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ORIGINAL ARTICLE **OPEN ACCESS**

Molecular Docking Study of Thiophene Carbohydrazide Analogues Against Folate Receptor α (Frα) Used to Design New Anti-Cancer Agents

Vaibhav Gawade[a*], Vitthal Chopade[b]
[a] PhD Scholar, Department of Pharmaceutical Chemistry, PES Modern College of Pharmacy, Pune-44, India
[b] Professor Department of Pharmaceutical Chemistry, PES Modern College of Pharmacy, Pune-44, India
Corresponding author's Email: gawadevaibhav6060@gmail.com

ABSTRACT
The main aim of this study was to examine the docking interaction of the novel Thiophene-carbohydrazide-containing compounds with FRα protein which is a novel target in cancer treatment. Protein structure AGF183(PDB5IZQ) obtained from a protein data bank and optimized using BIOVIA discovery studio molecular docking studies were conducted using PyRx 0.8 Autodock Vina software. The goal of this study was achieved by finding a novel 25 Thiophene-carbohydrazide containing compounds that docked with FRα with the result on the basis binding affinity score of compounds D1to D25 (-8.2,-10.2,-8.5,-8.8,-8.6,-9.3,-9.9,-10.4,-10,-8.8,-8.3,-9.8,-10,-9,-10.9,-8.9,-10.3,-9.4,-9.4,-8.4,-7.3,-9.7,-11,-9.1,-8.8 kcal/mol) in which compound in which D23 shows strong binding with FRα (-11kcal/mol) compared to standard drug methotrexate(-11.87kcal/mol) present molecular docking study shows that all compounds are FRα inhibitors. This study is useful for the synthesis of potential anticancer agents in the future.
Keywords:, *Human folate receptor α (FRα), Molecular docking; Anticancer, Autodock vina, malignant-tumor.*

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INTRODUCTION

Cancer is one of the most dangerous diseases in the world with the highest mortality rates. It is caused by uncontrolled rates of division of cells and abnormal growth. Other organs may be affected by this unrestricted proliferation [1]. One kind of receptor that is widely present in cells with epithelial cancers is the folate receptor (FR) [2]. In situations when folate content is insufficient, fast cell division necessitates extensive expression of FRα throughout the later stages of many malignancies [3]. As a result, FR overexpression has been extensively studied for its potential as an intriguing target that might be used for targeted nano-drug delivery and cancer diagnostics [4]. FAs can enter cells actively through folate receptors or the reduced folate carrier (RFC). (FR) by endocytosis or photocytosis. FA has 100–200 times greater affinity for FRα binding than RFC. Understanding the mechanism by which FA binds to the folate receptor would help understand the binding process and might potentially lead to the development of competitive drug binding. Disulfide linkages stabilize the globular protein that is the folate receptor [5]. It has two short α-helices (α-4, α-5), four short β-strands (β1-β4), four long α-helices (α-1, α-2, α-3, and α-6), and many loop regions. Many tryptophan residues in the FRα binding pocket can form a sizable hydrophobic environment that can hold the aromatic folate molecule. It also has several cysteine residues that have a high affinity for FA and can bind to it to aid in cellular absorption[6]. Numerous investigations have redirected their attention to the FRα isoform as a molecular target in numerous malignancies. These investigations have included those using FRα antibodies, high-affinity antifolates, folate-based imaging agents, medicines coated with folate, and delivery methods for folate-conjugated nanoparticles. A class of medications known as antifolates inhibits many enzymes, including thymidylate synthase (TS) and/or dihydrofolate reductase (DHFR), to prevent the effects of FA inside the cell. Antifolates such edatrexate (EDX), pralatrexate (PDX), raltitrexed (RTX), pemetrexed (PTX), methotrexate (MTX), and pralatrexed (PDX) bonded to FRα and destroyed cancer cells in recent clinical studies. These investigations also revealed that whereas certain antifolates, like MTX, RTX, and PDX, have similar binding affinities to FA to the receptor, others, like PTX, had higher affinities towards FRα than FA [7]. It's quite likely that each antifolate molecule's functional groups have a significant impact on how the antifolate molecules attach to the receptor. Nevertheless, ligand–receptor binding is also influenced by the amino acids within the receptor pocket, the stereochemistry of the structures, and the distance of each contact. Heterocyclic rings were present in the

