides of *Boc*-amino acids occurred with the formation of *N*-acetyl-substituted triazoloquinazolines under discussed conditions. The synthesized compounds structures were elucidated by IR-, NMR- spectroscopy and chromatography-mass-spectrometry. The directed search strategy allowed to identify a number of perspective compounds **1.2**, **1.3**, **1.11**-**1.15**, **3.2**, **3.3**, **3.11**, **3.12**, using the molecular docking and experimental formalin test. Some of the obtained agents by the level of anti-inflammatory activity exceeded the pharmacological standard Diclofenac sodium. The SAR analysis and functional groups responsible for anti-inflammatory activity were discussed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Commission on Bioethics of Zaporizhzhya State Medical University, Ukraine with Protocol No. 6 (19.09.2018).

HUMAN AND ANIMAL RIGHTS

No humans were used for the study that are the basis of this research. All experimental procedures and treatment on animals were carried out according to the European Convention and Regulations on the use of animals in biomedical research (European convention for the protection of vertebrate animal used for experimental and other scientific purposes, Council of Europe, Strasbourg, 1986).

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available in the Institutional Repository of Zaporizhzhia State Medical University, at http://dspace.zsmu.edu.ua/handle/123456789/10700.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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