Targeted search of hypoglycemic agents among *N*-substituted isoindoline-1,3-diones and its analogues

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It is known, that increasing of glucose level in the blood is an important factor at the risk of vascular complications in diabetes mellitus type 2 development. Taking this into account, short-acting priming regulators of glycemia (meglitinides) are designed, such as tableted sugar-reducing drugs with short acting insulin secretion stimulation. They are characterized by a slight decrease of glycohemoglobin content, the risk of body weight gain and decrease of efficacy during long-term usage despite their effectiveness. The solution of this problem can be as following: the creation of more effective drugs, which would contain known antidiabetic "pharmacophore" fragments able to provide a long-term hypoglycemic effect and having a polyvectoral mechanism of activity and effect both on symptoms of the disease and on disease etiology.

The aim of the work is targeted search of hypoglycemic isoindoline-1,3-dione derivatives and its hydrogenated analogues based on rational design, structural similarity to metglitinides, molecular docking and traditional pharmacological screening.

Materials and methods: laboratory utensils and organic solvents, "Stuart Scientific SMP30" melting point apparatus, ELEMENTAR vario EL Cube elemental analyzer, Bruker ALPHA FT-IR spectrometer, Varian-Mercury 400 ^{1}H NMR spectrometer, Agilent 1100 Series liquid chromatograph, Marvin Sketch 17.21, AutoDockTools-1.5.6, Discovery Studio 4.0.

Results. The targeted search of hypoglycemic agents among *N*-substituted isoindoline-1,3-diones and its analogues based on the structural similarity with existing active pharmaceutical ingredients, using molecular docking and traditional pharmacological screening was performed in the work. Mentioned compounds were synthesized by the refluxing of phthalic anhydride and its analogs with aminoalkyl-(alkaryl-,aryl-) carboxylic acids in the medium of the acetic acid. It was shown, that refluxing of 3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione with glycine under the given conditions resulted the retro Diels-Alder reaction and formation of (*Z*)-4-((carboxymethyl)amino)-4-oxobut-2-enoic acid. Elemental analysis, chromatomass-, IR- and ^{1}H-NMR spectral methods were used to prove the structure and individuality of the synthesized compounds.

Conclusion. A number of compounds were synthesized and chemically modified. Research of their hypoglycemic activity was carried out, that raveled a number of high active substances. Certain "structure – activity relations" were established and the perspective directions of their further chemical modification were substantiated.

Спрямований пошук гіпоглемічних агентів серед *N*-заміщених ізоіндолін-1,3-діонів та їх аналогів

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Відомо, що підвищення рівня глюкози у крові – важливий чинник ризику розвитку судинних ускладнень при цукровому діабеті 2 типу. Враховуючи це, розробили регулятори глікемії (меглітиніди) – цукрознижувальні засоби, механізм дії котрих спрямований на стимулювання секреції інсуліну протягом короткого проміжку часу. Незважаючи на ефективність, для них характерне незначне зменшення вмісту глікогемоглобіну, ризик набору маси тіла та зниження ефективності під час тривалого застосування. Вирішення цієї проблеми можливе тільки шляхом створення ефективніших препаратів, котрі б поєднували відомі антидіабетичні «фармакофорні» фрагменти, що здатні забезпечувати тривалий гіпоглікемічний ефект, впливати на симптоми захворювання і причини їх виникнення.

Мета роботи – спрямований пошук гіпоглікемічних агентів серед похідних ізоіндолін-1,3-діонів і його гідрованих аналогів на основі раціонального дизайну, структурної подібності до метглітинідів, молекулярного докінгу та традиційного фармакологічного скринінгу.

Матеріали та методи. Лабораторний посуд та органічні розчинники, апарат для визначення температури плавлення «Stuart Scientific SMP30», елементний аналізатор ELEMENTAR vario EL Cube, ІЧ спектрометр Bruker ALPHA FT-IR, ^{1}Н ЯМР-спектрометр Varian-Mercury 400, рідинний хроматограф Agilent 1100 Series, програмне забезпечення Marvin Sketch 17.21, Hyper Chem 8.0.8, AutoDockTools-1.5.6, Discovery Studio 4.0.

Результати. Виконали спрямований пошук гіпоглікемічних агентів серед *N*-заміщених ізоіндолін-1,3-діонів і його аналогів на основі структурної подібності з наявними активними фармацевтичними інгредієнтами з використанням молекулярного докінгу, традиційного фармакологічного скринінгу. Сполуки синтезували взаємодією фталевого ангідриду та його аналогів з аміноалкіл-(алкаріл-,арил-)

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карбоновими кислотами при нагріванні в оцтовій кислоті. Показано, що при нагріванні 3а,4,7,7а-тетрагідро-4,7-епоксиізобензофуран-1,3-діону з гліцином при заданих умовах відбувається реакція ретро Дільса–Альдера та утворюється (Z)-4-((карбоксиметил) аміно)-4-оксобут-2-енова кислота. Будову та індивідуальність синтезованих сполук доведено елементним аналізом, хромато-мас, ІЧ- і ^{1}Н-ЯМР спектральними методами.

Висновки. У результаті досліджень синтезували та хімічно модифікували ряд сполук, вивчили їхню гіпоглікемічну активність, виявили ряд високоактивних речовин, встановили певні закономірності «структура – дія» та обґрунтували перспективні напрями хімічної модифікації.

Ключові слова: карбонові кислоти, молекулярне док-моделювання, синтез, магнітно-резонансна спектроскопія, гіпоглікемічні засоби.

Актуальні питання фармацевтичної і медичної науки та практики. – 2018. – Т. 11, № 1(26). – С. 4–11

Направленный поиск гипогликемических агентов среди *N*-замещенных изоиндолин-1,3-дионов и их аналогов

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Известно, что повышение уровня глюкозы в крови является важным фактором риска развития сосудистых осложнений при сахарном диабете 2 типа. С учетом этого разработаны короткодействующие регуляторы гликемии (меглитиниды) – сахароснижающие средства, механизм действия которых направлен на стимулирование секреции инсулина в течение короткого промежутка времени. Несмотря на эффективность, для них характерно незначительное уменьшение содержания гликогемоглобина, риск набора массы тела и снижение эффективности при длительном применении. Решение этой проблемы возможно только путем создания более эффективных препаратов, объединяющих известные противодиабетические «фармакофорные» фрагменты, способные обеспечивать длительный гипогликемический эффект и влиять на симптомы заболевания и причины их возникновения.