chemical structures of two-thirds of anticancer medications that the FDA authorized between 2020 and 2023 [8]. Numerous receptor interactions have been demonstrated for heterocyclic rings, which are crucial for the body's metabolism and biological functions. They differ in mild contacts (such as hydrophobic, pi stack, and van der Waals) to strong interactions (like ionic and H-bonds) because of differences in ring size and hetero atomic structure. Over the last ten years, research has demonstrated that the heterocyclic rings included in the structure of all newly developed DHFR inhibitor antifolate medications are essential for both enhancing the drug's affinity for the folate receptor and blocking the enzymes in malignant cells [9]. In this case, multitargeting appears to be a potential strategy for novel antifolate medications.
need new molecules that act on FRα this problem was overcome by the present work that produced twenty new FA analogs with heterocyclic rings recently added to anticancer drugs, and examined how they affected the binding affinity of FRα. The analogs exhibiting the highest affinity for FRα interaction were chosen for a molecular dynamics analysis aimed at delving further into the binding mechanism. An existing drug such as methotrexate, and vintafolide act on Folate receptors as folate transporter it is highly cytotoxic drugs. The trial's data and safety monitoring board (DSMB) advised that the study be discontinued following a planned analysis of the data that revealed vintafolide was not able to increase patients' progression-free survival (PFS) from platinum-resistant ovarian cancer [10-11]. Need new molecules that act on FRα this problem was overcome by the present work design of twenty-five new molecules. The old research that has been published shows that all the molecules that have been designed have a similar structure to folic acid and our study makes them different because our molecules have a thiophene-2,5-carbohydrazide ring other than folic acid, which makes them very novel and that compound is very potent and high affinity towards the FRα.

MATERIAL AND METHODS

Computational Methods:

The designed structures were drawn using chemsketch. The structures were prepared using BIOVIA Discovery Studio to correct the tautomeric and ionization state. The optimized structures were subjected to energy minimization using MMFF94 force field with the steepest descent algorithm. The previously reported structure of FRα with a resolution of 3.60 Å was downloaded from the RCSB Protein data bank. The protein structure enhancement protocol was performed using BIOVIA Discovery Studio.Designed structures were subjected to a docking study against the FRα. The docking protocol was executed using the PyRx 0.8 program. Prepared protein and ligand structure were imported and selected in the Auto-Dock Vina wizard unit of PyRx 0.8 GiRD Size X(-5.9649), Y(20.3364), Z(-8.5258), Dimensions: X: 23.8028, y: 25.9727, Z: 25.0006 coordinates. 8 was the default value for exhaustiveness. Each compound's highest negative binding affinity docked pose was saved in pdb format, and BIOVIA Discovery Studio was used to analyze additional binding interactions.

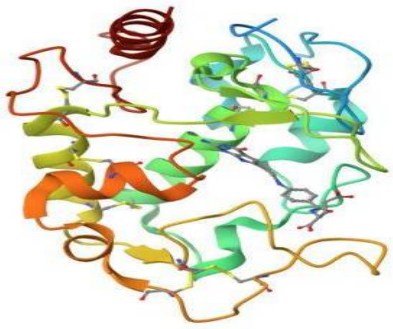
RESULT AND DISCUSSION

The docking study was applied to estimate the docking interaction of several docking studies was applied to estimate the docking interaction of several novel compounds which showed their formula in table no-1, with FRα AGF(183) 5IZQ. These compounds were selected because different studies used these in different applications. These proteins were selected depending on their activity in cancer.

