Directed Search of Biologically Active Compounds among Hydrogenated Isoindolylalkyl(alkaryl-, aryl-)carboxylic acids with Quinazoline Fragment, that Modify the Carbohydrate Metabolism: Design, Synthesis and Modification

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Abstract: An effective synthesis of (3*H*-quinazoline-4-ylidene)hydrazides of *N*-carboxyalkyl-(arylalkyl-, aryl-)-isoindoline-1,3-diones, using activated *N*-protected aminoacids and 4-hydrazinoquinazoline was proposed in the framework methodology of directed search of hypoglycemic agents (fragment-oriented design, molecular docking). These hydrazides *via* cyclocondensation under acid catalysis were converted to the corresponding 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)alkyl-(alkaryl-, aryl-)-hydroisoindole-1,3(2*H*)-diones. The structure of synthesized compounds was established, using IR-, ^{1}H and ^{13}C NMR spectroscopy and LC-MS and the features of spectral pattern were discussed. The results of pharmacological screening revealed a series of compounds, that are short-acting hypoglycemic agents like prandial regulators of glucose («Mitiglinide»). The SAR analysis showed, that the introduction of a hydrogenated 1,3-dioxoisoindole moiety bonded through «linker» groups with 4-hydrazinoquinazoline and triazolo[1,5-*c*]quinazoline cycles is reasonable in the context of searching short-acting hypoglycemic agents and requires further research.

Key words: (3*H*-quinazoline-4-ylidene)hydrazides of *N*-carboxyalkyl-(arylalkyl-, aryl-)-isoindoline-1,3-diones; 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)alkyl-(alkaryl-, aryl-)-hydroisoindole-1,3(2*H*)-diones; directed search; physico-chemical properties; spectral features; hypoglycemic activity

1. Introduction

Quinazoline derivatives and their condensed analogues have always attracted the attention of medicinal chemists as objects of advanced research, aimed at the elaboration of new drugs. This fact is explained by the high biological activity of as natural,[1-3] so synthetic quinazolines[4-19] and, undoubtedly, their wide ability to chemical modification.[10-13,18] In recent years, the interest to this heterocyclic system has increased greatly since the introduction of *in silico* approaches to the drug search strategy, combinatorial chemistry and high-throughput screening. These approaches have led to the discovery and creation of a number of «lead-compounds» and original drugs with antitumor, antihypertensive, diuretic, hypoglycemic and other biological activities.[4,6,7,17] It should be noted, that information about of biological targets and fragment-oriented design based on them[20,21] has played a key role in the creation of «therapeutic molecule» data. Using the above-mentioned search strategy we performed an attempt to one of the fragments-oriented design approaches based on the available results of hypoglycemic activity of *N*-carboxyalkyl-(arylalkyl-, aryl-) substituted hydrogenated isoindoline-1,3-diones[22], known hypoglycemic agents («Mitiglinide»[23,24] and «Apabetalone»[25]) and virtual screening. Enhancing the pharmacological activity the combination in the same molecule of these compounds with the «pharmacophore» quinazoline fragment was used (Figure 1).

Thus, the aim of this work is directed search of biologically active compounds, that modify the carbohydrate metabolism, based on unknown (3*H*-quinazoline-4-ylidene)hydrazides of hydrogenated isoindolylalkyl(alkaryl-, aryl-)carboxylic acids, their further modification to triazoloquinazolines, the study of their structure peculiarities and establishment of the «structure-activity relationship» for further optimization of their structure.

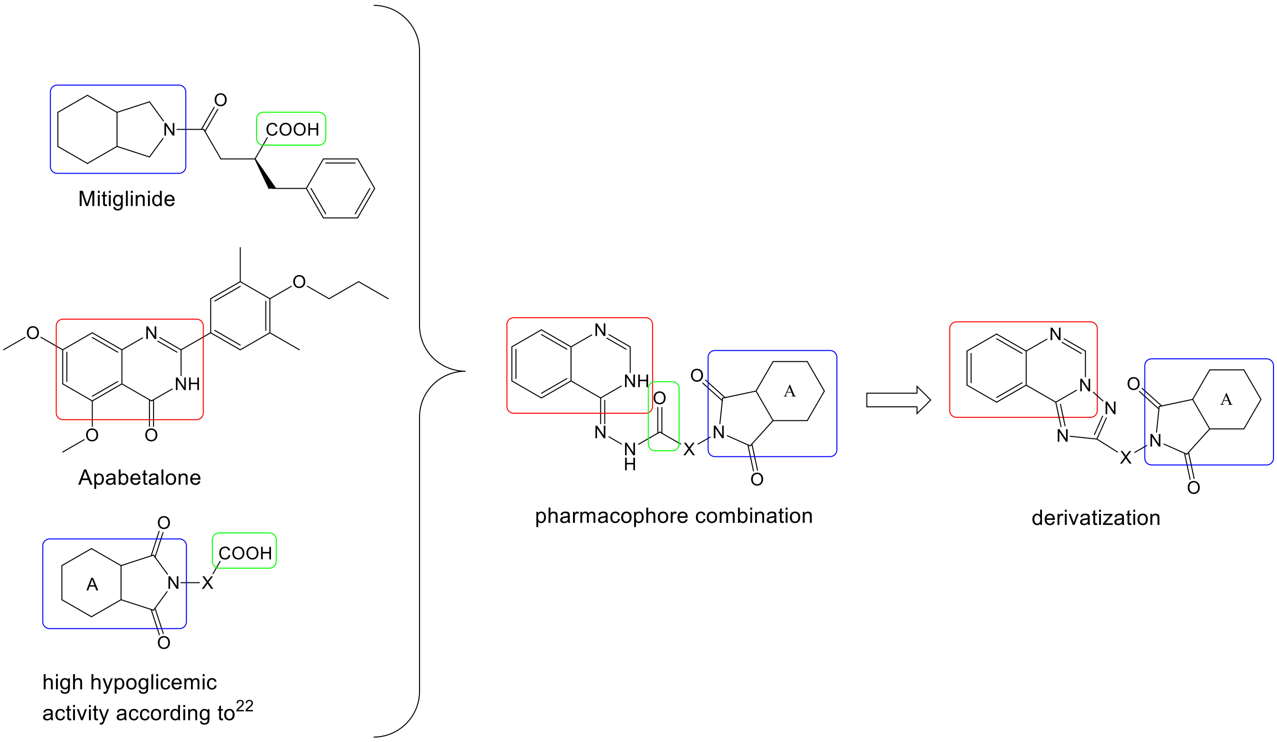


Figure 1 The search strategy of hypoglycemic agents based on the fragment-oriented design (combination of isoindole and quinazoline moieties in molecule)

2. Experimental Section

2.1. Chemistry

General Methods

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. IR spectra (4000–600 cm^{-1}) were recorded on a Bruker ALPHA FT-IR spectrometer using a module ATR eco ZnSe. ^{1}H NMR spectra (400 MHz) were recorded on «Varian-Mercury 400» spectrometer with $SiMe_4$ as internal standard in DMSO-d_6 solution. LC-MS spectra were recorded using chromatography/mass spectrometric system, 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.

Substances **1a-i** were synthesized according to the reported procedures.[22] Other starting materials and solvents were obtained from commercially available sources and used without additional purification.

2.2. Molecular docking

Pancreatic beta-cell KATP channel (PDB ID - 6BAA) was used as target protein to carry out molecular docking. «Metglitinide» and «Glibenclamide» were used as the reference drugs. The chemical formula of «Glibenclamide» was obtained from the mentioned PDB-file for calculating affinity value, and structure of «Metglitinide» was prepared as others ligands.[26]

Ligand preparation. Substances were constructed using Marvin Sketch 17.21 and saved as mol. Subsequently, using the Marvin Sketch 17.21 program[27], they were optimized with the help of the molecular-mechanical MM+ algorithm in conjunction with the semiempirical PM3 method of molecular modeling with the maximum number of cycles and the Polak-Ribiere algorithm. Molecular mechanics is used to obtain more realistic geometric values for most organic molecules, since it has a large number of parameters. The next step was to re-optimize MM+-optimized structures with using semiempirical PM3 molecular modeling method and the preservation of molecules in PDB files. Using Auto Dock Tools-1.5.6, PDBs were converted to PDBQT while the rotational number of link options was typical.

