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Research Paper

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Ergot Alkaloids against SARS-COV-2 Main Protease

I.V. Ferrari

Dept. Industrial Engineering, Tor Vergata, Rome, Italy

Author's Mail Id:ivanvitoferrari@gmail.com, Tel.: +003932352697

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Abstract— The present study based on the Docking approach it focused on Ergot alkaloids for instance Ergotamine, Dihydroergotamine, Ergocristine, and Dihydroergocristine, which they obtained excellent results of both Binding Energy, of about -11,29 kcal mol $^{-1}$; -12,16 kcal mol $^{-1}$; -12,03 kcal mol $^{-1}$ and -12,2 kcal mol $^{-1}$, respectively and in terms of estimation of inhibitory constants Ki (5,30 nM, 1,22 nM 1,52 nM, and 1, 14 nM, respectively. This has led to the conclusion, that they could be excellent candidates against SARS-COV-2 M protease, even though further in vitro and in vivo studies are needed to confirm this preliminary analysis.

Keywords— Docking analysis, Ergotamine and Dydroergotamine, M-^{pro}

I. INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19) is widely spread in the world.

Nowadays, measures are needed to limit its spread as much as possible more than ever and effective solutions to counter this viral infection.

Although there are several being validated and approved vaccines by the competent authorities, a highly effective anti-COVID-19 drug does not exist.

In scientific literature, there are several papers that focused on the study of discovering potential pharmacologically active molecules or drugs capable of reducing the negative effects of the infection. [1, 2, 3, 4].

Herein, this short communication report aims to investigate the role of Ergot alkaloids against SARS-COV-2 Main Protease by Molecular Docking approach [5, 6].

II. RELATED WORK

The main focus aims to investigate some of the active compounds, used in the treatment of migraine disorders, as a possible target against SARS-COV-2 Main protease.

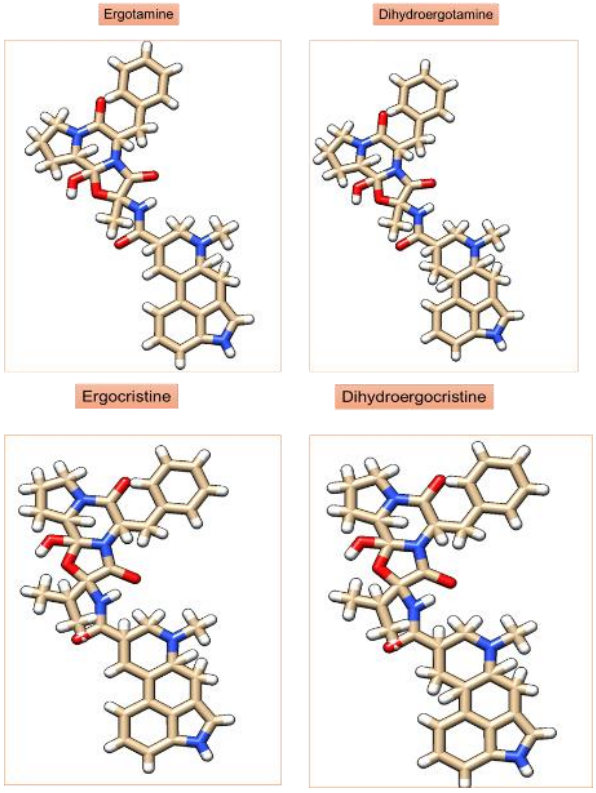

Figure 1. 2D structures investigated : Ergotamine, Dydroergotamine, Ergocristine and Dydroergocristine respectively.

III. METHODOLOGY

Parameters Docking for SARS-CoV-2- main replicase-protease (3CL-^{pro}):

-ID PDB 6XQS Chain A: Center X (8.60); Centre Y (1.91); Centre Z (25); Dimensions (Angstrom) (Å) X, Y, Z [= 19.00= , 19, 00 =19,00]; exhaustiveness = 8; Run 10.

Parameters Docking for Crystal structure of the chimeric protein of 5-HT1B-BRIL in complex with Dihydroergotamine *(PSI Community Target):*

-ID PDB 4IAQ Chain A: Center X (-22,15); Centre Y (9,08); Centre Z (22,22); Dimensions (Angstrom) (Å),[X (14,95)Y(21,13) Z (17,09); exhaustiveness = 8; Run 10.

Parameters Docking for Crystal structure of 5-HT2C in complex *with Ergotamine:*

-ID PDB 6BQG Chain A: Center X (20,33); Centre Y (33,71); Centre Z(55,77); Dimensions (Angstrom) (Å),[[X (10,69)Y(15,21) Z (18,55); exhaustiveness = 8; Run 10.