Docking of AGF(183) 5IZQ

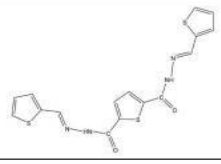
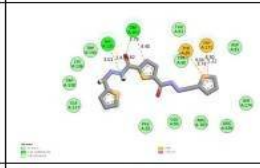
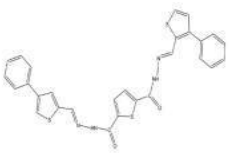
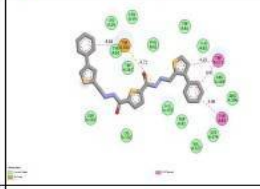
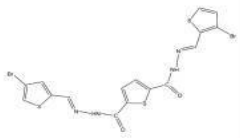
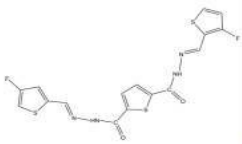
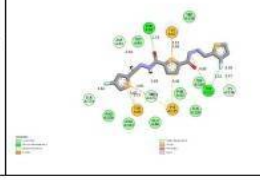
This protein has structure (13751) atoms and (1904) residues and 83A chain having chemical name N-(4-{[2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-6-yl) ethyl] amino} benzene-1-carbonyl)-L-glutamic acid with molecular formula C_{20} H_{22} N_6 O_6 shown in Fig.1. From this we can note that there are many active functional group, especially the nitrogen, sulphur, and oxygen atom These groups are founded clearly in amino acids (Gly),(Trp),(Lys),(Thr),(Tyr),(Asp),(Ser),(Arg),(Glu), (Phe)

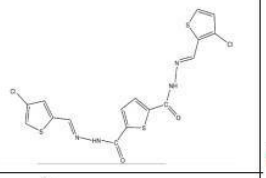
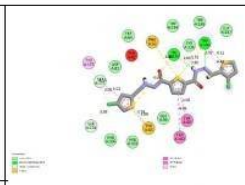
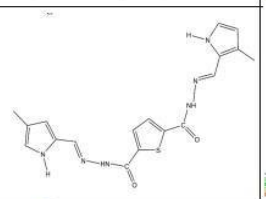
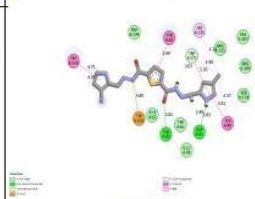
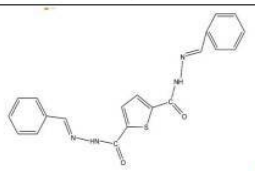
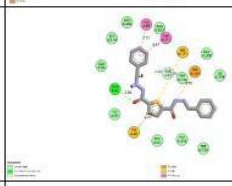
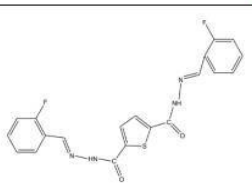
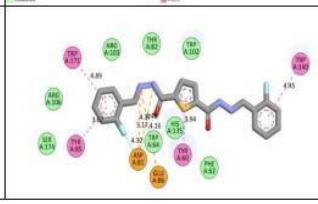
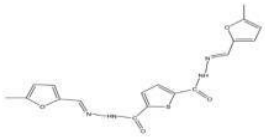
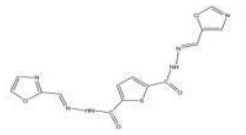
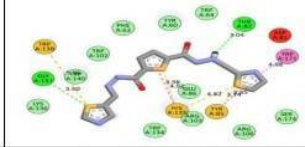
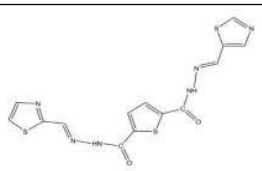
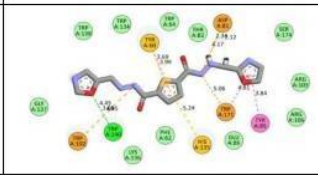
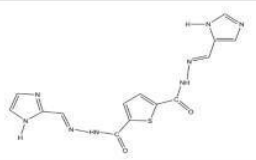
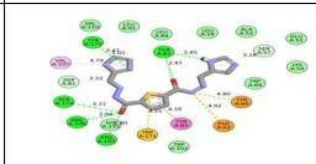
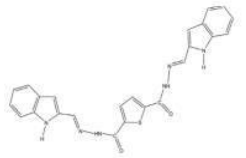
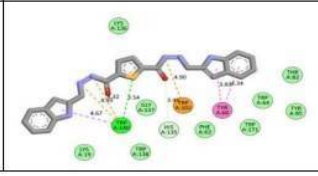
Figure1:The structural formula for AGF(183) 5IZQ Protien