Цель работы – направленный поиск гипогликемических агентов среди производных изоиндолин-1,3-дионов и их гидрированных аналогов на основе рационального дизайна, структурного сходства с метглитинидами, молекулярного докинга и традиционного фармакологического скрининга.

Материалы и методы: лабораторная посуда и органические растворители, аппарат для определения температуры плавления «Stuart Scientific SMP30», элементный анализатор ELEMENTAR vario EL Cube, ИК спектрометр Bruker ALPHA FT-IR, ^{1}Н ЯМР спектрометр Varian-Mercury 400, жидкостный хроматограф Agilent 1100 Series, программное обеспечение Marvin Sketch 17.21, Hyper Chem 8.0.8, AutoDockTools-1.5.6, Discovery Studio 4.0.

Результаты. Проведен направленный поиск гипогликемических агентов среди *N*-замещенных изоиндолин-1,3-дионов и их аналогов на основе структурного сходства с существующими активными фармацевтическими ингредиентами с использованием молекулярного докинга и традиционного фармакологического скрининга. Указанные соединения синтезированы взаимодействием фталевого ангидрида и его аналогов с аминоалкил-(алкарил-,арил) карбоновыми кислотами при нагревании в уксусной кислоте. Показано, что при нагревании 3а,4,7,7а-тетрагидро-4,7-эпоксиизо-, бензофуран-1,3-диона с глицином при заданных условиях протекает реакция ретро Дильса–Альдера и образуется (Z)-4-((карбоксиметил)амино)-4-оксобут-2-еновая кислота. Строение и индивидуальность синтезированных соединений доказано элементным анализом, хромато-масс, ИК- и ^{1}Н-ЯМР спектральными методами.

Выводы. В результате исследований синтезированы и химически модифицированы соединения, проведены исследования на их гипогликемическую активность, выявлен ряд высокоактивных веществ, установлены определенные закономерности «структура – действие» и обоснованы перспективные направления их дальнейшей химической модификации.

Ключевые слова: карбоновые кислоты, молекулярной стыковки моделирование, синтез, магнитно-резонансная спектроскопия, гипогликемические средства.

Актуальные вопросы фармацевтической и медицинской науки и практики. – 2018. – Т. 11, № 1(26). – С. 4–11

Introduction

It is known, that increasing of glucose level in the blood in post-meal periods (postprandial glycemia) is separate and very important factor at the risk of vascular complications in diabetes mellitus type 2 development [1,2]. Taking this into account, short-acting priming regulators of glycemia (meglitinides) are designed, such as tableted sugar-reducing drugs with short acting insulin secretion stimulation. The release of an insulin additional amount during 3–4 hours when it is necessary to normalize the sugar level in critical post-meal periods is physiological and it reproduces the early insulin secretion of healthy people. Prandial regulators are taken only with the main meal because the pancreas don`t deplete so rapidly and stimulation of insulin releasing doesn`t always occur. As a result, the risk of hypoglycemic reactions decreases. Meglitinides are being rapidly absorbed from the gastrointestinal tract which led to a maximum increase of the drug concentration in plasma after 1 hour. They are completely eliminated from the organism after 4–6 hours. This feature provides better control of postprandial glycemia. Metglinides are characterized by a slight decrease of the glycohemoglobin content (HbA1C, approximately 0.5–0.8 %), the risk of body weight gain, that is also typical for sulfonylureas and decrease of efficacy during long-term using despite the effectiveness of meglitinides [3,4]. The solution of this problem can be as following: the creation of more effective drugs among different classes of heterocyclic compounds, the combination of drugs, or drugs, that would contain known antidiabetic «pharmacophore» fragments able to provide a long-term hypoglycemic effect and having a polyvectoral mechanism

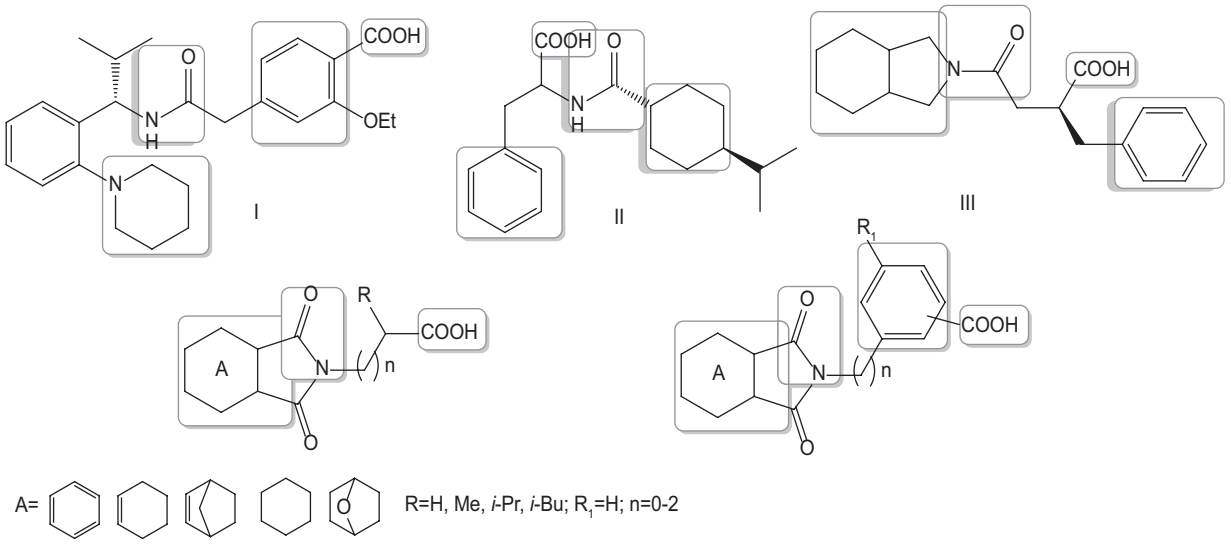


Fig. 1. Search strategy of hypoglycemic agents based on the structural similarity to the prandial glycemic regulators (I: repaglinide, II: nateglinide, III: mitiglinide).

of action and effect both on the symptoms of the disease and on disease etiology of this problem [5–8].

