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Molecular Docking Studies of Novel Tetrasubstituted Thiophene Analogues against SARS-CoV-2 Inhibitors for COVID-19

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ABSTRACT

The knowledge of various synthetic pathways and the diverse physicochemical parameters of such compounds draw the especial attention of medicinal chemists to produce combinatorial library and carry out exhaustive efforts in the search of lead molecules. The molecular docking showed that the binding energy in all active compounds ranged from -25.18 to -81.42 kcal/mol. If compared to the standard -89.71 kcal/mol). Compound code 2b and 2f were found to be potent with a docking score of -81.42 and -67.23 respectively. As the world's population increases and health problems expand accordingly, need to discover new therapeutics will become even more diring. The design of drug molecules arguably offers some of the greatest hopes for success in present and future era.

Keywords: Thiophene, Molecular docking, SARS-CoV-2 inhibitors, Hydroxychloroquine.

INTRODUCTION

Thiophene is a heterocyclic compound with the formula C_4H_4S, which has a five-membered ring with one sulphur as a heteroatom. In petroleum or coal thiophen and its products are present. Thiophene is derived from the Greek words theion, which means sulphur, and phaino, which means shining[1]. As on 21st September 2020; COVID-19 (novel RNA virus) has infected >31 million individuals and caused approximately 1 million global deaths. The novel human RNA virus is subjected to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which primarily gains entrance to cells via binding of SARS-CoV-2 Spike

glycoprotein to angiotensin converting enzyme 2 (ACE-2) and subsequent endocytosis[2-5]. Thiophene derivatives are well-known in medicinal chemistry for their therapeutic applications. Simple thiophenes are stable liquids that, in terms of boiling point and even odour, are very similar to their benzene counterparts. Coal tar distillates contain them. One of the classic anecdotes in organic chemistry is the discovery of thiophene in coal tar benzene[5]. Thiophene was found in benzene as a contaminant. When isatin (1Hindole-2,3- Dione) is combined with sulfuric acid and crude benzene, it produces a blue dye. Victor Meyer was effective in isolating the agent that caused this reaction. The material was discovered. Thiophene is a heterocyclic compound. Thiophene has a structure that is similar to that of pyrrole, and it behaves like a highly reactive benzene derivative due to the pie electron cloud[6-18]. The Principle behind the heating in microwave oven is because interaction of charged particle of reaction material with electromagnetic wavelength of particular frequency[19-28]. The phenomena of the producing heat by electromagnetic irradiation are either by conduction or collision. The application of green chemistry principles and practices renders regulation, control, clean-up, and remediation of the environment[29-38]. Because of ADME failure, it is important to conduct docking studies before pharmacological activity, as it is simple to predict the probable pharmacological activity by receptors with the help of structure of compounds. In the discovery of effective medicines for prevention and treatment[39-56]. It is necessary to enhance both enzymatic stability and membrane permeation in the formulating drug delivery system for protein and peptide drugs. Soon, someday, you might be making your own drugs at home. That is because researchers have adapted a 3D printer from basic, readily available medicinal active agents fed into a drug delivery system[57-59]. Molecular docking is an appealing scaffold for understanding medicinal biomolecular interactions in rational drug design as well as in the mechanical analysis in order, primarily noncovalently, to insert the molecule (ligand) into the favorite binders of the particular target area of the DNA/protein (receptor)[58]. The information gathered from the docking method can be used to demonstrate the binding energy, free energy and complex stability. The docking are currently used to forecast the preliminary ligand-receptor complex binding parameters. The main user interface continues to be expanded by commercial software programs. In the high end packages, new algorithms from industry and academia are easily implemented. Public domain packages are becoming more stable and deliver functionality that continues to double in speed every year and half computers surpassing some of the commercial offerings, while graphic displays have become more sophisticated and intuitive. All these components make molecular docking an important part of the design of drugs. In exciting new techniques

such as computational enzymology, genomics, and proteomic search engines, its function continues to be expanded[59-61].

MATERIALS AND METHODS

Molecular Docking Study:

The VLifeMDS 4.1 software was used to perform the molecular docking study. There are all six 1,2-diphenyl-1H-benzimidazole products. The molecular docking tool was designed to obtain a preferred interaction geometry of ligand-receptor complexes with minimum interaction energy assisted by various scoring functions[62].