Protein preparation. PDB files have been downloaded from a data bank of proteins.[26] Discovery Studio v17.2.0.16349 was used to remove water molecules and ligands from the file. After that, the protein was saved as PDB file. Polar hydrogen atoms were added, and the protein was saved as PDBQT into Auto Dock Tools-1.5.6. The search grid for docking the protein was set as following: center_x = 113, center_y = 191, center_z = 128, size_x = 22, size_y = 22, size_z = 22. Vina was used for proper docking. Discovery Studio v17.2.0.16349 was used for visualization.[28]

2.3. Pharmacology

2.3.1. Hypoglycemia activity test

Study of hypoglycemic activity was conducted on 150 Wistar white rats (male, weight 100-180 g., age 3.5 month) which were obtained from nursery of PE «Biomodelservice» (Kiev, Ukraine). Experiments on animals were done according to the bioethics principles.[23] Selected after quarantine animals by random sampling were divided in groups of 6 male - rats on the assumption of absence of external signs of diseases and homogeneity by weight (±15%). Experimental animals were not fed during 12 hours before injection of studied compounds. The weight of all animals was measured before experiment. Intragastric injection of studied compounds was conducted using atraumatic probe as water solution or finely dispersed suspension stabilized by Tween - 80 in a dose of 10 mg/kg. Intact and control groups received equivalent volume of water by the same way. Hypoglycemic activity of the synthesized compounds was evaluated *via* changes of glucose level before and after injection of the studied substances. Measurements of glucose level were carried out 2, 4 and 6 hours after injection. «Metformine» (50 mg/kg) was used as a reference drug.

Before the experiment the compounds were injected as an aqueous solution or 3-5% micronized water suspension, stabilized by Tween - 80 in a dose of 10 mg/kg using atraumatic probe in order to identify prandial hypoglycemic agents. Subsequently, after 60 minutes, 40% glucose solution was injected to rats at a dose of 3000 mg/kg. Hypoglycemic activity of the synthesized compounds was evaluated *via* changes of glucose level before and after injection of substances. Measurements of glucose level were carried out in 15, 30, 60 and 120 minutes after injection.

Statistical analysis was done using standard software complex, namely «Microsoft Office Excel 2003» and «STATISTICA® for Windows 6.0» (StatSoft Inc., № AXXR712D833214FAN5). For each estimated value arithmetic mean (M), and standard error of the mean (±m) were defined. During verification of statistical hypothesis, null hypothesis were declined if statistical criterion $p<0.05$.

The general procedure for the synthesis of (3*H*-quinazoline-4-ylidene)hydrazides *N*-carboxyalkyl- (arylalkyl-, aryl-)-isoindoline-1,3-diones (3a-i).

1.62 g (0.01 M) of *N,N'*-carbonyldiimidazole was added to a suspension of 0.01 M of the corresponding 2-(isoindoline-1,3-dione)alkyl-(alkyl-, arylalkyl-, aryl-)carboxylic acids (**1a-i**) in 30 ml of dioxane. The mixture was kept at temperature 60-70 °C for 50-60 minutes until the carbon dioxide was completely released. After addition of 1.6 g (0.01 M) 4-hydrazinoquinazoline (**2a**) the mixture was kept at a room temperature overnight or at 80 °C for 1.5 hour. Dioxane was distilled off. The water was added and the mixture was neutralized by 0.1 M of hydrochloric acid to pH 6-7. The solid product was filtered in the case of residue formation. If it was necessary, compounds were crystallized.

2-(1,3-Dioxooctahydro-2H-isoindole-2-yl)-N'-(quinazoline-4(3H)-ylidene)propanehydrazide (3a). Yield 61.9%; m.p. 100-102˚C; IR (cm^{-1}): 3297, 2917, 2849, 2693, 2353, 1704, 1615, 1550, 1472, 1386, 1194, 1130, 984, 759, 689; ^1H NMR, δ (ppm): 11.46 (s, 1H, 3-NH), 10.16/10.03 (s, 1H, NHCO), 7.80-7.61 (m, 2H, H-2,5), 7.37 (t, *J* = 7.9 Hz, 1H, H-7), 7.19 (t, *J* = 7.9 Hz, 1H, H-6), 7.10 (d, *J* = 8.0 Hz, 1H, H-8), 5.15/4.75 (q, *J* = 7.0 Hz, 1H, $\underline{CH}CH_3$), 2.82-2.65 (m, 2H, isoindole H-3a,7a), 1.85-1.64 (m, 4H, isoindole H-4,4',7,7'), 1.58/1/51 (d, *J* = 7.1 Hz, 3H, $CH\underline{CH_3}$), 1.47-1.25 (m, 4H, isoindole H-5,5',6,6'); LC-MS: m/z = 367 $[M]^+$; Anal. Calcd. for $C_{19}H_{21}N_5O_3$: C, 62.11; H, 5.76; N, 19.06; Found: C, 62.16; H, 5.82; N, 19.13.

4-((1,3-Dioxooctahydro-2H-isoindole-2-yl)methyl)-N'-(quinazoline-4(3H)-ylidene)benzohydrazide (3b). Yield: 72.6; m.p. 263-265 ˚C; IR (cm^{-1}): 3309, 3180, 3130, 2918, 2953, 2854, 2779, 2714, 1698, 1612, 1525, 1471, 1374, 1341, 1310, 1164, 1093, 906, 762, 690, 662, 646; ^1H NMR, δ (ppm): 11.51 (s, 1H, 3-NH), 10.52 (s, 1H, NHCO), 9.01-6.44 (m, 9H, H-2, 5,6,7,8, Ar H-2,3,5,6), 4.62 (s, 2H, $-CH_2-$), 2.98-2.89 (m, 2H, isoindole H-3a,7a), 1.90-1.58 (m, 4H, isoindole H-4,4',7,7'), 1.50-1.29 (m, 4H, isoindole H-5,5',6,6'); LC-MS, m/z = 430 [M+1], 431 [M+2]; Anal. Calcd. for $C_{24}H_{23}N_5O_3$: C, 67.12; H, 5.40; N, 16.31; Found: C, 67.19; H, 5.48; N, 16.38.

4-(1,3-Dioxooctahydro-2H-isoindole-2-yl)-N'-(quinazoline-4(3H)-ylidene)benzohydrazide (3c). Yield: 84.3%; m.p. 187-190 ˚C; IR (cm^{-1}): 3421, 3280, 2993, 2913, 2855, 1698, 1626, 1537, 1493, 1475, 1385, 1167, 1129, 759, 687, 615; ^{1}H NMR, δ (ppm): 11.60 (s, 1H, 3-NH), 10.65 (s, 1H, NHCO), 8.58-6.95 (m, 9H, H-2,5,6,7,8, Ar H-2,3,5,6), 3.15-3.08 (m, 2H, isoindole H-3a,7a), 1.97-1.70 (m, 4H, isoindole H-4,4',7,7'), 1.57-1.35 (m, 4H, isoindole H-5,5',6,6'); LC-MS, m/z = 416 [M+1], 417 [M+2]; Anal. Calcd. for $C_{23}H_{21}N_5O_3$: C, 66.49; H, 5.10; N, 16.86; Found: C, 66.54; H, 5.16; N, 16.93.

2-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindole-2-yl)-N'-(quinazoline-4(3H)-ylidene)propanehydrazide (3d). Yield: 71.8%; m.p. 201-203 ˚C, IR (cm^{-1}): 3289, 3214, 3069, 3012, 2960, 2910, 2886, 2850, 2780, 2683, 2410, 1702, 1603, 1566, 1466, 1420, 1383, 1325, 1198, 1117, 927, 776, 755, 685, 661; ^{1}H NMR, δ (ppm): 11.49 (s, 1H, 3-NH), 10.09/10.00 (s, 1H, NHCO), 7.81-7.65 (m, 2H, H-2,5), 7.49 (t, *J* = 7.8 Hz, 1H, H-7), 7.20 (t, *J* = 7.8 Hz, 1H, H-6), 7.11 (d, *J* = 8.4 Hz, 1H, H-8), 5.89 (m, 2H, isoindole H-5,6), 5.13/4.71 (q, *J* = 7.9, 7.2 Hz, 1H, $\underline{CH}CH_3$), 3.05-2.90 (m, 2H, isoindole H-3a,7a), 2.46-2.01 (m, 4H, isoindole H-4,4',7,7'), 1.44 (d, *J* = 7.1 Hz, 3H, $CH\underline{CH_3}$); LC-MS, m/z = 368 [M+3]; Anal. Calcd. for $C_{19}H_{19}N_5O_3$: C, 62.46; H, 5.24; N, 19.17; Found: C, 62.49; H, 5.28; N, 19.23.