All analyzed proteins were carefully prepared with Chimera software [7] before starting the Molecular Docking, through Autodock 4 by with AMDOCK programme [8].

IV. RESULTS AND DISCUSSION

The first important step in the field of Drug Discovery regarding the role of a drug for a given investigation target is undoubtedly a computational analysis.

Bioinformatics scientists often use "Molecular Docking" and "Virtual Screening" (V.S.) as tools to select, from a large number of drugs analyzed to a few pharmacologically active molecules that could have an effective role for subsequent analyzes.

Indeed, in our case, this study focused on the role of potential Ergot alkaloids against SARS-COV-2 Main Protease.

Ergotamine (namely Cafergot) is an alpha-1 selective adrenergic agonist vasoconstrictor used to treat migraines with or without aura and cluster headaches [10]. Dihydroergotamine (as known as Migranal) is an ergot alkaloid used in the acute treatment of migraine headache and cluster headache [10]. Dihydroergocristine is Ergocristine in which a single bond replaces the double bond between positions 9 and 10. It is used as the Mesylate salt for the symptomatic treatment of mental deterioration associated with cerebrovascular insufficiency and in peripheral vascular disease. It has a role as an adrenergic antagonist and a vasodilator agent [11, 12].

Particular attention, these molecules were selected and investigated at VS, through Autodock 4 [9].

The next step focuses on comparing Docking Results between SARS-COV-2 M^{pro} with a Reference protein (PDB 4IAQ and PDB 4IAQ) respectively.

Generally speaking, it is important to underline to be the presence of the same Ligands, contained inside of the control protein, to verify the effective action in terms of Binding Energies. This is one of the typical control methods called the Validation docking protocol.

Indeed, in Figure 2 there is a comparison of Cristalized Dydroergotamine (PDB 4IAQ, in Blue Color) and Docked Dydroergotamine -14.10 kcal mol^{-1}, estimated by Autodock Vina with Pyrx Software (in Red color), while in Figure 3 are shown 2D diagram interactions Docked Dydroergotamine.

In figure 4 is an outright a comparison of Cristalized (PDB 6BQG, in Blue Color) and Docked Ergotamine -14.00 kcal mol^{-1}, estimated by Autodock Vina with Pyrx Software (in Red color while in figure 5 is shown 2D diagram interactions Docked Ergotamine.

Table 1. Comparison Binding Energies of Ergot alkaloids, kcal mol^{-1}, against SARS.CoV-2 Main Protease, (ID PDB 6XQS), calculated by Autodock 4 with AMDock Software

AMDOCK

AUTODOCK 4	*Binding energy (kcal mol^{-1})*
ERGOTAMINE	-11.29
DIHYDROERGOTAMINE	-12.16
ERGOCRISTINE	-12.03
DIHYDROERGOCRISTINE	-12.20

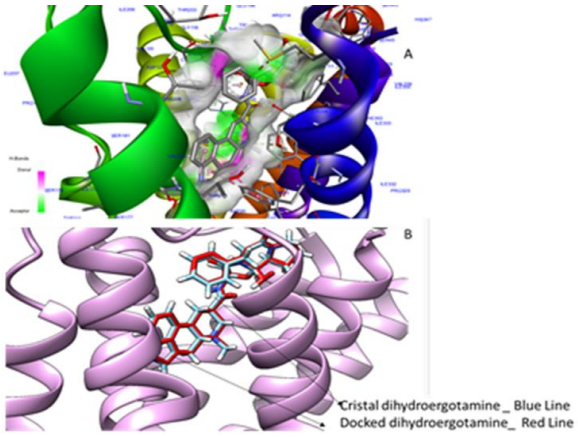

Figure 2 . a) 3D structure Dydroergotamine in Binding site of Crystal structure the chimeric protein of 5HT1 b) Comparison Cristalized (Blue Colour) and Docked Dydroergotamine -14,10 kcal/mol, estimated by Autodock Vina with Pyrx Software (Red colour) (PDB 4IAQ).

