Design of Hydrogenated Isoindolylalkyl(Alkaryl-, Aryl-)Carboxylic Acids with Quinazoline Fragment, that Modify the Carbohydrate Metabolism

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Abstract- Fragment-oriented design, namely molecular docking of N-carboxyalkyl-(aralkyl-, aryl-)-isoindoline-1,3-diones' (3H-quinazoline-4-ylidene)hydrazides and 2-([1,2,4]triazolo[1,5-c]quinazoline-2-yl-)alkyl-(alkaryl-, aryl-)-hydroisoindole-1,3(2H)-diones allowed to reveal substances that modify the carbohydrate metabolism. The results of pharmacological screening revealed several compounds, which are short-acting hypoglycemic agents like prandial regulators of glucose (Mitiglinide).

Keywords - (3*H*-quinazoline-4-ylidene)hydrazides of *N*-carboxyalkyl-(aralkyl-, 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, design, docking studies, hypoglycemic activity.

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, so synthetic quinazolines and, undoubtedly, their wide ability to chemical modification. 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 «leader compounds» and original drugs with antitumor, antihypertensive, diuretic, hypoglycemic and other biological activities.

The purpose of paper is to find biologically active compounds, that modify the carbohydrate metabolism, based on hydrogenated isoindolylalkyl(alkaryl-, aryl-)carboxylic acids with quinazoline fragment by means of *in silico* studies and to establish the «structure-activity relationship» for further optimization of their structure.

The layout of the main body

Docking studies of *N*-carboxyalkyl-(aralkyl-, aryl-)-isoindoline-1,3-diones' (3*H*-quinazoline-4-ylidene)hydrazides and 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)alkyl-(alkaryl-, aryl-)-hydroisoindole-1,3(2*H*)-diones (Fig. 1) towards an ATP-sensitive potassium channel (or KATP channel, PDB ID - 6BAA) were conducted on the first stage of the study [1]. 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. According to the obtained data of affinity the most promising compounds were selected for the synthesis and further studying of their hypoglycemic activity.

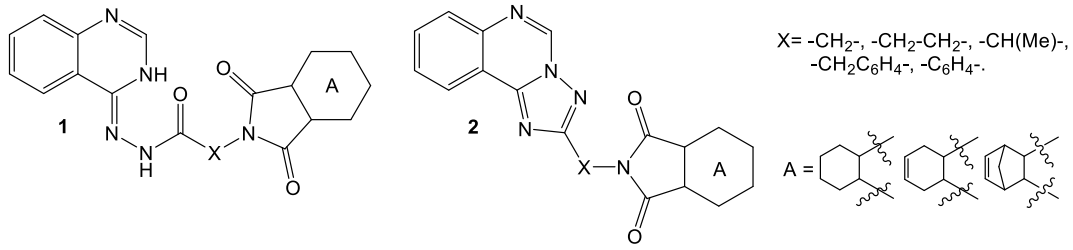
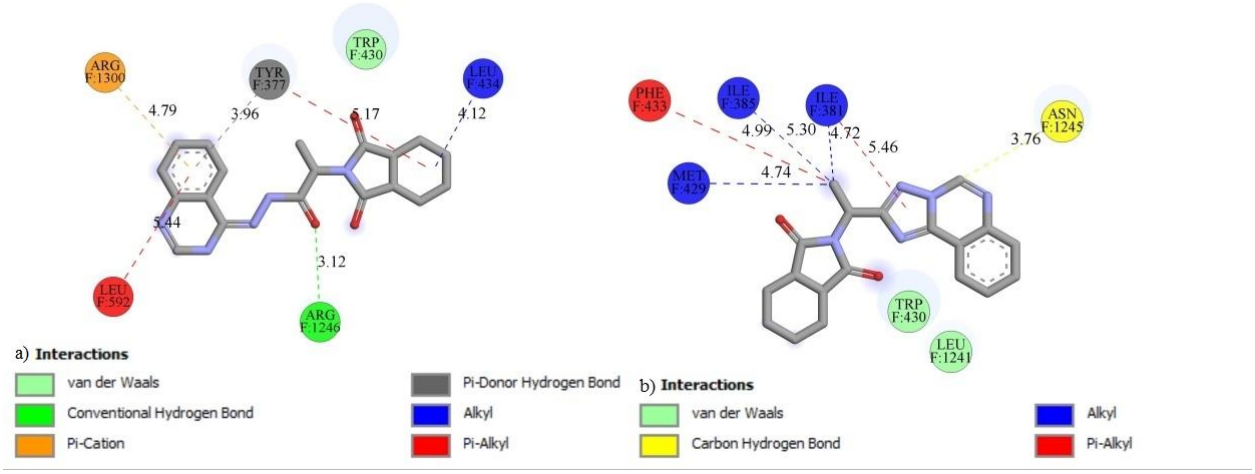


Fig. 1. Structures of *N*-carboxyalkyl-(aralkyl-, aryl-)-isoindoline-1,3-diones' (3*H*-quinazoline-4-ylidene)hydrazides (**1**) and 2-([1,2,4]triazolo[1,5-*c*]quinazoline-2-yl-)alkyl-(alkaryl-, aryl hydroisoindole-1,3(2*H*)-diones (**2**), that were used for docking

Substances were constructed and optimized using Marvin Sketch 17.21 [2]. In Auto Dock Tools-1.5.6, PDBs were converted to PDBQT format, which were used in Vina for docking [3]. And finally, Discovery Studio v17.2.0.16349 was used for interactions visualization of obtained compounds' conformations according to the docking.