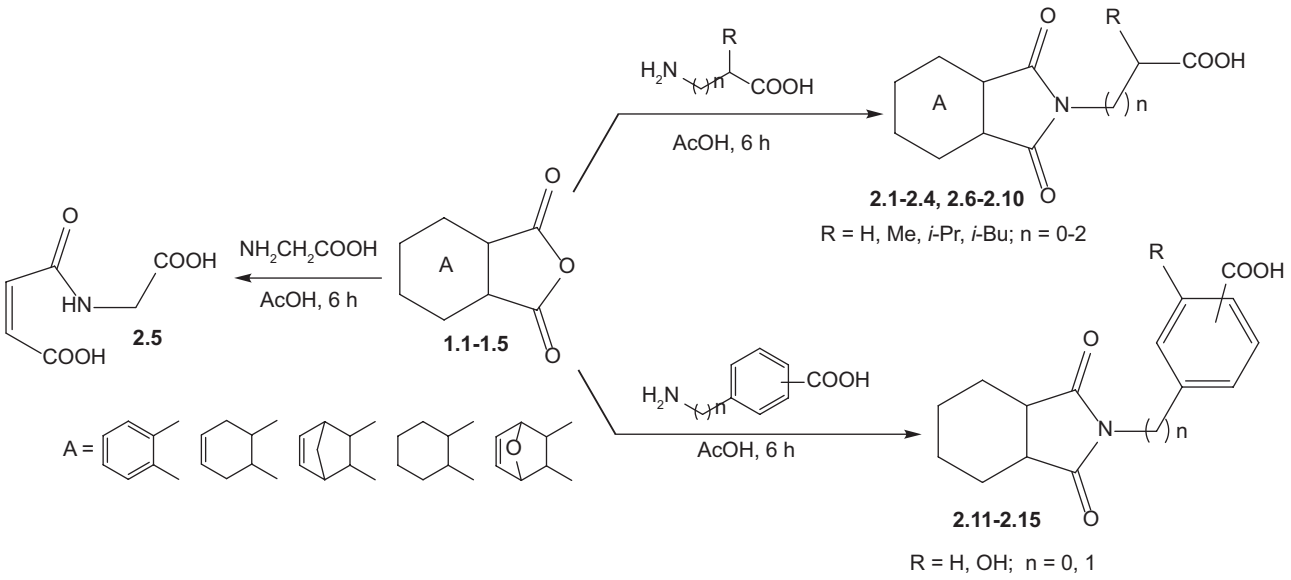
So, the search of hypoglycemic agents among derivatives of isoindoline-1,3-diones and its hydrogenated analogues based on the rational design such as structural similarity to meglitinides, molecular docking and traditional pharmacological screening is **the aim of this work**.

Results and discussion

The simultaneous combination of fragments alike to metglinide in one molecule is interesting because of its structural modification and further pharmacological study of hypoglycemic action. The first stage of the work was to create virtual combinatorial library consisting of 80 compounds. Structures were also analyzed to determine possible interactions with proteins that are responsible for the hypoglycemic action mechanism (*Table 1*). Such strategy is rational, taking into account the availability of initial cyclic anhydrides (phthalic and its structural analogues) and aminoacids. And what it is important, that stated strategy provides the possibility to synthesize different isoindoline-1,3-diones and its hydrogenated analogues connected through "linker" fragments with the carboxyl function group (*Fig. 1*).

A series of cyclic imides (**2.1–2.4**) were synthesized at the subsequent stage of the study by the interaction of anhydrides (**1.1–1.5**) with glycine in the medium of acetic acid. It`s interesting to note, that interaction of 3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione (**1.5**) with glycine, revealed elimination of furan (the retro Diels-Alder reaction) under the given conditions. Amide of maleic acid (**2.5**) was isolated as an individual compound as the result of the mentioned reaction (*Scheme 1*).

Scheme 1.



The results of the pharmacological screening of compounds **2.1–2.5** showed, that compound **2.4** (*Table 1*) is the most promising for further structural modification. Taking into account the above mentioned facts, the further strategy of hypoglycemic agents search, was to modify the substituent of the second position in compound **2.4** using various amino-alkyl-(alkaryl-,aryl-)carboxylic acids. Especially when their synthesis (like the previous compounds) was estimated to refluxing of the starting compounds in the medium of acetic acid during 6 hours. In this case, the individual imides were formed with satisfactory yields (**2.6–2.15**, *scheme 1*). It is important, that aminoacids with branched alkyl substituents or structural analogues of *p*-aminobenzoic acid didn`t require special reaction conditions.