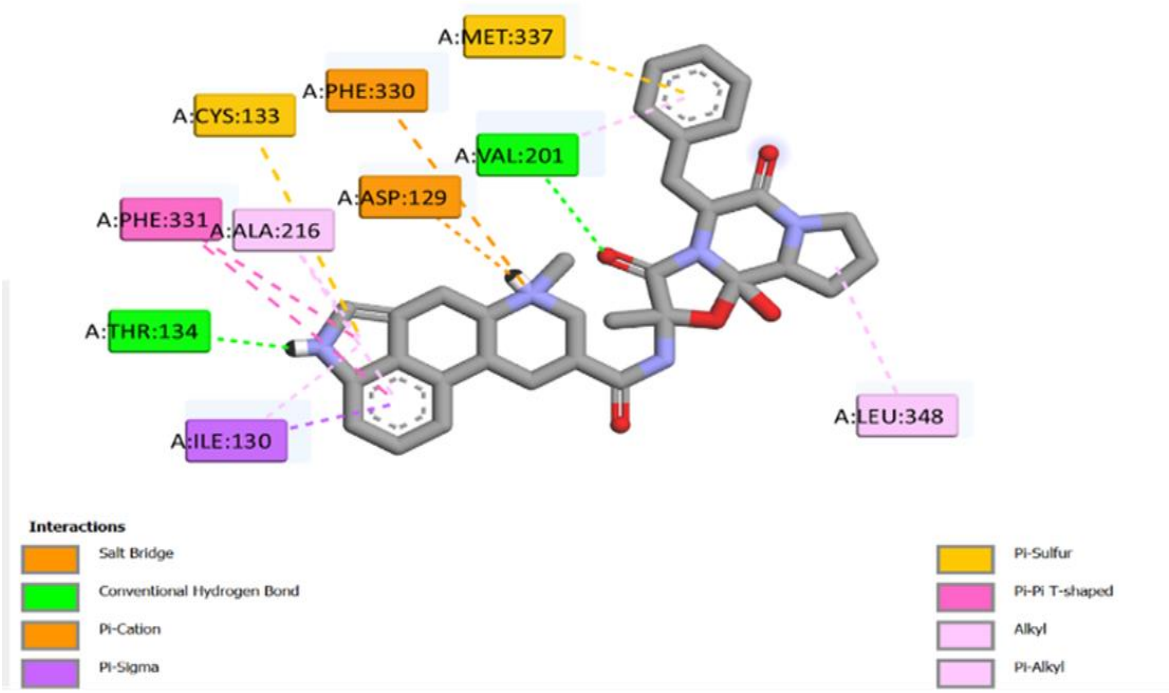

Figure 3. 2D Diagram interactions of Docked Dydroergotamine, n crystal structure of the chimeric protein 5 HT1-B-BRIL(PDB 4IAQ,) characterized by Discovery Studio Biovia software.