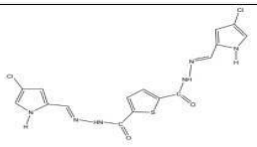
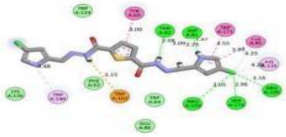
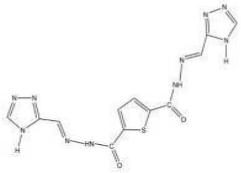
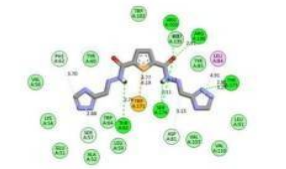
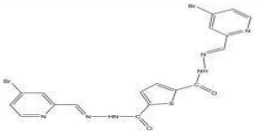
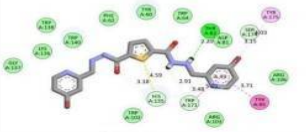
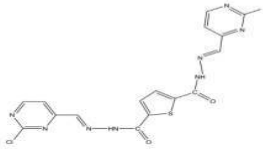
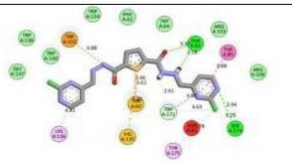
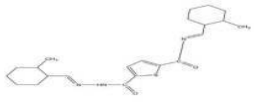
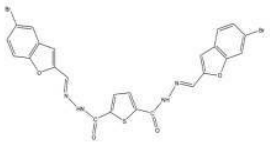
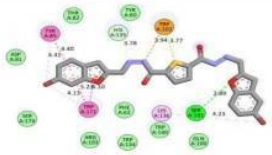
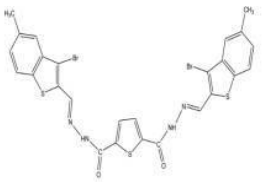
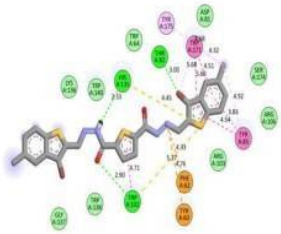
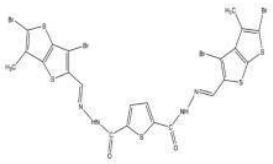
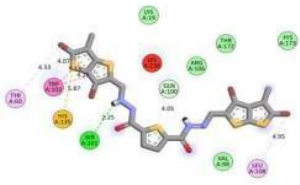
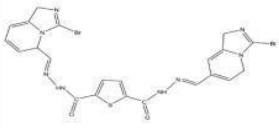
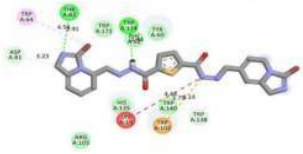


Docking with compounds(D1-D25)

The result for (AGF(183) 5IZQ) protein with the binding score energy as(score value) was determined. Where(score value)means the interactions of the proteins to interact with different medicines to characterize the best docking as shown in fig.1.The values observed that (D1 ,D2 ,D3 ,D4 ,D5 ,D6 ,D7 ,D8 ,D9 ,D10 ,D11 ,D12,D13,D14,D15,D16,D17,D18,D19,D20,D21,D22,D23,D24,D25) having energy score values(-8.2,-10.2,-8.5,-8.8,-8.6,-9.3,-9.9,-10.4,-10,-8.8,-8.3,-9.8,-10,-9,-10.9,-8.9,-10.3,-9.4,-9.4,-8.4,-7.3,-9.7,-11,-9.1,-8.8) respectively. This is evidence that all compounds have higher score values compared to the D21 compound. Table(1) shows that compound D23 has a more stable value (-11), while compound D22 was less stable with a value(-7.3) compared to methotrexate(-11.87).