Compound **2** is the result of the reaction, according to the molecular ion [M+1] of LC-MS spectra, which confirms the regioselectivity of the process. However, the imides **2.1–2.4**, **2.6–2.15** formation was proved with the help of ^{1}H NMR spectra for sure. Thus, in the spectra of these compounds there were no signals of amide groups, except compound **2.5**, in which the signal of the amide proton resonated as a triplet at the 9.44 ppm. In addition, the spectrum of compound **2.5** was characterized by two doublets at the 6.53 ppm and the 6.21 ppm with J = 12.7 Hz, which confirmed the presence of -CH=CH-fragment with *cis*-geometry of the molecule and the retro Diels-Alder reaction. Whereas, in the spectra of compounds **2.1–2.4**, **2.6–2.15**, a specific set of signals was recorded, this characterized the presence of different saturated isoindole cycle. Thus, in the spectrum of compound **2.1**, magnetically equivalent two proton singlets at the 7.87 and at the 7.83 ppm at fourth, fifth, sixth, seventh positions were recorded, that indicate its aromaticity. Instead, in the spectrum of compound **2.2** there was a two proton multiplet of an unsaturated H-5,6 bond at the 5.86 ppm, a multiplet at the 3.17 ppm (H-3a, 7a) and two doublets at the 2.32 and at the 2.21 ppm with J = 14.2 Hz, due to the structure peculiarity of the partial hydrogenated fragment of the molecule. In the spectrum of compound **2.3**, signals of protons of stereotropic methylene group were additionally recorded at the 1.66 and at the 1.60 ppm with J = 8.4 Hz. A series of multiplet signals in a strong field at the 3.52–2.18 ppm (H-3a, 7a), at the 2.10–1.50 ppm (H-4, 7) and at the 1.54–1.19 ppm (H-5, 6) were characteristic for the spectra of compounds **2.4**, **2.6–2.15**. In some cases they undergo further splitting due to the presence of an asymmetric Carbone atom (compounds **2.7**, **2.8**, **2.10**) and indicate the presence of a perhydrogenated isoindole cycle. It is also important, that compounds **2.1–2.15** have a characteristic singlet signal of the proton of carboxylic acid in the range of the 13.81–12.01 ppm. The aliphatic protons of compounds **2.1–2.4**, **2.6–2.10** were characterized by a "classical" multiplicity, which depend on the proton environment and the presence of an asymmetric center. Thus, the singlet protons of the -CH_2- group in the second position of compounds **2.1–2.4**, **2.11** were recorded at the 4.60, 4.27, 4.00, 3.85 and 4.02 ppm, respectively. The addition of the aliphatic residue (compounds **2.7**, **2.8**) led to the multiplicity change of the methylene groups (triplets or multiplets) and the signal offset to the lower magnetic fields (3.55–1.87 ppm). While, asymmetry center led to a characteristic dissociation of the -CH- groups: quadruplet at the 4.59 ppm (compound **2.6**), doublets at the 4.14 and 4.60 ppm and multiplets at the 1.89–1.58 ppm (**2.9**, **2.10**). Besides, methyl group also undergo additional splitting: doublets at the 1.37 ppm (**2.6**), doublets at the 1.08 and 0.80 ppm (**2.9**) and doublets at the 0.95 and 0.90 ppm (**2.10**). The aromatic protons of the compounds (**2.11**, **2.12**) were registered as the A_2B_2-system, with two doublets (H^2, H^6 and H^3, H^5) at the 7.91, 8.01 ppm and 7.34, 7.41 ppm, respectively. Replacing of carboxyl group in the second position (compound **2.14**) led to the multiplicity protons change and they were not "classical", as multiplets at the 8.04 ppm (H-3), 7.65 ppm

Table 1. Hypogycemic activity of synthesized compounds (%)

Compounds	Dose, mg/kg	Hypoglycemic activity, %			
		Starting level	2 h	4 h	6 h
Control	–	100.0	93.5	103.7	95.1
2.1	25.0	100.0	76.6	79.1	90.5
2.1	50.0	100.0	87.8	79.7	94.1
2.2	25.0	100.0	117.6	101.1	113.7
2.2	50.0	100.0	166.7	168.0	98.5
2.3	25.0	100.0	112.8	90.9	103.3
2.3	50.0	100.0	92.8	88.0	92.4
2.4	25.0	100.0	67.9	76.7	76.7
2.4	50.0	100.0	65.2	75.8	71.4
2.5	25.0	100.0	105.0	91.0	96.5
2.5	50.0	100.0	104.4	95.8	98.4
2.6	25.0	100.0	61.6	56.4	54.8
2.6	50.0	100.0	97.2	90.3	104.0
2.7	25.0	100.0	111.0	82.0	84.8
2.7	50.0	100.0	108.9	97.5	90.8
2.8	25.0	100.0	81.6	92.5	82.9
2.8	50.0	100.0	100.8	90.2	92.2
2.9	25.0	100.0	108.7	86.5	84.7
2.9	50.0	100.0	93.4	90.6	78.5
2.10	25.0	100.0	92.1	97.1	94.6
2.10	50.0	100.0	77.7	90.4	98.5
2.11	25.0	100.0	90.2	87.8	88.6
2.11	50.0	100.0	98.0	121.5	128.5
2.12	25.0	100.0	91.8	82.8	99.6
2.12	50.0	100.0	86.3	93.9	96.8
2.15	25.0	100.0	90.1	93.4	94.7
2.15	50.0	100.0	87.9	90.8	97.3
Diaformine	150.0	100.0	**67.6**	**62.3**	**66.1**

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

Compounds	Investigated proteins and types of interactions with amino acid residues		
	DPP4, PDB ID - 2RGU	γ-PPAR, PDB ID - 2XKW	HSD11B1, PDB ID - 3QQP
2.4	TYR547[a], SER630[a], TYR631[a], TYR662[a], TYR666[a], ASN710[a], TYR662[a], TYR662[a], TYR547[b]	CYS285[a], SER342[a], SER342[a]	SER170[a], ALA172[a], LEU217[a]
2.6	ARG125[a], TYR547[a], SER630[a], TYR631[a], TYR662[a], TYR666[a]	CYS285[a], SER289[a]	SER170[a], SER170[a], ALA172[a], TYR183[a]
2.8	ARG125[a], TYR547[a], SER630[a], TYR631[a], TYR662[a]	ARG288[a], ARG288[a], ILE326[a]	TYR183[a], TYR183[a], TYR177[a]
Mitiglinide	TYR662[a], TYR662[a], SER630[a], PHE357[b], TYR547[b], TYR547[b]	ARG288[a], ER289[a], LEU340[a], RG288[c], ARG288[b], RG288[b], ILE341[b], ILE341[b], ALA292[b], ILE326[b], MET329[b]	SER170[a], ALA172[a], TYR183[a], TYR177[b], LEU126[b], VAL180[b], ALA226[b], TYR183[b], VAL180[b]
Diaformine	GLU205[c], GLU206[c], TYR662[a], GLU205[a], TYR662[a], SER630[a], HIS740[a]	CYS285[a], TYR473[a], PHE282[a], TYR327[a]	SER170[a], SER170[a], LEU215[a]

a: hydrogen; **b**: hydrophobic; **c**: electrostatic.