3-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindole-2-yl)-N'-(quinazoline-4(3H)-ylidene)propanehydrazide (3e). Yield: 68.4%; m.p. 135-137 ˚C, IR (cm^{-1}): 3489, 3409, 3343, 3230, 3128, 3106, 3078, 3010, 2988, 2939, 2859, 2699, 1693, 1611, 1527, 1471, 1440, 1379, 1106, 755, 687; ^{1}H NMR, δ (ppm): 11.53 (s, 1H, 3-NH), 10.03/9.52 (s, 1H, NHCO), 7.88 (d, *J* = 7.2 Hz, 1H, H-5), 7.74 (s, 1H, H-2), 7.37 (t, *J* = 7.3 Hz, 1H, H-7), 7.20 (t, *J* = 7.5 Hz, 1H, H-6), 7.13 (d, *J* = 7.8 Hz, 1H, H-5), 5.95-5.76 (m, 2H, isoindole H-5,6), 3.67 (m, 2H, $CH_2\underline{CH_2}N$), 3.24-3.08 (m, 2H, isoindole 3a,7a), 2.82 (t, *J* = 7.5 Hz, 2H, $\underline{CH_2}CH_2N$), 2.48-2.11 (m, 4H, isoindole H-4,4',7,7'); LC-MS, m/z = 366 [M+1], 367 [M+2]; Anal. Calcd. for $C_{19}H_{19}N_5O_3$: C, 62.46; H, 5.24; N, 19.17; Found: C, 62.43; H, 5.18; N, 19.13.

4-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindole-2-yl)-N'-(quinazoline-4(3H)-ylidene)benzohydrazide (3f). Yield: 94.3%; m.p. 261-263 ˚C, IR (cm^{-1}): 3418, 3311, 3205, 3168, 3120, 3089, 3056, 3023, 2979, 2915, 2850, 1704, 1612, 1536, 1495, 1474, 1445, 1386, 1177, 845, 759, 687, 625; ^{1}H NMR, δ (ppm): 11.58 (s, 1H, 3-NH), 10.65/9.99 (s, 1H, NHCO), 8.55-7.03 (m, 9H, H-2,5,6,7,8, Ar H-2,3,5,6), 6.15-5.81 (m, 2H, isoindole H-5,6), 3.39-3.19 (m, 2H, isoindole H-3a,7a), 2.69-2.20 (m, 4H, isoindole H-4,4',7,7); LC-MS, m/z = 414 [M+1], 415 [M+2]; Anal. Calcd. for $C_{23}H_{19}N_5O_3$: C, 66.82; H, 4.63; N, 16.94; Found: C, 66.89; H, 4.70; N, 17.01.

2-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-yl)-N'-(quinazoline-4(3H)-ylidene)acetohydrazide (3g). Yield: 71.6%; m.p. 168-170 ˚C, IR (cm^{-1}): 3462, 3292, 3208, 3168, 3133, 3089, 3054, 3029, 2994, 2904, 2858, 2783, 1728, 1632, 1539, 1489, 1477, 1439, 1391, 1173, 845, 761, 683, 629; ^{1}H NMR, δ (ppm): 11.51 (s, 1H, 3-NH), 10.27/9.66 (s, 1H, -NHCO-), 7.90 (d, *J* = 7.2 Hz, 1H, H-H-5), 7.80 (s, 1H, H-2), 7.40 (t, *J* = 7.3 Hz, 1H, H-7), 7.19 (t, *J* = 7.4

Hz, 1H, H-6), 7.13 (d, *J* = 8.0 Hz, 1H, H-8), 6.18-6.07 (m, 2H, isoindole H-5,6), 4.73/4.37 (s, 2H, CH_2), 3.50-3.38 (m, 2H, isoindole H-3a,7a), 3.39-3.27 (m, 2H, isoindole H-4,7), 1.76-1.55 (m, 2H, isoindole H-8,8'); LC-MS, m/z = 364 [M+1], 365 [M+2]; Anal. Calcd. for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27; Found: C, 62.87; H, 4.77; N, 19.34.

4-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-yl)methyl)-N'-(quinazoline-4-yl)benzohydrazide (3h). Yield: 88.1%; m.p. 265-267 ˚C; IR (cm^{-1}): 3376, 3060, 2990, 2962, 2914, 2849, 2690, 1695, 1611, 1525, 1471, 1375, 1339, 1167, 1093, 907, 763, 722, 690, 659, 644; ^{1}H NMR, δ (ppm): 11.43 (s, 1H, 3-NH), 10.55 (s, 1H, s, 1H, -NHCO), 8.18 (d, *J* = 7.4 Hz, 1H, H-5), 7.94-7.72 (m, 3H, H-2, Ph H-2,6), 7.55 (t, *J* = 7.3 Hz, 1H, H-7), 7.44-7.16 (m, 4H, H-6,8, Ph H-3,5), 6.04-5.86 (m, 2H, isoindole H-5,6), 4.46 (s, 2H, $-CH_2-$), 3.42-3.34 (m, 2H, isoindole H-3a,7a), 3.34-3.29 (m, 2H, isoindole H-4,7), 1.74-1.48 (m, 2H, isoindole H-8,8'); LC-MS, m/z = 440 [M+1], 441 [M+2]; Anal. Calcd. for $C_{25}H_{21}N_5O_5$: C, 68.33; H, 4.82; N, 15.94; Found: C, 68.41; H, 4.88; N, 16.01.

4-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-yl)-N'-(quinazoline-4-yl)benzohydrazide (3i). Yield: 99.9%; m.p. 187-189 ˚C; IR (cm^{-1}): 3476, 3310, 3284, 3028, 2982, 2929, 2856, 2780, 1693, 1614, 1548, 1495, 1474, 1389, 1185, 760, 744, 721, 688, 615; ^{1}H NMR, δ (ppm): 10.63 (s, -NHCO-), 8.21 (d, *J* = 7.2 Hz, 1H, H-5), 8.03-7.89 (m, 3H, H-2, Ph H-2,6), 7.59 (t, *J* = 7.4 Hz, 1H, H-7), 7.50-7.34 (m, 2H, H-6,8), 7.26 (d, *J* = 7.9 Hz, 2H, Ph H-3,5), 6.31-6.19 (m, 2H, isoindole H-5,6), 3.60-3.48 (m, 2H, isoindole H-7a,3a), 3.46-3.28 (m, 2H, isoindole H-4,7), 1.82-1.54 (m, 2H, isoindole H-8,8'); LC-MS, m/z = 426 [M+1], 428 [M+3]; Anal. Calcd. for $C_{24}H_{19}N_5O_3$: C, 67.76; H, 4.50; N, 16.46; Found: C, 67.83; H, 4.58; N, 16.53.

The synthesized compounds are yellow, soluble in DMF, DMSO, dioxane, slightly soluble in alcohol, insoluble in water.

The general procedure for the synthesis of 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)alkyl-(alkaryl-, aryl-)-hydroisoindole-1,3(2*H*)-diones (4a-i).

0.01 M of corresponding hydrazides (**3a-i**) was dissolved in 25 ml of glacial acetic acid and was refluxed for 6 hours. The mixture was cooled. In the case of forming residue it was filtered. In the case of a solution, acetic acid was distilled under vacuum. The resulting precipitate was stirred with mixture of methanol and water and it was filtered. If it necessary the precipitate can be crystallized.