Derivative	Structure	Docking	Docking Score(kcal/mol)
D1			-8.2
D2			-10.2
D3			-8.5
D4			-8.8

D5			-8.6
D6			-9.3
D7			-9.9
D8			-10.4
D9			-10
D10			-8.8
D11			-8.3
D12			-9.8
D13			-10

D14			-9
D15			-10.9
D16			-8.9
D17			-10.3
D18			-9.4
D19			-9.4
D20			-8.4
D21			-7.3
D22			-9.7

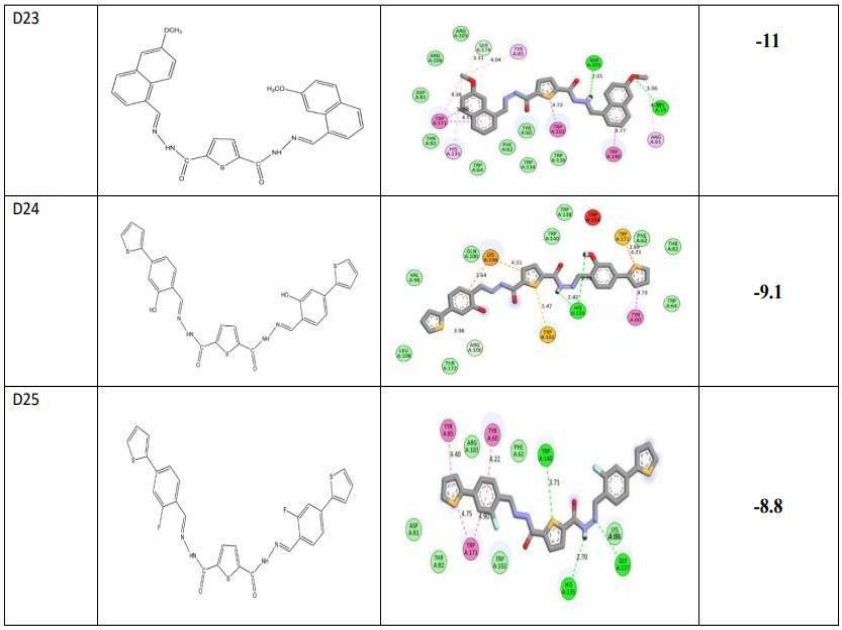


Figure 2:Score values for docking of AGF(183) 5IZQ protein with Compound (D1-D25)