(H-6), 7.59 ppm (H-5), 7.24 ppm (H-4). Whereas, compound **2.13** with the carboxyl group in position 3, had "classical" multiplicity with two doublets at the 8.42 and 7.68 ppm (H-6 and H-4), a singlet at the 7.98 ppm (H-2) and triplet at the 7.51 ppm (H-5 Ph). The compound **2.15** was characterized by two doublets at the 7.87 and 7.20 ppm (H-6 and H-4), multiplets at the 6.73–6.55 ppm (H-3) and singlet of OH-group at the 6.80 ppm.

The preliminary screening of hypoglycemic activity was conducted according to the standard method [9]. Results showed, that compound **2.4** has the highest activity among the corresponding isoindolylacetic acids (**2.1–2.4**) and reduced the glucose level throughout the experiment by 23.3–34.8% in dose 25.0 and 50.0 mg/kg (*Table 1*).

The modification of the molecule (compound **2.4**) by lengthening or branching of "linker" alkyl residue between the heterocycle and the carboxylic group (**2.6–2.10**) wasn`t justified in all cases. Thus, insignificant hypoglycemic activity was character for compounds **2.7–2.10**, with reduction of the glucose level on 2.9–21.5 % in doses 25.0 and 50.0 mg/kg throughout the experiment. However, the compound **2.6** was the most active in the dose 25.0 mg/kg and reduced the glucose level during 2 hours of the experiment on 38.4%. It is important, that the hypoglycemic activity of compound **2.6** also maintained during 4 and 6 hours of the experiment, thus exceeding the activity of drug-comparison, named "Diaformin" at 5.9 and 11.3 % respectively. Replacing the alkyl "linker" group on the alkaryl (**2.11**) and aryl (**2.12**, **2.15**) groups showed, that they also exhibit insignificant hypoglycemic activity. These compounds don`t decrease glucose level reliably compared to the control.

Analysis of pharmacological screening and molecular docking results was carried out to establish promising directions for further modification, which allowed to reveal the main types of interactions of the most active compounds (**2.4**, **2.6**, **2.8**), mitiglinide and diaformine with the amino acid residues of the active centers of the HSD11B1, γ-PPAR and DPP4 proteins (*Table 1*). These proteins were selected according to the literature data, as the main targets for creation of drugs for the treatment of Type 2 diabetes [10–12]. It was found, that mitiglinide and compounds **2.4**, **2.6** and **2.8** have common types of interactions. So, with the DPP4, mitiglinide and the synthesized compounds have the largest number of identical interactions with the amino acid residues involved in forming the complex in the active center of the protein. Namely, hydrogen bonds and hydrophobic interactions with TYR662, SER630 and TYR547. In addition, such hydrogen bonds were observed for the synthesized compounds: with TYR631, TYR666 and ASN710 – compound **2.4**, with ARG125, TYR631 and TYR666 – compound **2.6** with ARG125 and TYR666 – compound **2.8**. Compounds **2.4**, **2.6**, **2.8** and mitiglinide have such same interactions with HSD11B1: SER170, ALA172, TYR183 and TYR177 (*Fig. 2*).

Thus, conducted investigations of hypoglycemic activity allowed to identify a number of high active compounds, to establish "structure – activity relations" and to substantiate the perspective directions for their further modification. The above will be solved by replacing of the carboxylic group on carboxamide, sulfamide, sulfonylureas groups or modification of the isoindole cycle itself.

Experimental part

Molecular docking. 11-β-Hydroxysteroiddehydrogenase type 1 (HSD11B1, PDB ID - 3QQP), γ-peroxisomal receptor (γ-PPAR, PDB ID - 2XKW) and dipeptidylpeptidase-4 (DPP4, PDB ID - 2RGU) were used as target proteins to carry out molecular docking. These goals were chosen as the main enzymes responsible for hypoglycemic activity [9]. Metglitinide, repaglinide and nateglinide were used as reference drugs. These structures were obtained from PDB-protein bank for calculating affinity values.

Preparation of the ligand. Substances were constructed using Marvin Sketch 6.3.0 and saved as mol. Subsequently, using