Protein Preparation

PanDDA analysis group deposition-Crystal Structure of COVID-19 main protease in complex with Z219104216 (PDB code- 5R82)

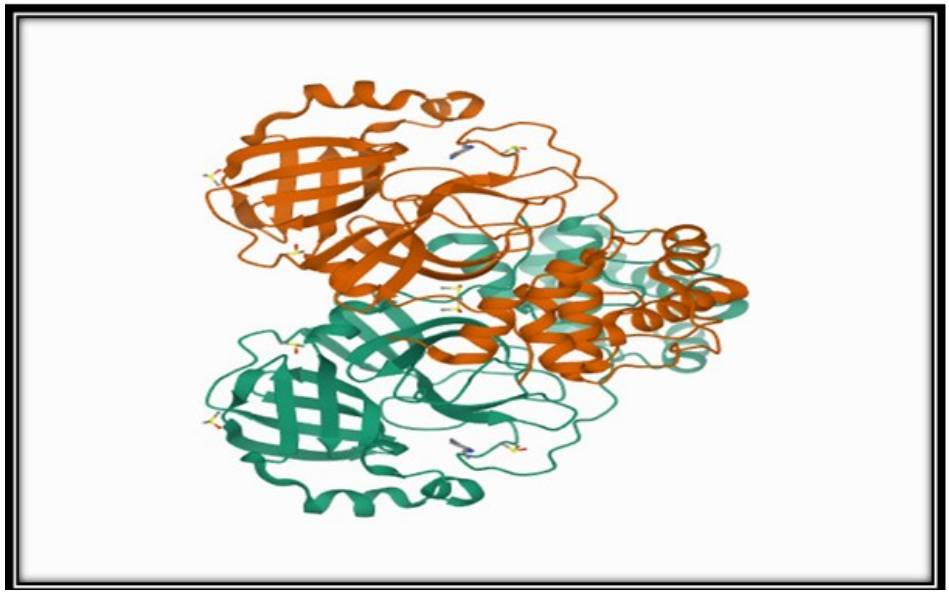

Fig 1. 3D View of Structure of PanDDA analysis group deposition-Crystal Structure of COVID-19 main protease in complex with Z219104216 (PDB code- 5R82)

Ligand preparation

The 2D structures of the compounds were built and then converted into 3D. Then, using MMFF, the 3D structures were energetically minimized to the rms gradient of 0.01[63].

Identification of cavities

Based on their size and hydrophobic surface area, all the cavities that are present in the receptor are classified and ranked. Considering the dimensions and the hydrophobic surface area, as an active site, the cavity is considered to be the best void[64].

Scoring function

The dock score measures binding affinity with a recognized 3D structure of a given protein-ligand complex[65-66].

Table-1: Test compounds used in study

Sr. no	Compound code	Name of compound
1	2a	Methyl 2-benzoylamino-5-(4-methylbenzoyl)-4-methylthiophene-3-carboxylate
2	2b	Methyl 2-benzoylamino-5-(4-methoxybenzoyl)-4-methylthiophene-3-carboxylate
3	2c	Methyl 2-benzoylamino-5-(4-nitrobenzoyl)-4-methylthiophene-3-carboxylate
4	2d	Methyl 2-benzoylamino-5-(3-nitrobenzoyl)-4-methylthiophene-3-carboxylate
5	2e	Methyl 2-benzoylamino-5-(2,4-dichlorobenzoyl)-4-methylthiophene-3-carboxylate
6	2f	Methyl 2-(2-furoylamino)-5-(4-methoxybenzoyl)-4-methylthiophene-3-carboxylate

RESULTS AND DISCUSSION

The compound code (2a-f) shown in the table and the compound code 2b and 2f minimum dock score were found to be potent, with a docking score of -81.42 and -67.23 respectively. Where the main interaction between ligand and receptor can be observed, the best pose obtained by docking results is reported. At the binding pocket, all designed compounds follow a very similar conformation, showing interaction of hydrogen bond with amino acids of ARG188, aromatic interaction with amino acids of ASP159, MET49, HIE164, ASN142, ASN15B, ASN119, ASN142, MET165 and GLN1719. The standard dock score was found to be -89.71

Table-2: Docking score of Pyrazole acrylic acid based oxadiazole and amide derivatives by using GRIP Batch docking.

Compound code	Name of compound	Docking score (Kcal/mol)
2a	Methyl 2-benzoylamino-5-(4-methylbenzoyl)-4-	

	methylthiophene-3-carboxylate	-58.64
2b	Methyl 2-benzoylamino-5-(4-methoxybenzoyl)-4-methylthiophene-3-carboxylate	-81.42
2c	Methyl 2-benzoylamino-5-(4-nitrobenzoyl)-4-methylthiophene-3-carboxylate	-25.18
2d	Methyl 2-benzoylamino-5-(3-nitrobenzoyl)-4-methylthiophene-3-carboxylate	-49.83
2e	Methyl 2-benzoylamino-5-(2,4-dichlorobenzoyl)-4-methylthiophene-3-carboxylate	-42.20
2f	Methyl 2-(2-furoylamino)-5-(4-methoxybenzoyl)-4-methylthiophene-3-carboxylate	-67.23
Standard	Hydroxychloroquine	-89.71

CONCLUSION

The docking experiments were carried out and the docking score was compared with the Hydroxychloroquine reference compound. The compounds code 1d showed higher binding score.

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