Molecular docking analysis was utilised to analyze the possible binding mode of the designed inhibitors with Crystal structure of human folate receptor alpha. Docking analysis was utilised as initial scrutiny to identify the potential candidates from the designed inhibitors which can further explored for development of anticancer agents targeting human folate receptor alpha. Total 25 designed Structures were scrutinized against human folate receptor alpha. All Designed Inhibitors showed binding affinity ranging from -8.2 kcal/mol to -11 kcal/mol. D1 showed binding affinity of -8.2 kcal/mol and was found to be interacting with human folate receptor alpha via formation of hydrogen bond interaction with TRP102, HIS135, Carbon hydrogen bond HIS135, pi sulphur interaction with TYR85, TRP171, pi-pi T shaped interaction with TRP102 and,PHE62 and vander waal interactions with GLY137,TRP138,LYS136,TRP140, THR82,TYR60,ASP81,SER174,ARG106, ARG103,GLU86,PHE62. D2 exhibited binding affinity of -10.2 kcal/mol and interacted with the target with formation of pi cation interaction with TRP102, pi-pi T shaped interaction with TYR85, TRP171 and vander waal interactions with SER101,LUS136, HIS135, ASP81,VAL107, SER174, ARG106,ARG103,THR82,TRP64, PHE62,LEU59,LYS19, TYR60, TRP140.The compound D3 showed binding affinity of **-8.5** kcal/mol with formation of interaction like carbon hydrogen bond with SER174, Pi Sulphur interaction with TRP102,HIS135,TYR85, Alkyl interaction with TRP140,LYS136,TYR175, Pi-Pi t SHAPED interaction with TRP171,TYR60 and vander waal interactions with GLY137,TRP138, ARG103,ARG106,ASP81,GLU86,TRP64,TRP134,PHE62. The compound D4 was found to have of **-8.8** kcal/mol with formation of interaction like hydrogen bond interaction with THR82,TRP102, carbon hydrogen bond interaction with SER174,ASP81,LYS136,TRP171, Pi cation interaction with TYR85,HIS135,TYR60, Pi sulphur interaction with TYR85,HIS135,TYR60, and vander waal interactions with TRP64,TRP134,TRP140,PHE62,GLN100,GLUY86,ARG103,ARG106. D5 showed binding affinity of -8.6 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with HIS135,TRP140 Carbon hydrogen bond with TRP171,SER174 , pi sulphur interaction with PHE62,TYR85, pi-pi T shaped interaction with TYR60,TRP102, Alkyl interaction with TYR175 and vanderwaal interactions with ASP81,TRP64,TRP134, TRP138,GLY137, LYS136,ARG106, ARG103,GLU86. D6 interacted with binding affinity of -9.3 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with THR82, ASP81 Carbon hydrogen bond with TRP171, pi cation interaction with TRP102, pi-pi T shaped interaction with TRP140,TYR60,TYR85, Alkyl interaction with HIS135 and vander waal interactions with TRP134,ARG103,VAL107,ARG106,SER174,PHE62,TRP64,GLU86. Molecule no D7 is having binding affinity -9.96 kcal/mol of interacted with formation of hydrogen bond with THR82, carbon hydrogen bond with ASP81, pi cation interaction with TRP102, Pi sulfur interaction with HIS135, TYR60, pi-pi T shaped interaction TYR85,TRP171 and vander waal interactions with PHE62,TRP140,TRP138,TRP64, GLU86,SER174,ARG106,ARG103, TRP134,GLN100,LYS136 Molecule no D8 is having binding affinity **-10.4** kcal/mol and interacted with pi cation interaction with ASP81,GLU86 , pi-pi T shaped interaction TRP140,TRP171,TYR85, TYR60, halogen interaction with ASP81 and vander waal interactions with ARG106,SER174,ARG103, THR82,TRP102, HIOS135,TRP64,PHE62. D9 is having

binding affinity **-10** kcal/mol and interacted with pi cation interaction with ASP81,TRP102,TRP0171, pi-pi T shaped interaction TRP140,TYR85,TRP140 and vander waal interactions with SER174,THR82, TRP64,HIS135, PHE62,ARG103. D10 showed binding affinity of -8.8 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with TRP140, Pi Cation interaction with TRP102,ASP81,TRP171, pi sulphur interaction with TYR60,HIS135 , pi-pi T shaped interaction with TYR85, and vander waal interactions with GLY137,TRP138,TRP134,TRP64, THR82,SER82,SER174,ARG103, ARG106, GLU86,PHE62,LYS136. D11 showed binding affinity of -8.3 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with GLY137,THR82 , Pi Cation interaction with TRP138,HIS135,TYR85 , pi sulphur interaction with TRP171, pi-pi T shaped interaction with TYR85, alkyl interaction with TRP171 and vander waal interactions with GLY137,TRP138,TRP134,TRP64,THR82, SER174,ARG103, ARG106,GLU86,PHE62,LYS136. D12 showed binding affinity of -9.8 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with TYR175,SER174, ARG106,ARG103, THR82, carbon hydrogen bond interaction with HIS135,TRP102,SER57,ASP81, Pi Cation interaction with TYR60,PHE62, pi sulphur interaction with TRP171, pi-pi T shaped interaction with TYR85, alkyl interaction with VAL107 and vander waal interactions with VAL110,LEU91,LEU84,LEU59, ALS52,GLU51,LYS54, TRP64, TRP102.