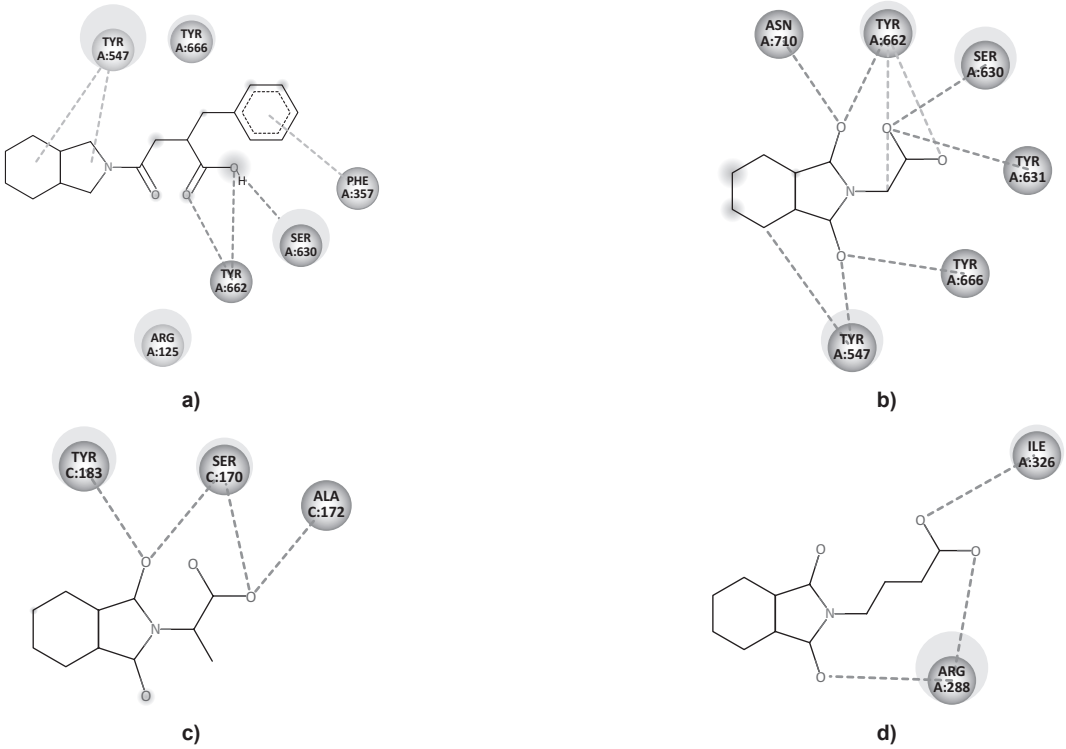


Fig. 2. Visualization of affinity according to the docking a) mitiglinide with DPP4; b) compound **2.4** with DPP4; c) compound **2.6** with HSD11B1; d) compound **2.8** with *γ*-PPAR.

the Marvin Sketch 6.3.0 program [13], 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, due to the fact that 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.

Preparation of protein. PDB files have been downloaded from a data bank of proteins [14]. Discovery Studio 4.0 was used to remove water molecules and ligands from the file. After that, the proteins were saved as PDB files. 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 = -23.247, center_y = 41.137, center_z = 5.939, size_x = 12, size_y = 14, size_z = 10 for 3QQP; center_x = 16.251, center_y = 6.145, center_z = 45.867, size_x = 14, = 18 size_y, size_z = 20 for 2XKW; center_x = 51.123, center_y = 48.163, center_z = 37.781, size_x = 16, size_y = 12, = 12 size_z for 2RGU [15]. Vina was used for proper docking. Discovery Studio 4.0 was used for visualization.

Experimental chemical part. Melting points were determined in open capillary tubes in a "Stuart Scientific SMP30" apparatus and were uncorrected. The elemental analyses (C, H, N) were performed using the ELEMENTAR vario EL Cube analyzer (USA). Analyses were indicated by the symbols of the elements or functions within ± 0.3 % of the theoretical values. IR spectra (4000–600 cm^{-1}) were recorded on a Bruker ALPHA FT-IR spectrometer (Bruker Bioscience, Germany) using a module for measuring attenuated total reflection (ATR). ^{1}H NMR spectra (400 MHz) were recorded on Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometers with TMS as internal standard in DMSO-d_6 solution. LC-MS were recorded using chromatography/mass spectrometric system which consists of high performance liquid chromatograph "Agilent 1100 Series" (Agilent, Palo Alto, CA, USA) equipped with diode-matrix and mass-selective detector "Agilent LC/MSD SL" (atmospheric pressure chemical ionization – APCI). The starting reagents and solvents were obtained from commercially available sources and were used without further purification.

The general method for the synthesis of compounds (2.1–2.15): (0.01 M) Aminoalkyl-(alkaryl-,aryl-)carboxylic acid was added to a solution (0.01 M) of the corresponding anhydride (**1.1–1.5**) in 10 ml of glacial acetic acid. The reaction mixture was heated and refluxed for 6 hours. Acetic acid was distilled under vacuum after 10 ml of water was added to the residue, cooled to 0° C., the precipitate was filtered and dried. It was crystallized from methanol if it was necessary.

2-(1,3-Dioxoisoindoline-2-yl)acetic acid (2.1). Yield: 89.3 %; Mp.: 193-196 °C; ^{1}H NMR, δ (ppm): 12.79 (s, -COOH), 7.87 (s, 2H, H-5,6), 7.83 (s, 2H, H-4,7), 4.27 (s, 2H, -CH_2-); LC-MS, *m/z* = 206 [M+1]; *Anal. Calcd.* for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83; Found: C, 58.65; H, 3.52; N, 6.95.

2-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindole-2-yl)acetic acid (2.2). Yield: 70.1 %; Mp.: 102-105 °C; ^{1}H NMR, δ (ppm): 12.69

(s, 1H, -COOH), 5.86 (m, 2H, H-5,6), 4.00 (s, 2H, -CH_2-), 3.17 (m, 2H, H-3a,7a), 2.32 (d, *J* = 14.2 Hz, 2H, H-4,7), 2.21 (d, *J* = 14.2 Hz, 2H, H-4,7); LC-MS, *m/z* = 210 [M+1]; *Anal. Calcd.* for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70; Found: C, 57.49; H, 5.38; N, 6.79.

2-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindole-2-yl)acetic acid (2.3). Yield: 77 %; Mp.: 191-194 °C; ^{1}H NMR, δ (ppm): 12.46 (s, 1H, -COOH), 6.04 (s, 2H, H-5,6), 3.85 (s, 2H, -CH_2-), 3.37 (m, 2H, H-3a,7a), 3.30 (m, 2H, 4,7), 1.66 (d, *J* = 8.4 Hz, 1H, 8-CH_2-), 1.60 (d, *J* = 8.4 Hz, 1H, 8-CH_2-); LC-MS, *m/z* = 222 [M+1]; *Anal. Calcd.* for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33; Found: C, 59.82; H, 5.09; N, 6.41.

2-(1,3-Dioxooctahydro-2H-isoindole-2-yl)acetic acid (2.4). Yield: 76.2 %; Mp.: 75-79 °C; ^{1}H NMR, δ (ppm): 12.01 (s, -COOH), 4.02 (s, 2H, -CH_2-), 2.93 (m, 2H, H-3a,7a), 1.78 (m, 4H, H-4,7), 1.45 (m, 4H, H-5,6); LC-MS, *m/z* = 213 [M+1]; *Anal. Calcd.* for $C_{10}H_{13}NO_4$: C, 56.8; H, 6.20; N, 6.63; Found: C, 57.11; H, 6.29; N, 6.71.