The visualization of the interaction of the structures with the active site of KATP channel (Figure 2) showed, that investigated compounds revealed similar interaction to Glibenclamide. Such, common interactions for 2-(1,3-dioxooctahydro-2*H*-isoindole-2-yl)-*N*'-(quinazoline-4(3*H*)-ylidene)propanehydrazide (**1.1**) 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 2-(1-{[1,2,4]triazolo[1,5-c]quinazolin-2-yl}ethyl)-octahydro-1H-isoindole-1,3-dione (**2.1**) were as following: hydrogen bond with the amino acid residue ASN1245 (3.76Å) and hydrophobic interaction with the residue MET429 (4.74Å). Affinity of compounds **1.1** and **2.1** towards the active center of KATP channel according to the docking studies were -8.2 and -8.5 kcal/mol, while for Mitiglinide and Glibenclamide -7.5 kcal/mol and -8.4 kcal/mol, respectively. This may indicate, that stated class of compound might have ability to act as Glibenclamide does.



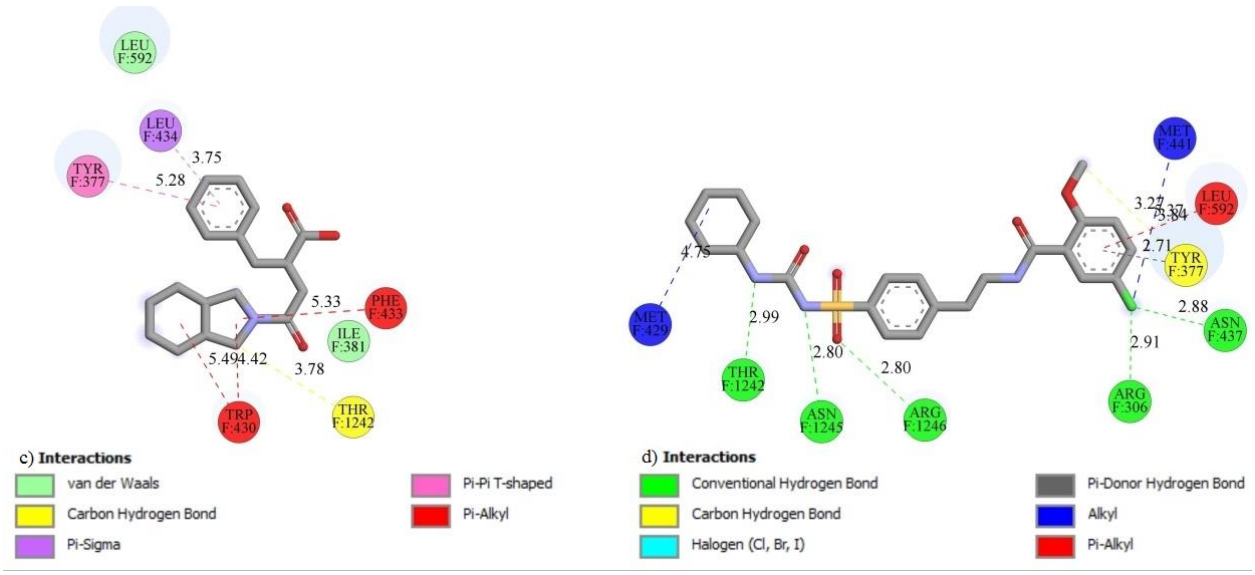


Fig. 2. Visualization of affinity according to the docking a) compound **1.1** with KATP channel; b) compound **2.1** with KATP channel; c) Mitiglinide with KATP channel; d) Glibenclamide with KATP channel.

Currently, 18 compounds among mentioned derivatives were synthesized according to the know methodic [4]. Moreover, they were tested for their hypoglycemic activity. Among leader turned to by two compounds, namely discussed 2-(1,3-dioxooctahydro-2*H*-isoindole-2-yl)-*N*'-(quinazoline-4(3*H*)-ylidene)propanehydrazide (**1.1**) and 2-(1-{[1,2,4]triazolo[1,5-c]quinazolin-2-yl}ethyl)-octahydro-1H-isoindole-1,3-dione (**2.1**).

Conclusion

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. Molecular docking to KATP channel, PDB ID-6BAA 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. 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.

Acknowledgments

The work was performed with the financial support of «Enamine Ltd» (Kyiv, Ukraine).

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