D13 showed binding affinity of -10 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with TRP140 , carbon hydrogen bond interaction with HIS135 , Pi Cation interaction with TRP102, pi-pi T shaped interaction with TYR60, and vander waal interactions with LYS136,LYS19,TRP138,GLY137,PHE62,TRP171,TRP64,THR82,TYR85.D14 showed binding affinity of -9kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with THR82,ASP81,ARG103,SER174,ARG106,Pi Cation interaction with TRP102, pi-pi T shaped interaction with TYR60,TRP171,THR85, , alkyl interaction with TRP140,HIS135 , and vander waal interactions with LYS136,PHE62,TRP134,TRP64,GLU86. D15 showed binding affinity of -10.9 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with ARG103,ARG106,TYR175, carbon hydrogen bond interaction with PHE62,SER57,ASP81,Pi Cation interaction with TRP171, alkyl interaction with LEU84 and vander waal interactions with VAL56,LYS54,GLU51,ALA52,LEU59,TRP64, VAL107,VAL110, LEU91,TYR85, TRP102,TYR60,VAL56.D16 showed binding affinity of -8.9 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with THR82, carbon hydrogen bond interaction with HIS135,SER174, alkyl interaction with TYR175, pi-pi T shaped interaction with TYR85 and vander waal interactions with GLY137,LYS136, TRP140,TRP138, PHE62,TYR60, TRP64,ASP81,ARG106,ARG103,TRP102.D17 showed binding affinity of -10.3 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with SER174,THR82 , Pi Cation interaction with TRP102, pi sulphur interaction with TYR60,HIS135, , pi-pi T shaped interaction with TYR85, alkyl interaction with LYS136 and vander waal interactions with TRP138,GLY137,TRP140,TRP134,PHE62, TRP64,ARG103,ARG106.D18 showed binding affinity of -9.4 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with LYS19, carbon hydrogen bond interaction with TRP134, alkyl interaction with TRP140,TRP171 and vander waal interactions with ARG81,TRP102,TRP138,TYR85,THR82,TRP64,PHE62,HIS135.D19 showed binding affinity of -9.4 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with SER101, carbon hydrogen bond interaction with HIS135, Pi Cation interaction with TRP102, pi sulphur interaction with TRP171, pi-pi T shaped interaction with TYR85,TRP171, alkyl interaction with LYS136 and vander waal interactions with ASP81,THR82, TYR60,PHE62,TRP134, ARG103,SER174, GLN100. D20 showed binding affinity of -8.4 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with HIS135,THR82,TRP102 , Pi Cation interaction with PHE62,TYR60 , pi sulphur interaction with TRP171, pi-pi T shaped interaction with TRP171,TYR85 alkyl interaction with TYR175 and vander waal interactions with LYS136,TRP140,TRP64, ASP81,SER174,ARG106, ARG103,TRP138, GLY137. D21 showed binding affinity of -7.3 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with SER101 carbon hydrogen bond interaction with GLN100 , Pi Cation interaction with TYR60,PHE62, pi sulphur interaction with HIS135 pi-pi T shaped interaction with TRP102, alkyl interaction with TYR60,LEU108 and vander waal interactions with LYS19,ARG106,THR172, HIS173,VAL98. D22 showed binding affinity of -9.7 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with THR82,TRP134 carbon hydrogen bond interaction with ASP81,PHE82 Pi Cation interaction with TRP102, alkyl interaction with TRP64 and vander waal interactions with ASP81,TROP171,TYR60,PHE62, HIS135,TRP140,ARG103.D23 showed binding affinity of -11 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with SER101,carbon hydrogen bond interaction with SER174 , Pi Cation interaction with TYR60,PHE62, pi sulphur interaction with TRP171, pi-pi T shaped interaction with TRP140,TRP171,TRP102 , alkyl interaction with ARG61 and vander waal interactions with ASP81,ARG106,ARG103,TRP64,PHE62,