(Z)-4-((Carboxymethyl)amino)-4-oxobut-2-enoic acid (2.5). Yield: 59.9 %; Mp.: 115-118 °C; ^{1}H NMR, δ (ppm): 13.81 (s, 1H, -COOH), 9.44 (t, 1H, -C(O)NH-), 6.53 (d, *J* = 12.7 Hz, 1H, =C*H*-COOH), 6.21 (d, *J* = 12.7 Hz, 1H, =C*H*-C(O)NH-), 3.93 (d, *J* = 5.4 Hz, 2H, -CH_2-); LC-MS, *m/z* = 172 [M+1]; *Anal. Calcd.* for $C_6H_7NO_5$: C, 41.63; H, 4.08; N, 8.09; Found: C, 41.69; H, 4.13; N, 8.12.

2-(1,3-Dioxooctahydro-2H-isoindole-2-yl)propanoic acid (2.6). Yield: 30.5 %; Mp.: 149-151 °C; IR (cm^{-1}): 1744, 1676, 1405, 1188, 1083, 893, 853, 767, 736, 619; ^{1}H NMR, δ (ppm): 12.67 (s, 1H, -COOH), 4.59 (q, *J* = 7.1 Hz, 1H, -CH-), 2.98-2.86 (m, 2H, H-3a,7a), 1.78-1.54 (m, 4H, H-4,7), 1.37 (d, *J* = 3.0 Hz, 3H, -CH_3), 1.32-1.18 (m, 4H, H-5,6); LC-MS, *m/z* = 226 [M+1]; *Anal. Calcd*. for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22; Found: C, 58.74; H, 6.82 ; N, 6.31.

3-(1,3-Dioxooctahydro-2H-isoindole-2-yl)propanoic acid (2.7). Yield: 38,8 %; Mp.: 83-85 °C; IR (cm^{-1}): 3119, 2945, 2924, 2898, 2857, 1768, 1738, 1668, 1532, 1452, 1394, 1334, 1302, 1288, 1253, 1197, 1178, 1162, 1138, 1098, 1062, 1048, 1034, 1000, 956, 926, 908, 894, 876, 836, 809, 781, 745, 688, 658, 644, 609; ^{1}H NMR, δ (ppm): 12.19 (s, 1H, -COOH), 3.55 (t, *J* = 7.2 Hz, 2H, -C$H_2$$CH_2$COOH), 2.86 (m, 2H, H-3a,7a), 2.50-2.39 (m, 2H, -CH_2CH_2COOH), 1.76-1.63 (m, 2H, H-4,7), 1.62-1.50 (m, 2H, H-4,7), 1.41-1.19 (m, 4H, H-5,6); LC-MS, *m/z* = 226 [M+1]; *Anal. Calcd.* for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22; Found: C, 58.77; H, 6.83; N, 6.29.

4-(1,3-Dioxooctahydro-2H-isoindole-2-yl)butanoic acid (2.8). Yield: 95.6 %; Mp.: 90-91 °C; IR (cm^{-1}): 2945, 1705, 1667, 1455, 1440, 1402, 1376, 1344, 1198, 1162, 1145, 1066, 891, 865, 833, 810, 784, 763, 631, 613; ^{1}H NMR, δ (ppm): 11.85 (s, 1H, -COOH), 3.42 (t, *J* = 6.5 Hz, 2H, -C$H_2$$(CH_2)_2$COOH), 2.86 (m, 2H, -$(CH_2)_2CH_2$COOH), 2.18 (m, 2H, H-3a,7a), 1.89-1.70 (m, 4H, H-4,7, -CH_2C$H_2$$CH_2$COOH), 1.69-1.58 (m, 2H, H-4,7), 1.41 (m, 4H, H-5,6); LC-MS, *m/z* = 240 [M+1]; *Anal. Calcd.* for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85; Found: C, 60.31; H, 7.22; N, 5.90.

2-(1,3-Dioxooctahydro-2H-isoindole-2-yl)-3-methylbutanoic acid (2.9). Yield: 80 %; Mp.: 100-103 °C; IR (cm^{-1}): 3141, 2965, 2937, 2861, 1758, 1737, 1668, 1453, 1401, 1379, 1348, 1226, 1173, 1144, 1132, 1121, 1082, 1069, 1046, 981, 972, 897, 856, 830, 811, 781, 767, 741, 727, 714, 684, 654, 628, 615; ^{1}H NMR, δ (ppm): 12.59 (s, 1H, -COOH), 4.14 (d, *J* = 8.3 Hz, 1H, -C*H*-$CH(CH_3)_2$), 3.02-2.83 (m, 2H, H-3a,7a), 1.89-1.60 (m, 5H, H-4,7, -CH-C*H*$(CH_3)_2$), 1.54-1.31 (m, 4H, H-5,6), 1.08 (d, *J* = 6.5 Hz, 3H, -CH_3), 0.80 (d, *J* = 6.5 Hz, 3H, -CH_3); LC-MS, *m/z* = 254 [M+1]; *Anal. Calcd.* for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53; Found: C, 61.76; H, 7.63; N, 5.59.

2-(1,3-Dioxooctahydro-2H-isoindole-2-yl)-4-methylpentanoic acid (2.10). Yield: 61.3 %; Mp.: 104-106 °C; IR (cm^{-1}): 3168, 2973, 2944, 2933, 2864, 1762, 1741, 1672, 1456, 1412, 1376, 1351, 1226, 1176, 1140, 1129, 1121, 1086, 1072, 1046, 991, 969, 895, 852, 830, 812, 781, 771, 741, 727, 709, 683, 649, 629, 613; ^{1}H NMR, δ (ppm): 12.19 (s, 1H, -COOH), 4.60 (d, *J* = 8.3 Hz, 1H, -C*H*-$CH_2$$CH(CH_3)_2$), 3.52-3.48 (m, 2H, H-3a,7a), 2.13-1.87 (m, 4H, H-4,7, -CH-C$H_2$$CH(CH_3)_2$), 1.78-1.58 (m, 3H, H-4,7, -CH-CH_2C*H*$(CH_3)_2$), 1.49-1.31 (m, 4H, H-5,6), 0.95 (d, *J* = 6.5 Hz, 3H, -CH_3), 0.90 (d, *J* = 6.5 Hz, 3H, -CH_3). LC-MS, *m/z* = 268 [M+1]; *Anal. Calcd.* for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24; Found: C, 62.99; H, 8.03; N, 5.31.