(2-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (4a). Yield: 62.9 %; m.p. 200-203 ˚C; IR (cm^{-1}): 2922, 2843, 2690, 2359, 1705, 1381, 1342, 1195, 899, 770; ^{1}H NMR, δ (ppm): 9.40 (s, 1H, H-5), 8.39 (d, *J* = 7.6 Hz, 1H, H-10), 8.03 (d, *J* = 7.9 Hz, 1H, H-7), 7.88 (t, *J* = 8.1 Hz, 1H, H-8), 7.76 (t, *J* = 7.3 Hz, 1H, H-9), 5.49 (q, *J* = 6.7 Hz, 1H, $\underline{CH}CH_3$), 3.01-2.86 (m, 2H, isoindole 3a,7a), 1.89 (d, *J* = 7.0 Hz, 3H, $CH\underline{CH_3}$), 1.86-1.69 (m, 4H, isoindole H-4,4’,7,7’), 1.59-1.23 (m, 4H, isoindole H-5,5’,6,6’); ^{13}H NMR, δ (ppm): 179.41/179.29 (C-1,3 isoindole), 166.16 (C-2l), 150.74 (C-5), 142.69 (C-10b), 139.27 (C-6a), 132.80 (C-8), 129.63 (C-7), 128.99 (C-9), 123.46 (C-10), 117.76 (C-10a), 44.28 (-$CHCH_3$), 40.35 (C-3a,7a isoindole), 23.44/23.36 (C-4,7 isoindole), 21.53/21.48 (C-5,6 isoindole), 15.82 (CH_3); LC-MS, m/z = 350 [M+1], 352 [M+2]; Anal. Calcd. for $C_{19}H_{19}N_5O_2$: C, 65.32; H, 5.48; N, 20.04; Found: C, 65.39; H, 5.52; N, 20.11.

2-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)benzyl)hexahydro-1H-isoindole-1,3(2H)-dione (4b). Yield: 55.6 %; m.p. 248-250 ˚C; IR (cm^{-1}): 2957, 2929, 2854, 2456, 1689, 1479, 1423, 1397, 1334, 1165, 899, 775, 742; ^{1}H NMR, δ (ppm): 9.48 (s, 1H, H-5), 8.55 (d, J = 7.7 Hz, 1H, H-10), 8.26 (d, J = 8.1 Hz, 2H, Ar H-2,6), 8.06 (d, J = 8.4 Hz, 1H, H-7), 7.90 (t, J = 7.9 Hz, 1H, H-8), 7.81 (t, J = 7.6 Hz, 1H, H-9), 7.45 (d, J = 7.9 Hz, 2H, Ar H-3,5), 4.64 (s, 2H, CH_2), 2.98-2.93 (m, 2H, isoindole 3a,7a), 1.87-1.57 (m, 4H, isoindole H-4,4’,7,7’), 1.54-1.26 (m, 4H, isoindole H-5,5’,6,6’); LC-MS, m/z = 412 [M+1], 413 [M+2]; Anal. Calcd. for $C_{24}H_{21}N_5O_2$: C, 70.06; H, 5.14; N, 17.02; Found: C, 70.12; H, 5.18; N, 17.11.

2-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)phenyl)hexahydro-1H-isoindole-1,3(2H)-dione (4c). Yield: 74.6 %; m.p. < 300 ˚C; IR (cm^{-1}): 2989, 2924, 2863, 1701, 1514, 1477, 1445, 1357, 1164, 1122, 899, 769, 749, 713, 628; ^{1}H NMR, δ (ppm): 9.50 (s, 1H, H-5), 8.57 (d, J = 7.9 Hz, 1H, H-10), 8.41 (d, J = 8.4 Hz, 2H, Ar H-2,6), 8.07 (d, J = 8.2 Hz, 1H, H-7), 7.96 (t, J = 7.6 Hz, 1H, H-8), 7.82 (t, J = 7.5 Hz, 1H, H-9), 7.49 (d, J = 8.4 Hz, 2H, Ar H-3,5), 3.13 (m, 2H, isoindole 3a,7a), 1.97-1.72 (m, 4H, isoindole H-4,4’,7,7’), 1.57-1.39 (m, 4H, isoindole H-5,5’,6,6’); LC-MS, m/z = 398 [M+1], 400 [M+2]; Anal. Calcd. for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62; Found: C, 69.58; H, 4.91; N, 17.71.

2-(1-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)ethyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4d). Yield: 71.2 %; m.p. 180-184 ˚C; IR (cm^{-1}): 2954, 2899, 1701, 1493, 1387, 1360, 1214, 900, 773, 706; ^{1}H NMR, δ (ppm): 9.39 (s, 1H, H-5), 8.41 (d, J = 7.8 Hz, 1H, H-10), 8.02 (d, J = 8.3 Hz, 1H, H-7), 7.87 (t, J = 7.6 Hz, 1H, H-8), 7.76 (t, J = 7.5 Hz, 1H, H-9), 5.93 (m, 2H, isoindole H-5,6), 5.47 (q, J = 7.1 Hz, 1H, $\underline{CH}CH_3$), 3.38-3.09 (m, 2H, isoindole 3a,7a), 2.58-2.49 (m, 2H, isoindole H-4,7), 2.37-2.15 (m, 2H, isoindole H-4’,7’), 1.83 (d, J = 7.1 Hz, 3H, $CH\underline{CH_3}$); LC-MS, m/z = 348 [M+1], 349 [M+2]; Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16; Found: C, 65.66; H, 4.98; N, 20.13.

2-(2-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)ethyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4e). Yield: 40.0 %; m.p. 165-167 ˚C; IR (cm^{-1}): 2982, 2843, 2828, 2712, 1693, 1399, 1362, 1325, 1211, 1157, 1010, 929, 904, 770, 698; ^{1}H NMR, δ (ppm): 9.37 (s, 1H, H-5), 8.43 (d, J = 7.6 Hz, 1H, H-10), 8.03 (d, J = 8.3 Hz, 1H, H-7), 7.88 (t, J = 7.9 Hz, 1H, H-8), 7.77 (t, J = 7.5 Hz, 1H, H-9), 5.94-5.66 (m, 2H, isoindole H-5,6), 3.85 (t, J = 7.3 Hz, 2H, $CH_2\underline{CH_2}N$), 3.20-2.97 (m, 4H, $\underline{CH_2}CH_2N$, isoindole 3a,7a), 2.50-2.40 (m, 2H, isoindole H-4,7), 2.32-2.06 (m, 2H, isoindole H-4’,7’); LC-MS, m/z = 348 [M+1], 349 [M+2]; Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16; Found: C, 65.74; H, 5.02; N, 20.23.

2-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4f). Yield: 82.25 %; m.p. 250-253 ˚C; IR (cm^{-1}): 1703, 1514, 1478, 1446, 1360, 1315, 1177, 899, 842, 751, 717, 672; ^{1}H NMR, δ (ppm): 9.50 (s, 1H, H-5), 8.56 (d, *J* = 8.3 Hz, 1H, H-10), 8.39 (d, *J* = 8.3 Hz, 2H, Ar H-2,6), 8.20 (d, *J* = 8.5 Hz, 1H, H-7), 8.06 (t, *J* = 8.6 Hz, 1H, H-8), 7.86 (t, *J* = 8.6 Hz, 1H, H-9), 7.44 (d, *J* = 8.4 Hz, 2H, Ar H-3,5), 6.05-5.92 (m, 2H, isoindole H-5,6), 3.12-2.85 (m, 2H, isoindole 3a,7a), 2.66-2.56 (m, 2H, isoindole H-4,7), 2.37-2.23 (m, 2H, isoindole H-4’,7’); LC-MS, m/z = 396 [M+1], 397 [M+2]; Anal. Calcd. for $C_{23}H_{17}N_5O_2$: C, 69.86; H, 4.33; N, 17.71; Found: C, 69.94; H, 4.41; N, 17.80.

2-([1,2,4]Triazolo[1,5-c]quinazoline-2-ylmethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (4g). Yield: 85.8 %; m.p. 215-217 ˚C; IR (cm^{-1}): 2994, 2863, 2812, 1721, 1514, 1475, 1446, 1368, 1323, 1183, 899, 846, 751, 721, 682; ^{1}H NMR, δ (ppm): 9.40 (s, 1H, H-5), 8.43 (d, *J* = 7.6 Hz, 1H, H-10), 8.03 (d, *J* = 7.6 Hz, 1H, H-7), 7.89 (t, *J* = 7.5 Hz, 1H, H-8), 7.78 (t, *J* = 7.5 Hz, 1H, H-9), 6.15 (s, 2H, isoindole H-5,6), 4.73 (s, 2H, NCH_2), 3.46 (s, 2H, isoindole H-4,7), 3.37 (s, 2H, isoindole H-3a,7a), 1.67 (dd, *J* = 20.6, 8.0 Hz, 2H, isoindole H-8,8’); LC-MS, m/z = 346 [M+1], 348 [M+3]; Anal. Calcd. for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28; Found: C, 66.17; H, 4.46; N, 20.32.