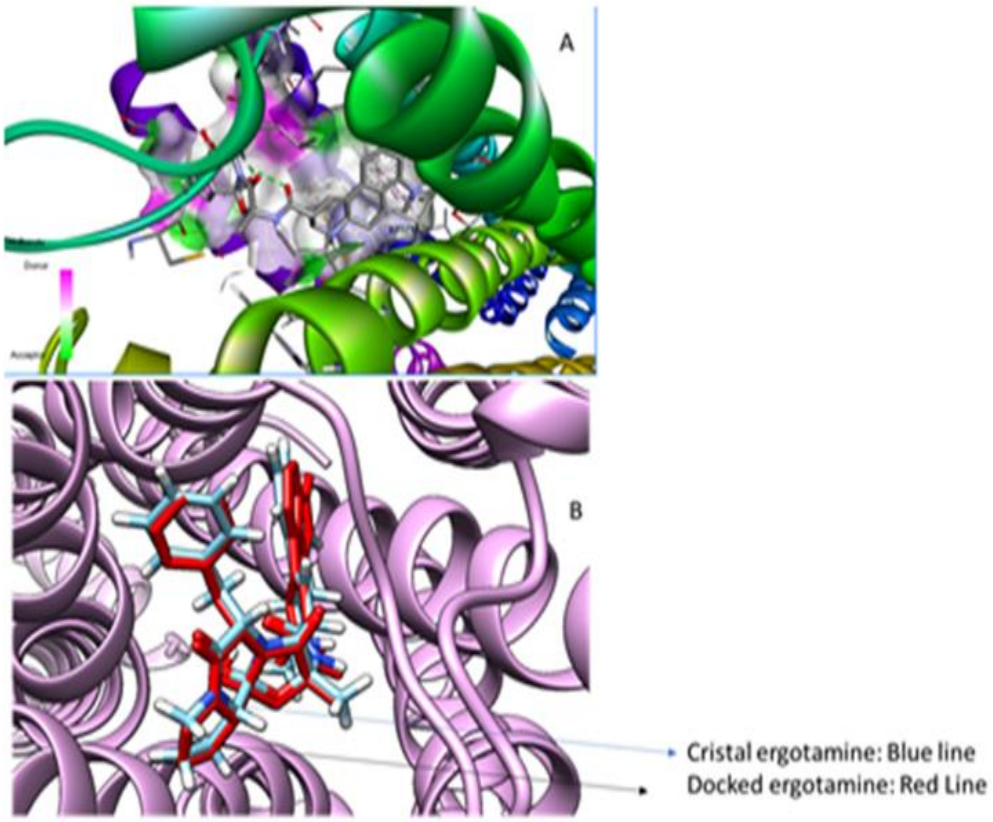

Figure 4 . a) 3D structure Ergotamine in Binding site of Crystal structure OF 5HT2C protein (PDB 6BQG) b) Comparison Cristalized (Blue Colour) and Docked Ergotamine -14,00 kcal/mol, estimated by Autodock Vina with Pyrx Software (Red colour)

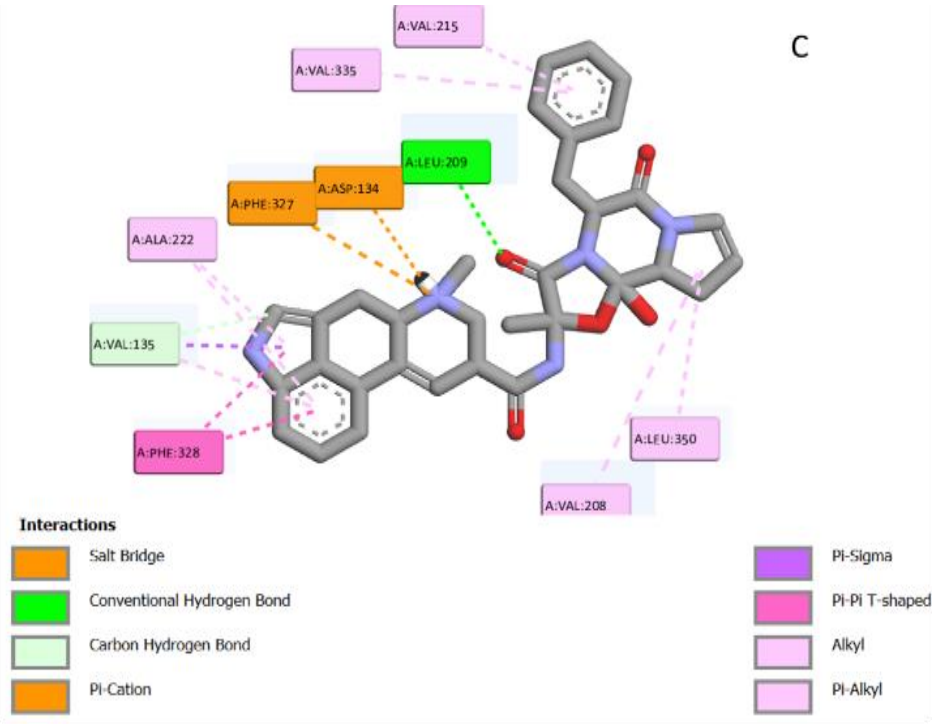

Figure 5. c) 2D Diagram interactions of Docked Ergotamine, in Crystal structure of 5-HT2C, characterized by Discovery Studio Biovia software.

V. CONCLUSION AND FUTURE SCOPE

This in Silico study, has demonstrated a potentially active role of Ergot alkaloids against SARS-COV-2 Main Protease.

If we compare, Binding Energies between Dydroergotamine and Ergotamine when located in the active site of SARS-COV-2 M^{pro} versus when they bind in the active site in control proteins (PDB 4IAQ and PDB 4IAQ) respectively. It can be seen that there is a minor affinity of about 2 kcal mol -1, in terms of Binding Affinity, when they bind to the Coronavirus protease.

However, this does not affect their theoretically potential activity and ability to block this virus. These Ergot alkaloids have reported about -12 kcal mol^{-1} value score, a very high value in terms of affinity when compared to many drugs previously investigated and subjected to studies in the literature such as the case of many antivirals for example Remdesivir.

However, it should be emphasized subsequent studies are needed to confirm their potential Anti-COVID-19 activity.

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AUTHORS PROFILE

Ivan Vito Ferrari has published more than 10 research papers in reputed international journals and His main research work focuses on Bioinformatic Tools, Electrochemistry field and Polymer Science. He obtained PhD in Industrial Engineering and Master Degree in Industrial Biotechnology at the University of Rome Tor Vergata.

