A New View on FXIa Potent Inhibitors: Virtual Screening, Pharmacophore Analysis and Molecular Docking of 2'-Amino-5'-Carbamoyl-3'-Cyano-2-Oxo-3'H-Spiro[indoline-3,4'-pyridine]-2-Thiolate Derivate

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Abstract: *nicotinonitriles, nicotinamides and their partially saturated analogs represent a promising class of heterocyclic compounds with an interesting range of biological activities. One of the most accessible and efficient approaches to the synthesis of functionalized nicotinamides is based on the reaction of active methylene malonamides with 1,3-C_3 dielectrophiles. Synthesized compounds were subjected to virtual screening using GalaxySagittarius and SwissTargetPrediction services which led to the discovery of FXIa inhibition activity in one of the compounds. In order to validate the result of virtual screening pharmacophore analysis was produced with Molecular Operating Environment software. Moreover, structural approach well known as molecular docking and the most promising method in silico was used with Molegro Virtual Docker. As a target for docking was chosen FXIa (7MBO) in a complex with milvexian. After proper protein preparing interaction of a ligand and a biotarget was evaluated with scoring-functions MolDockScore and HBond. According to ADMET data obtained after virtual assessment the hit-compound is supposed to be soluble, well absorbed in gastrointestinal tract and non-carcinogenic. The results of in silico studies allow to represent the ligand as a perspective platform for further FXIa high-selective inhibitor development.*

Key words: *blood coagulation factors, anticoagulants, pharmacophore analysis, molecular docking, blood coagulation factors inhibitors*

Introduction

Today there is an urgent need for the development of new anticoagulant drugs that can prevent pathological conditions without much interfering with normal hemostasis. For instance, low-molecular-weight inhibitors of the blood coagulation factor XIa show great potential as therapeutic agents for the development of such drugs.

In this study using the methods of structure-based design, 5 compounds were identified as potential inhibitors of blood coagulation factor XIa.

Materials and methods

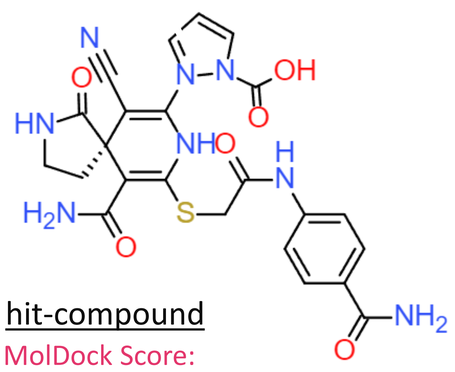
At the first stage virtual screening based on QSAR was carried out with GalaxySagittarius for the focused library of selected druglike compounds that had already been synthesized. The main criterion for selection was anti-FXIa activity.

A pharmacophore analysis of known inhibitors of factor XIa (such as milvexian) was performed with MOE in order to identify the pharmacophore.

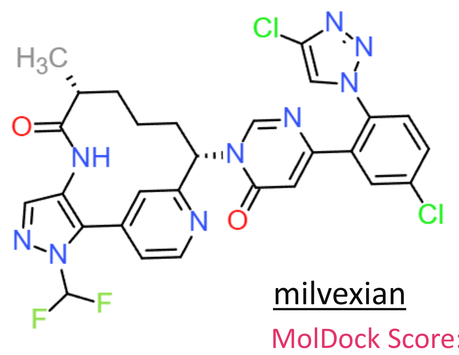
Then molecular docking was carried out with Molegro Virtual Docker. The results are shown.

Results

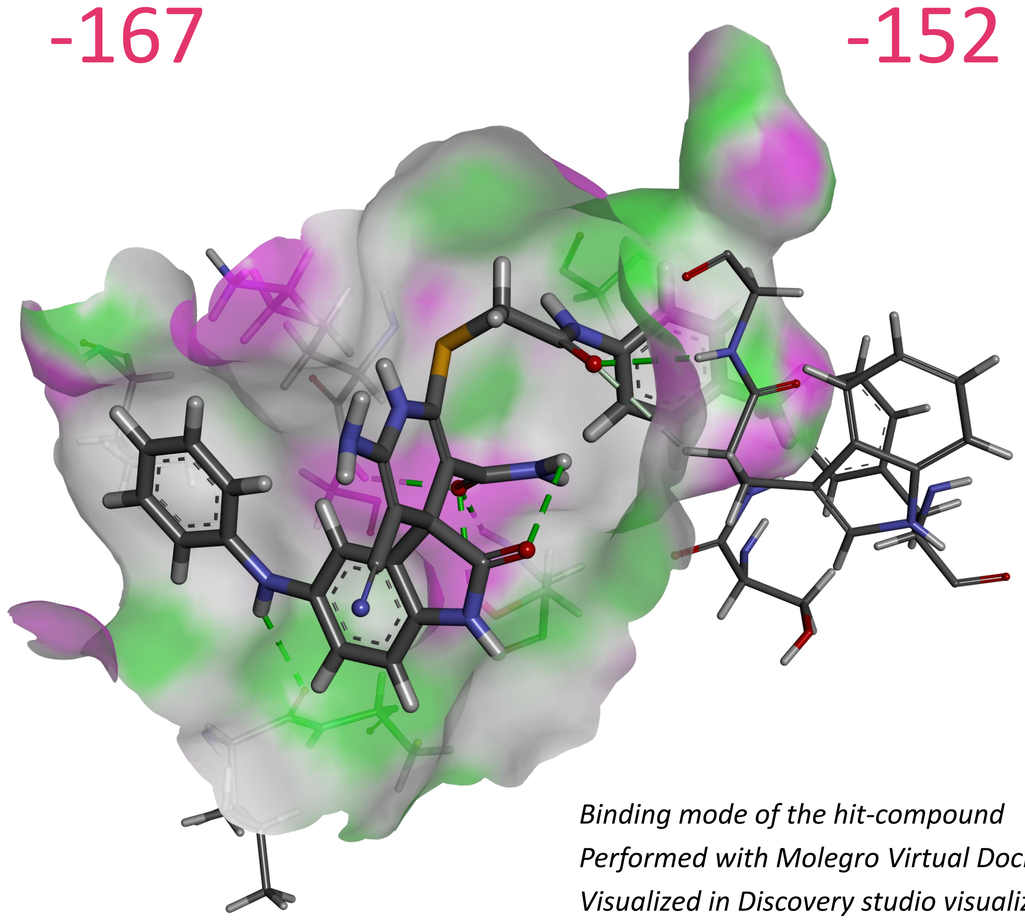
2'-Amino-5'-Carbamoyl-3'-Cyano-2-Oxo-3'H-Spiro [indoline-3,4'-pyridine]-2-Thiolate Derivates were found to be perspective FXIa inhibitors.



hit-compound
MolDock Score:
-167



milvexian
MolDock Score:
-152



Binding mode of the hit-compound
Performed with Molegro Virtual Docker
Visualized in Discovery studio visualizer

Conclusions

The results of the study confirm that the N-carboxyl-pyrazoline group is as effective of a bioisosteric building-block as the N-difluoromethyl-pyrazolyl group in milvexian.

Additionally, the absence of halogen atoms suggests that the designed compound may have lower toxicity.

The hit found in this study can be applied for further structural optimization processes to increase potency against factor XIa.

Literature cited

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