2-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)benzyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (4h). Yield: 33.06 %; m.p. 219-221 ˚C; IR (cm^{-1}): 2996, 2974, 2918, 1695, 1515, 1476, 1420, 1386, 1334, 1160, 1118, 899, 769, 756, 727, 714; ^{1}H NMR, δ (ppm): 9.48 (s, 1H, H-5), 8.56 (d, *J* = 8.2 Hz, 1H, H-10), 8.24 (d, *J* = 7.1 Hz, 2H, 1,4-phenylene H-2,6), 8.06 (d, *J* = 8.2 Hz, 1H, H-7), 7.91 (t, *J* = 8.2 Hz, 1H, H-8), 7.81 (t, *J* = 8.2 Hz, 1H, H-7, H-9), 7.40 (d, *J* = 7.2 Hz, 1H, 1,4-phenylene H-3,4), 5.95 (s, isoindole H-5,6), 4.48 (s, 2H, $-NCH_2-$), 3.37 (s, 2H, isoindole H-4,7), 3.32 (s, 2H, isoindole H-3a,7a), 1.63 (dd, *J* = 22.0, 8.5 Hz, 2H, isoindole H-8,8’); ^{13}C NMR, δ (ppm): 177.75 (C-1,3; isoindole), 169.81 (C-2), 153.47 (C-5), 143.95 (C-10b), 137.96 (C-6a), 135.40 (C-4; Ar), 134.92 (C-5,6; isoindole), 132.76 (C-8), 131.69 (C-1a; Ar), 129.55 (C-7), 129.01 (C-9), 128.90 (C-2,6; Ar), 127.51 (C-3,5; Ar), 123.81 (C-10), 114.13 (C-10a), 52.36 (C-8; isoindole), 45.87 (C-4,7; isoindole), 44.87 (C-3a,7a; isoindole), 41.49 ($-NCH_2-$); LC-MS, m/z = 422 [M+1], 424 [M+3]; Anal. Calcd. for $C_{25}H_{19}N_5O_2$: C, 71.25; H, 4.54; N, 16.62; Found: C, 71.31; H, 4.58; N, 16.68.

2-(4-([1,2,4]Triazolo[1,5-c]quinazoline-2-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (4i). Yield: 86.87 %; m.p. 269-271 ˚C; IR (cm^{-1}): 2982, 2932, 2861, 2812, 1703, 1477, 1447, 1357, 1186, 899, 838, 778, 744, 708, 669, 608; ^{1}H NMR, δ (ppm):

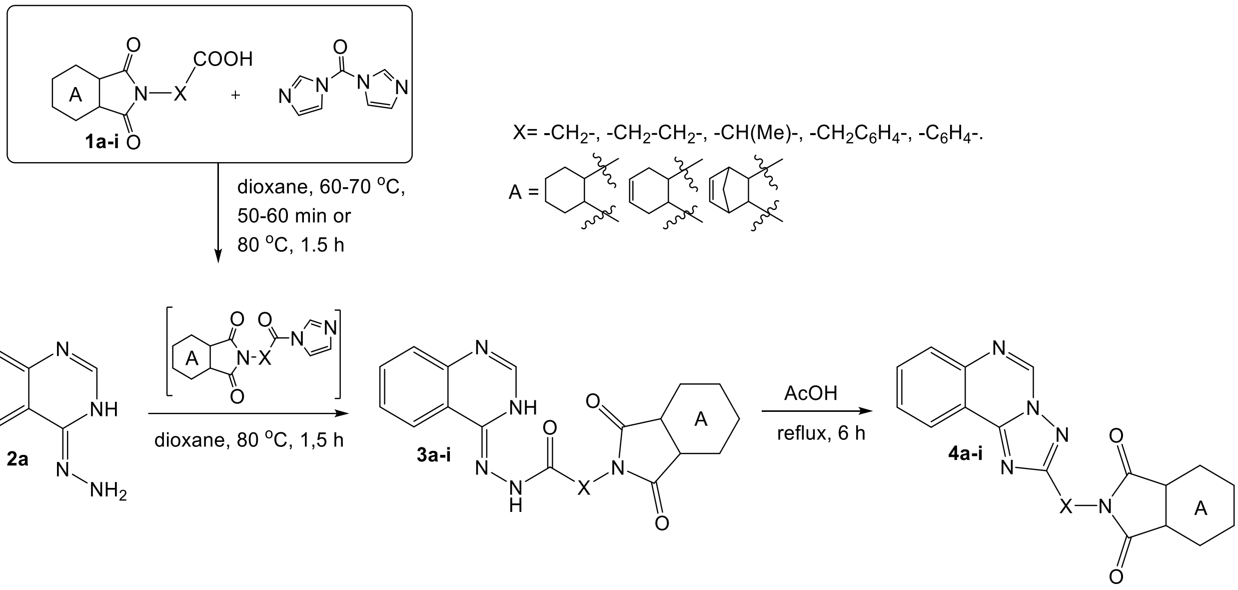
9.50 (s, 1H, H-5), 8.57 (d, *J* = 7.7 Hz, 1H, H-10), 8.36 (d, *J* = 7.8 Hz, 2H, 1,4-phenylene H-2,6), 8.07 (d, *J* = 7.7 Hz, 1H, H-7), 7.91 (t, *J* = 7.7 Hz, 1H, H-8), 7.82 (t, *J* = 7.7 Hz, 1H, H-9), 7.32 (d, *J* = 7.7 Hz, 2H, 1,4-phenylene H-3,5), 6.27 (s, 2H, isoindole H-5,6), 3.52 (s, 2H, isoindole H-4,7), 3.43 (s, 2H, isoindole H-3a,7a), 1.59 (dd, *J* = 20.7, 7.9 Hz, 2H, isoindole H-8,8'); LC-MS, m/z = 408 [M+1], 409 [M+2]; Anal. Calcd. for $C_{24}H_{17}N_5O_2$: C, 70.75; H, 4.21; N, 17.19; Found: C, 70.82; H, 4.28; N, 17.23.

The synthesized compounds are yellow, soluble in DMF, DMSO, dioxane, slightly soluble in alcohol, insoluble in water.

3. Results and discussion.

3.1. Chemistry

As it has been mentioned above, the combination in one molecule of «pharmacophore» fragments, which are responsible for hypoglycemic effect is interesting as well as structural modification and further study of pharmacological screening. Thus, following the search strategy *N*-carboxyalkyl-(arylalkyl-, aryl-)isoindoline-1,3-diones (**1a-i**) were utilized in reaction with *N*,*N'*-carbonyldiimidazole for obtaining corresponding imidazolides, in the first stage of the study (Scheme 1). The last ones formed previously unknown hydrazides (**3a-i**) in reaction with 4-hydrazinoquinazoline (**2a**). The presence of anhydrous dioxane and the temperature control (not above 80 ˚C) is obligatory for the regioselectivity of the reaction. Reaction products **3a-i** are formed with high yields and in most cases they don't need additional purification. The appearance in the ^{1}H NMR spectrum of low-field broad singlet of exocyclic *NH*-group proton of the quinazoline ring at the range of 11.60-11.46 ppm and *NH*-protons signal of the hydrazide fragment at the 10.65-9.52 ppm indicates the **3a-i** compounds formation. It is important to note, that some hydrazides, like **3a**, **3d-3g** are characterized by doubling of *NH*-protons signals of the hydrazide fragment due to prototropic tautomerism in DMSO, resulting in appearance aromatic and aliphatic protons in the form of multiplets or double signals. Besides, the IR-spectra of hydrazides (**3a-i**) are characterized by -C=O groups band valence vibrations of isoindole fragments at the 1728-1693 cm^{-1} and -C(O)NH-groups («amide-I») at the 1632-1603 cm^{-1}, valence-deformation vibrations of the N-H and C-N («amide-II») bonds at the 1566-1525 cm^{-1} as well as the band of *NH*-groups valence vibrations at the range of the 3489-3168 and 3180-2993 cm^{-1}.