TYR60,TRP134, TRP138.D24 showed binding affinity of -9.1 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with HIS135, carbon hydrogen bond interaction with ARG106, Pi Cation interaction with TRP171,LYS136, pi sulphur interaction with TRP102, pi-pi T shaped interaction with TYR60 and vander waal interactions with VAL98,LEU108,THR172,GLN100,TRP140,TRP138,PHE62, THR82,TRP64.D25 showed binding affinity of -8.8 kcal/mol and was found to be interacting with via formation of hydrogen bond interaction with HIS135,GLY137,TRP140 carbon hydrogen bond interaction with HIS135,TRP102,SER57,ASP81, Pi Cation interaction with TYR60,PHE62, pi sulphur interaction with TRP171, pi-pi T shaped interaction with TYR85,TYR60,TRP171, and vander waal interactions with ARG103,PHE62,TRP102,THR82.ASP81 shown in fig.2.

DISCUSSION

In present study we have selected a new target FRα, there are very few drug acts on it. We searched a lot of papers but there are only 3-4 drugs that act on the FRα receptor.

In one research article we found out that docking results of methotrexate on FRα is -11.84 kcal/mol [10]. But it is analogues of folic acid and it is highly toxic compound with resistance has developed. That's why we need a new drug that's acts on FRα. We got another research paper in which developed thiophene nanocarries for targeting FRα [11]. Form that we learned thiophene has FRα inhibitory activity. We are designing a structure having a basic moiety of Thiophene-2,5-carbohydrazide with different aromatic and heterocyclic rings with substitution of electron-donating, electron-withdrawing groups all compounds show inhibitory activity against Folate receptor α in which D23 containing the main nucleus Thiophene-2,5-carbohydrazide substituted with naphthyl ring with methoxy group attachment of Polycyclic ring with electron withdrawing group increases inhibitory activity So the compound D23 was surrounded by different amino acid groups in protein the active polar site was contacted between the compound with the protein by ASP81, Arg106, Arg103, Trp64, Phe62, Tyr60, Trp134, Trp138 by electron-donating methoxy group, and (Tyr85) Which was attached by (π)aromatic system .While the compound D21 was in contact with a methyl group(Tyr60) by (π)aromatic system.

If we compare the compound D23 with methotrexate, We can note that this compound has a methoxy group in the formula of the structure. This indicates that the compound was more polar and active compared to other compounds which also have active groups like (NH_2,=O). For this reason, the compound D23 was more stable compared to the methotrexate and vintafolide.

CONCLUSION

A total of twenty-five thiophene-2,5-dicarbohydrazide derivatives with different aromatic rings were created and aligned with FRα.Every chemical has demonstrated higher binding energies. The findings showed that the inner region of the FRα active site interacts with ASP81, Arg106, Arg103, Trp64, Phe62, Tyr60, Trp134, and Trp138. These findings suggest that electron-donating and electron-withdrawing groups on aromatic, polycyclic, and heterocyclic rings are important for increasing the binding affinity towards FRα.

However, due to the time frame and resources available, the effort made here presented a theoretical prediction of features required for potential lead candidates. Many aspects to reach the clinical stage should be investigated and more work should be done so that current efforts are not left unfinished. Existing only two drugs such as methotrexate and vintafolide act on FRα this drug has limitations. It is suggested that the compounds can be synthesized for anticancer activity. Having the compounds synthesized will allow for the confirmation of activity to be ascertained .These twenty-five compounds should not only be considered for lead optimization but also could be used in the conjugation of nanoparticles for drug delivery for enhanced FA recognition by FRα, especially in the treatment of cancer.

COMPETING INTERESTS

Not applicable

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Ethical Approval – our work is based on computational studies. Ethical approval not required.

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Declaration-None

Author Contribution-All Author contribution to study conceptions and design. Material preparation, analysis was performed by VC. The first draft of the manuscript was written by VG and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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