4-((1,3-Dioxooctahydro-2H-isoindole-2-yl)methyl)benzoic acid (2.11). Yield: 78.5 %; Mp.: 175-178 °C; IR (cm^{-1}): 2930, 2852, 2519, 1771, 1674, 1608, 1574, 1555, 1512, 1448, 1415, 1391, 1355, 1334, 1317, 1278, 1201, 1183, 1167, 1141, 1115, 1092, 1067, 1030, 1014, 982, 941, 924, 910, 829, 806, 786, 753, 695, 680, 646, 611; ^{1}H NMR, δ (ppm): 12.57 (s, 1H, -COOH), 7.91 (d, *J* = 6.8 Hz, 2H, H-2,6 Ph), 7.34 (d, *J* = 6.8 Hz, 2H, H-3,5 Ph), 4.60 (s, 2H, - CH_2Ph), 2.94 (m, 2H, H-3a,7a), 1.72 (m, 4H, H-4,7), 1.39 (m, 2H, H-5,6); LC-MS, *m/z* =2 88 [M+1]; *Anal. Calcd.* for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88; Found: C, 66.93; H, 6.06; N, 4.95.

4-(1,3-Dioxooctahydro-2H-isoindole-2-yl)benzoic acid (2.12). Yield: 74 %; Mp.: 227-229 °C; IR (cm^{-1}): 3121, 2939, 2923, 2899, 2854, 1710, 1669, 1603, 1510, 1447, 1433, 1416, 1371, 1353, 1301, 1231, 1206, 1188, 1162, 1125, 1111, 1083, 1058, 1030, 1013, 969, 951, 905, 889, 861, 845, 806, 786, 763, 738, 691, 672, 635, 624; ^{1}H NMR, δ (ppm): 13.01 (s, 1H, -COOH), 8.01 (d, *J* = 8.2 Hz, 2H, H-2,6Ph), 7.41 (d, *J* = 8.2 Hz, 2H, H-3,5Ph), 3.24 (m, 2H, H-3a,7a), 1.76 (m, 4H, H-4,7), 1.39 (m, 4H, H-5,6); LC-MS, *m/z* = 274 [M+1]; *Anal. Calcd.* for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 66.02; H, 5.59; N, 5.21.

3-(1,3-Dioxooctahydro-2H-isoindole-2-yl)benzoic acid (2.13). Yield: 88 %; Mp.: 275-282 °C; ^{1}H NMR, δ (ppm): 12.92 (s, 1H, -COOH), 8.42 (d, 1H, H-6Ph), 7.98 (s, 1H, H-2Ph), 7.68 (d, 1H, H-4Ph), 7.51 (t, 1H, H-5Ph), 3.22 (m, 2H, H-3a,7a), 1.89-1.73 (m, 4H, H-4,7), 1.46 (m, 4H, H-5,6); LC-MS, *m/z* = 274 [M+1]; *Anal. Calcd.* for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 66.05; H, 5.61; N, 5.23.

2-(1,3-Dioxooctahydro-2H-isoindole-2-yl)benzoic acid (2.14). Yield: 52 %; Mp.: 192-194 °C; ^{1}H NMR, δ (ppm): 12.87 (s, 1H, -COOH), 8.04 (m, 1H, H-3Ph), 7.65 (m, 1H, H-6Ph), 7.59 (m, 1H, H-5Ph), 7.24 (m, 1H, H-4Ph), 3.02 (m, 2H, H-3a,7a), 2.10-1.68 (m, 4H, H-4,7), 1.51 (m, 4H, H-5,6); LC-MS, *m/z* = 274 [M+1]; *Anal. Calcd.* for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13; Found: C, 66.99; H, 5.62; N, 5.19.

4-(1,3-Dioxooctahydro-2H-isoindole-2-yl)-2-hydroxybenzoic acid (2.15). Yield: 69.3 %; Mp.: 158-160 °C; ^{1}H NMR, δ (ppm): 9.42 (s, -COOH), 7.87 (d, 1H, H-6Ph), 7.20 (d, 1H, H-4Ph), 6.80 (s,1H, -OH), 6.73-6.55 (m, 1H, H-3Ph), 3.24-2.94 (m, 2H, H-3a,7a), 1.83 (m, 2H, H-4,7), 1.49 (m, 4H, H-5,6); LC-MS, *m/z* = 290 [M+1]; *Anal. Calcd.* for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; Found: C, 62.35; H, 5.34; N, 4.89.

Synthesized compounds (**2.1–2.15**) are white or yellow crystalline substances, insoluble in water, soluble in organic solvents. They were purified by crystallization from methanol for analyses.

Pharmacology. *Hypoglycemia activity test*. Study of hypoglycemic action was conducted on 124 Wistar white rats wich (male, weight 260–280 g., age 3.5 month) obtained from nursery of PE "Biomodelservice" (Kyiv, Ukraine). Experiments on animals were carried out according to bioethics principles. Animals selected after quarantine 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 weights of all animals were measured before experiments. Intragastric injection of studied compounds were conducted using atraumatic probe as water solution or finely dispersed suspension stabilized by Tween 80 in dose 10 mg/kg. Intact and control groups obtained equivalent volume of water by the same way. Hypoglycemic action of synthesized compounds was evaluated via changes of glucose level before and after injection of studied compounds. Measurements of glucose level were carried out in 2, 4, 6 and 8 hours 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 $P < 0.05$.

Conflicts of Interest: authors have no conflict of interest to declare.
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