Scheme 1 The synthesis of *N*-carboxyalkyl-(arylalkyl-, aryl-)-isoindoline-1,3-diones' (3*H*-quinazoline-4-ylidene)hydrazides and hydrogenated 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)alkyl-(alkaryl-, aryl-)-isoindole-1,3(2*H*)-diones

The formed hydrazides **3a-i** were subjected to cyclocondensation by known methods.[29] As we expected, intermediate [1,2,4]triazolo[4,3-*c*]quinazolines are subjected to the recyclic isomerization by the Dimroth rearrangement in acidic catalysis conditions with 2-(2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)-alkyl-(arylalkyl-, aryl-)-1*H*-isoindole-1,3(2*H*)-dione formation (**4a-i**, Scheme 1).[29,30] Signals of triazine[1,5-*c*]quinazoline ring protons namely the low-field singlet of H-5 singlet at the 9.50-9.37 ppm, doublet signals of ABCD-system at the 8.57-8.39 ppm (H-10) and 8.20-8.03 ppm (H-7) and triplets at the 8.06-7.87 ppm (H-8) and 7.86-7.76 ppm (H-9) are typical to the ^{1}H NMR spectra of compounds **4a-i**. It is important, that the aromatic proton signals of compounds **4a-i**, in comparison with compounds **3a-i**, undergo a significant paramagnetic shift what indicated the formation of an electron-deficient tricyclic system. In favor of compounds **4a** and **4h** formation also indicates the appearance of the characteristic signals of *sp*^{2}-hybridized C-2 atoms at the 169.81-166.16 ppm and C-5 at the 153.47-150.74 ppm of triazino[1,5-*c*]quinazoline ring in the ^{13}C NMR spectra.[29]

In addition, the ^{1}H NMR spectra of compounds **3a-i**, **4a-i** are characterized by signals of the corresponding hydrogenated isoindoline moieties. Thus, a totally hydrogenated isoindole moiety of compounds **3a-3c** and **4a-4c** in the ^{1}H NMR spectra is registrated as a set of multiplet signals of axial and equatorial protons at the 3.15-2.65 ppm (H-3a, H-7a), at the 1.97-1.58 ppm (H-4,4',7,7') and at the 1.59-1.23 ppm (H-5,5',6,6'). The hexahydroisoindole moiety (compounds **3d-3f**, **4d-4f**) in the ^{1}H NMR spectra is characterized by multiplet signals of H-5,6 at the 6.15-5.66 ppm and a set of multiplet of axial and equatorial protons at the 3.24-2.90 ppm (H-3a, H-7a), 2.69-2.01 ppm (H-4,4',7,7'). Whereas, the hexahydro-4,7-methanoisoindole moiety (compounds **3g-3i**) in the ^{1}H NMR spectra is characterized by multiplet signal of H-5,6 at the 6.31-5.86 ppm and a set of multiplet signals at the 3.60-3.34 ppm (H-3a, H-7a), 3.46-3.27 ppm (H-4,7) and 1.82-1.48 ppm (H-8,8'). The multiplicity of indicated signals in the compounds **4g-4i** differs slightly: the H-5,6 signals are recorded at the 6.27-5.95 ppm, H-4,7 at the 3.52-3.37 ppm, H-3a, H-7a at the 3.43-3.32 ppm and doublet of doublets H-8,8' at the 1.67-1.59 ppm. In addition, there are signals of «linker» alkyl-, aryl- groups for which the corresponding multiplicity and chemical shift of protons are typical to the ^{1}H NMR spectra.[31]

In the IR spectra of compounds **4a-i** there are no bands of vibrations of exchangeable protons differing from compounds **3a-i**, whereas the bands of C=O groups of isoindole fragments at the 1721-1689 cm^{-1} and $\nu_{C=C}$-aromatic rings bonds at the 1515-1381 cm^{-1}, non-flat deformation vibrations of $\gamma_{=C-H}$-bond at the 899-608 cm^{-1} and intensive bands of symmetric and antisymmetric valence vibrations of -CH$_2$ groups at the 2989-2359 cm^{-1} are present.

3.2. Hypoglycemic assay for preliminary *in vivo* testing

The screening results of hypoglycemic activity (Table 1) showed, that synthesized compounds have different effects on glucose level in the blood of experimental animals. Thus, the compounds **3a**, **3f**, **3h**, **4a**, **4c** and **4f** decrease the glucose level on the second hour of the experiment on 13.99%, 4.09%, 11.86%, 18.47%, 3.18% and 8.61% respectively, substantially yielded to the action of «Metformine». It is important, that only compounds **3a**, **3h**, **4f** keep this activity on the fourth hour of the experiment (reduce glucose level on 27.87%, 10.51% and 2.65% respectively). While the compounds **3b**, **3c**, **3e**, **3i**, **4b**, **4e** and **4i** under the given experimental conditions, on the contrary, increased glucose level on the second hour of the experiment from 4.89 to 15.79% (Table 1).

Table 1 The synthesized compounds' influence on glucose level in blood of experimental animals (%)

Comp.	Initial glucose level	Glucose level in 2 h	%	Glucose level in 4 h	%	Glucose level in 6 h	%
Intact group	6.12+0.12	6.60±0.08	+7.84	5.62±0.14	-8.17	5.85±0.13	-4.41
3a	7.93±0.83	6.82±0.69	-13.99	5.72±0.49	-27.87	8.46±0.79	+6.68
3b	6.46±0.12[a]	6.94±0.34	+7.43	8.08±0.79	+25.08	8.28±0.95	+28.17
3c	6.12±0.17[a]	6.80±0.29	+11.11	7.30±0.74	+19.28	7.02±0.65	+14.70
3e	6.68±0.96	7.62±0.17[a]	+14.07	8.14±0.27	+21.86	8.04±0.15[a]	+20.36
3f	5.38±0.35	5.16±0.17[a]	-4.09	5.80±0.29	+7.81	5.42±0.29	+0.74

3h	5.90±0.23[a]	5.20±0.19	-11.86	5.28±0.21	-10.51	5.20±0.19[a]	-11.86
3i	6.56±0.05[a]	7.20±0.17[a]	+9.75	7.72±0.07[a]	+17.68	7.72±0.20	+17.68
4a	6.82±0.22	5.56±0.27	-18.47	7.34±0.45	+7.62	6.88±0.17[a]	+0.88
4b	6.12±0.23	6.94±0.39	+13.39	7.08±0.47	+15.68	6.78±0.35	+10.78
4c	6.28±0.34	6.08±0.26	-3.18	6.56±0.33	+4.46	6.30±0.13[a]	+0.32
4e	6.28±0.06[a]	7.10±0.13[a]	+13.06	7.58±0.33	+20.70	8.36±0.41	+33.12
4f	6.04±0.20	5.52±0.33	-8.61	5.88±0.17[a]	-2.65	5.34±0.21	-11.59
4h	5.72±0.41	6.00±0.28	+4.89	5.16±0.35	-9.79	4.98±0.37	-12.94
4i	6.46±0.07[a]	7.48±0.08[a]	+15.79	8.50±0.43	+31.58	8.20±0.26	+26.93
Metformine	5.50±0.20[a]	3.71±0.08[a]	-67.60	3.42±0.06[a]	-62.30	3.64±0.06[a]	-66.10

[a] – differences reliable ($p \le 0.05$) comparison to intact group of rats.

The insulinotropic effect of prandial glucose regulators comes very quickly unlike other oral hypoglycemic agents. Insulin secretion stimulation from *β*-cells of the pancreas islands is formed in 5-7 minutes («Mitiglinide», «Nateglinide») or in 10-30 minutes after using («Repaglinide») these drugs in response to food intake. This is achieved by closing ATP-dependent potassium canals in the membrane of *β*-cells due to their depolarization. Molecular docking to KATP channel, PDB ID-6BAA was conducted, for a number of synthesized compounds (**3a**, **3f**, **3h**, **4a**, **4c**, **4f** and **4i**), taking into account the search strategy. It allowed to identify main interaction types of the synthesized compounds, «Mitiglinide» and «Glibenclamide» with the amino acid residues with active channel centers and select compounds for further studies (Table 2).[32]

Table 2 Types of investigated compounds' interactions with amino acid residues of the target active center according to the docking studies

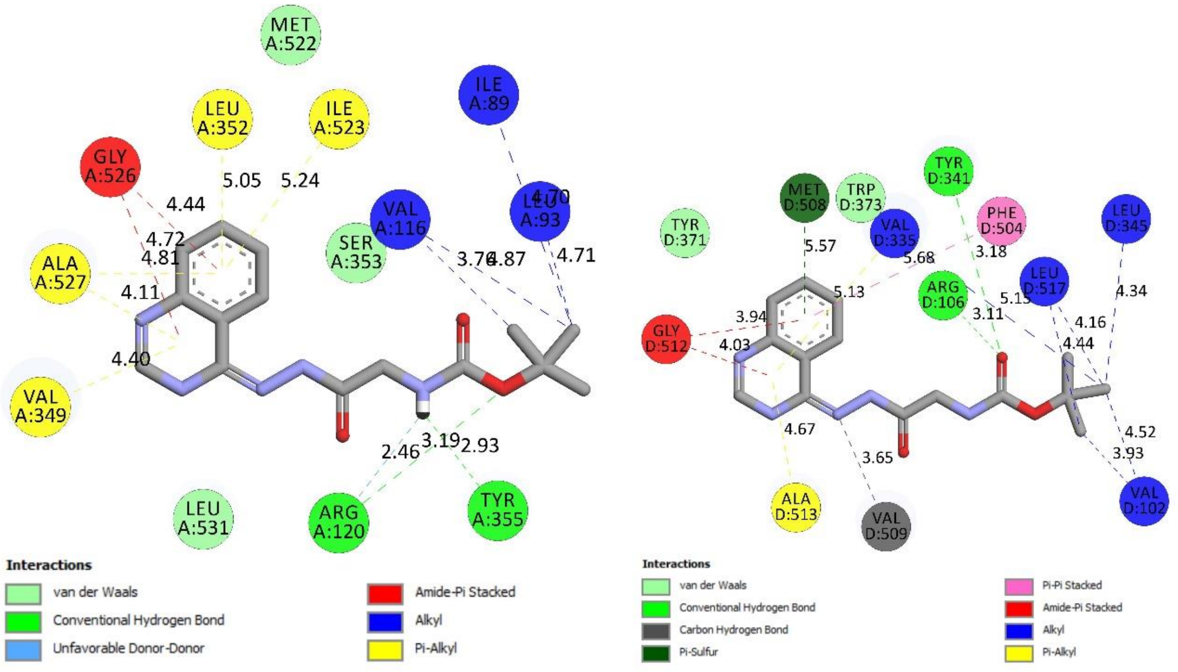
	Investigated protein and types of interactions with amino acid residues	
Comp.	Affinity, kcal/mol	KATP channel, PDB ID-6BAA
3a	-8.2	ARG1246[a], ARG1300[b], TYR377[a], LEU434[c], TYR377[c], LEU592[c].
3f	-8.2	ARG1300[a], ASP1304[b], ILE381[c], TRP430[c], PHE433[c], ARG1300[c], ALA1303[c].
3h	-8.2	SER1238[a], ARG1246[a], HASN1245[a], TRP430[c], ILE381[c].

4a	-8.5	ASN1245[a], ILE381[c], ILE385[c], MET429[c], PHE433[c], ILE381[c].
4c	-9.5	THR588[a], LEU592[c], PHE591[c], TYR377[c]. TYR377[c], LEU592[c].
4f	-9.5	THR588[a], LEU592[c], TYR377[c], TYR377[c], PHE591[c].
4h	-10.1	THR1242[a], SER1238[a], TRP430[c], LEU434[c], TYR377[c], TRP430[c], MET429[c], TRP430[c], TRP430[c], ILE381[c], LEU434[c].
4i	-9.0	ARG1145[a], ARG1300[a,b], TRP1297[c], TRP1297[c], TRP1297[c], TRP1297[c], TRP1297[c], PHE591[c], TRP430[c], PHE433[c], LEU592[c].
Mitiglinide	-7.5	THR1242[a], LEU434[c], TYR377[c], TRP430[c], TRP430[c], PHE433[c].
Glibenclamide*	-8.4	ARG306[a], ASN437[a], THR1242[a], ARG1246[a], ASN1245[a], TYR377[a], ASN437[a], TYR377[a], MET441[c], MET429[c], LEU592[c].

[a] - hydrogen; [b] - electrostatic; [c] - hydrophobic

*- data according to X-ray structure of protein.[32]

The visualization of the interaction of the structures with the active site of KATP channel (Figure 2) showed, that compound **3a** and **4a** revealed similar interaction to «Glibenclamide». Such, common interactions for compound **3a** were: two hydrogen bonds with the amino acid residues ARG1246 (3.12Å), TYR377 (3.96Å) and two hydrophobic interactions with the residues LEU592 (5.44Å), TYR377 (5.17Å). And common interactions for compound **4a** were as following: hydrogen bond with the amino acid residue ASN1245 (3.76Å) and hydrophobic interaction with the residue MET429 (4.74Å). This may indicate, that stated class of compound might have ability to act as «Glibenclamide» does.



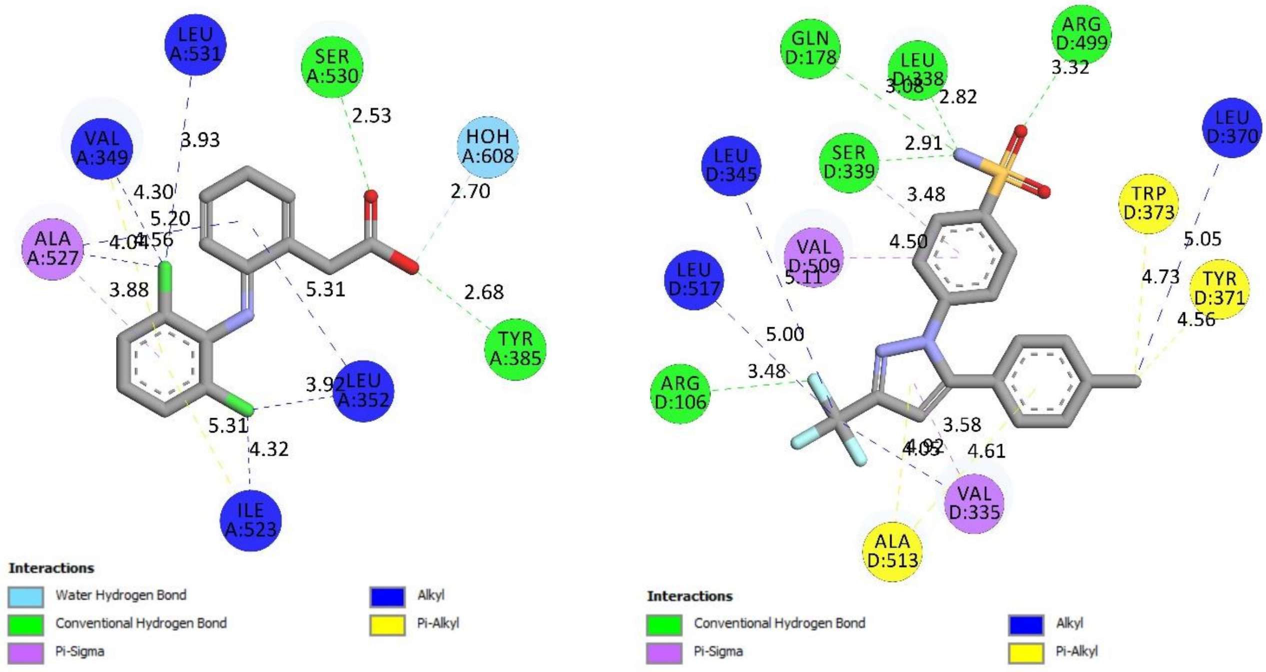


Figure 2 Visualization of affinity according to the docking a) compound **3a** with KATP channel; b) compound **4a** with KATP channel; c) «Mitiglinide» with KATP channel; d) «Glibenclamide» with KATP channel.

Hypoglycemic activity studying in the shorter of the experimental period with a previous glucose loading allowed to establish, that compounds **3a**, **3f**, **3h**, **4a**, **4f** reduced glucose level on 19.34%, 17.54%, 18.85%, 25.09% and 9.51% respectively on the 15 minute of the experiment, compared to control group (Table 3). It is important, that the hypoglycemic effect of these compounds is maintained throughout the experiment from 30 to 120 minutes. While compounds **4c**, **4h** and **4i** didn't affect glucose level and in some cases even increased it throughout the experiment.

Table 3 Influence of synthesized compounds on glucose level in blood of experimental animals in the short term of the experiment

Comp.	Initial glucose level	Glucose level in 15 min	Glucose level in 30 min	Glucose level in 60 min	Glucose level in 120 min
Control group	5.84±0.05	6.10±0.21	6.60±0.08	5.62±0.14	5.85±0.13
3a	4.34±0.12^{a}	4.92±0.59	4.68±0.54	4.93±1.14	3.84±0.51
3f	5.12±0.15^{a}	5.03±0.14^{a}	4.87±0.19^{a}	5.23±0.12^{a}	5.12±0.34
3h	4.48±0.23	4.95±0.21	4.92±0.19^{a}	5.41±0.24	5.32±0.16^{a}
4a	3.98±0.13^{a}	4.63±0.31	4.52±0.22	4.49±0.14^{a}	5.54±0.11^{a}
4c	5.83±0.27	6.23±0.17^{a}	6.93±0.26	6.08±0.19^{a}	6.12±0.20

4f	5.34±0.22	5.52±0.23	5.48±0.22	5.52±0.15[a]	5.32±0.17[a]
4h	5.87±0.25	6.13±0.31	6.54±0.27	5.89±0.24	5.93±0.21
4i	6.10±0.21	8.50±0.58	6.78±0.85	6.34±0.49	5.98±0.38

[a] – differences reliable ($p \le 0.05$) comparison to control group of rats.

SAR - analysis showed, that the compounds with (3*H*-quinazoline-4-ylidene)hydrazides (**3a**, **3f**, **3h**) or [1,2,4]triazolo[1,5-*c*]quinazoline (**4a**, **4f**) moeities bonded through the ethyl (**3a**, **4a**) or phenyl (**3f**, **3h**, **4f**) «linker» groups with a hydrogenated isoindoline ring have hypoglycemic effect in the short term of the experiment. Modification of compounds and their further studies on hypoglycemic activity are going to be continue.

4. Conclusions

The synthesis of *N*-carboxyalkyl-(arylalkyl-, aryl-)-isoindoline-1,3-diones' (3*H*-quinazoline-4-ylidene)hydrazides was carried out using activated *N*-protected aminoacids and 4-hydrazinoquinazoline. The synthesized hydrazides were converted into the corresponding hydrogenated 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl)-alkyl-(alkaryl-, aryl-)-isoindole-1,3(2*H*)-diones by cyclocondensation under the conditions of acidic catalysis. The structure of synthesized compounds was established, using IR-, ^{1}H and ^{13}C NMR spectroscopy and LC-MS and the features of spectral pattern were discussed. Search strategy of hypoglycemic drugs based on the «fragment-oriented design» revealed a number of perspective compounds, which are short-acting drugs like prandial glucose regulators. Conducted SAR-analysis showed, that the introduction of hydrogenated 1,3-dioxoisoindole moiety bonded *via* «linker» group with 4-hydrazynoquinazoline and triazolo[1,5-*c*]quinazoline cycle is reasonable in the context of searching short-acting hypoglycemic agents and requires further research.

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6. References

1. B. M. Santosh, P. A. Narshinha, *Tetrahedron* **2006**, *62,* 9787–9826.
DOI:10/1016/j.tet.2006.07.098
2. J. P. Michael, *Nat Prod Rep* **2007**, *24,* 223–246.
DOI:10.1039/B509528J
3. U. A. Kshirsagar, *Org Biomol Chem* **2015**, *13(36),* 9336-9352.
DOI:10.1039/c5ob01379h
4. A. N. Parvez, R. Arpana, M. Imran, *IJPBA* **2011**, *2(6),* 1651-1657.
5. P. S. Theivendren, V. K. Palanirajan, *Res In Pharm* **2011**, *1(1),* 1-21.
6. G. Marzaro, A. Guiotto, A. Chilin, *Expert Opin Ther Pat* **2012**, *22(3),* 223-252.

DOI:10.1517/13543776.2012.665876

7. S. Ravez, O. Castillo-Aguilera, P. Depreux, L. Goossens *Expert Opin Ther Pat* **2015**, *25(7)*, 1-16.

DOI:10.1517/13543776.2015.1039512

8. A. O. Olayinka, Y. A. Oluwatosin, D. V. Aderohunmu, F. E. Owolabi, A. O. Olomieja. *Am J Drug Discov Dev* **2017**, *7*, 1-24.

DOI:10.3923/ajdd.2017.1.24

9. S. Srivastava, S. Srivastava, *IJPSR* **2015**, *6(9)*, 1206-1213. http://www.ijpsr.info/docs/IJPSR15-06-09-102.pdf.

10. D. Wang, F. Gao, *Chem Cent J* **2013**, *7(95)*, 1-15.

DOI:10.1186/1752-153X-7-95

11. I. Khan, A. Ibrar, N. Abbas, A. Saeed, *Eur J Med Chem* **2014**, *76*, 193-244. **DOI**:10.1016/j.ejmech.2014.02.005

12. A. Mohammad, *Int J Med Chem* **2014**, *27*, 1-27.

DOI:10.1155/2014/395637

13. V. G. Ugale, S. B. Bari, *Eur J Med Chem* **2014**, *80*, 447-501. **DOI**:10.1014/j.ejmech.2014.04.072

14. O. Voskoboynik, S. Kolomoetsch, G. Berest, I. Nosulenko, Yu. Martunenko, S. Kovalenko, *Chem Heterocyc Compd* **2017**, *53(3)*, 256-272.

DOI:10.1007/s10593-017-2048-2

15. A. G. Reddy, V. H. Babu, Y. J. Prakash Rao, *JCPS* **2017**, *10(3)*, 1492-1504.

16. Z. Chaban, St. Harkov, T. Chaban, O. Klenina, V. Ogurtsov, I. Chaban, *Pharmacia* **2017**, *64(3)*, 52-66. https://www.researchgate.net/publication/322731545.

17. A. Hameed, M. al-Rashida, M. Uroos, S. A. Arshia, M. Ishtiaq, K. M. Khan, *Expert Opin Ther Pat* **2018**, *28 (4)*, 281-297.

DOI:10.1080/13543776.2018. 1432596

18. Ol. Antypenko, S. Kholodnyak, K. Schabelnyk, L. Antypenko, S. Kovalenko, *Chem Heterocyc Compd* **2017**, *53(3)*, 292-309.

DOI:10.1007/s10593-017-2051-7

19. O. Kolomoets, O. Voskoboynik, Ol. Antypenko, G. Berest, I. Nosulenko, V. Palchikov, O. Karpenko, S. Kovalenko, *Acta Chim. Slov* **2017**, *64*, 902-910.

DOI: 10.17344/acsi.2017.3575

20. P. J. Hajduk, J. Greer, *Nat Rev Drug Discov* **2007**, *6(3)*, 211-219.

DOI:10.1038/nrd2220

21. D. A. Erlanson, *Berlin Heidelberg: Springer-Verlang* **2012**, 1-32.

DOI:10.1007/978-3-642-27540-1

22. Yu. Martunenko, M. Kazunin, O. Antypenko, Ye. Selivanova, S. Kovalenko, S. Trzhetsynskyi, *Current issues in pharmacy and medicine: science and practice* **2018**, *11 (1)*, 4-11.

DOI:10.14739/2409-2932

23. H. Ohnota, T. Koizumi, N. Tsutsumi, M. Kobayashi, S. Inoue, F. Sato, *J Pharmacol Exp Ther* **1994**, *269(3)*, 489-495.
24. W. J. Malaisse, *Expert Opin Pharmaco* **2008**, *9(15)*, 2691-2698.
25. https://www.drugbank.ca/unearth/q?c=_score&d=down&query=quinazolines&searcher=drugs.
26. Protein Data Bank, pdb. Retrieved from [http://www.pdb.org.](http://www.pdb.org)
27. MarvinSketch version: 17.21.0, ChemAxon (http://www.chemaxon.com).
28. O. Trott, A. J. Olson, *J Comput Chem* **2010**, *31*, 455-461.

DOI:10.1002/jcc.21334

29. S. Kovalenko, L. Antypenko, A. Bilyi, S. Kholodnyak, O. Karpenko, O. Antypenko, N. Mykhaylova, T. Los', O. Kolomoets', *Sci Pharm* **2013**, *81(2)*, 359-392. **DOI**:10.3797/scipharm.1211-08
30. El H. Sayed, El Ashrya, S. Nadeem, M. R. Shah, Ye. El Kilanyd, *Adv Heterocycl Chem* **2010**, *101*, 161-228.
31. E. Breitmaier, Structure Elucidation By NMR In Organic Chemistry: A Practical Guide, John Wiley &Sons, Ltd. **2002**, 258.
32. M. M. Gregory, B. Kandasamy, F. DiMaio, C. Yoshioka, S. Show-Ling, *eLife* **2017**, *6*. **DOI**:10.7554/elife.31054