Larix Publications
Journal of Pharma Research
http://www.jprinfo.com/
Vol. 12, Issue 06, 2023 ISSN: 2319-5622

Research Article

IDENTIFICATION AND DESIGN OF SMALL MOLECULE HNF4α MODULATORS BY PHARMACOPHORE BASED VIRTUAL SCREENING APPROACH

Padma Bhavani B *[1] and Dr. M. Sunitha Reddy [2]
[1,2]*Centre for Pharmaceutical Sciences, Institute of Science and Technology, JNTUH, Kukatpally, Hyderabad, Telangana, India. 500085*

Received on: 03-11-2023; Revised and Accepted on: 10-12-2023

ABSTRACT

Objective*: Hepatocyte Nuclear Factor 4 alpha (HNF4α) is an adopted orphan protein with endogenous ligand as free fatty acid discovered in the recent years. It has prominent role in controlling the genes that are responsible for the development and functioning of various body organs like liver, pancreas, kidney and gut. The objective is to find out the small molecules that can modulate the functioning of HNF4α using computer aided drug designing.*

Methods*: Docking based virtual screening was performed for the hit molecules obtained from the pharmacophore-based database screening. Top ten hits are studied for pharmacokinetic and toxicity profile. Selected leads are further analyzed for interactions and novel quinazolinone based molecules are designed.*

Results: *Using Pharmit server, based on BIM 5078, pharmacophore-based screening of databases has been done that resulted in 5000 hits. Out of these 2011 PubChem molecules are virtually screened using PyRx. Top 10 (scores ranging from -12 to -10) are studied for ADMET and protox filtration. Two quinazolinone based molecules are found to be inactive for all possible toxicity predictions.*

Conclusion: *Novel quinazolinone based analogous are proposed for synthesis and further biological studies can be done to evaluate the functioning of small molecule HNF4α modulators.*

Keywords: *HNF4α, pharmacophore, docking based virtual screening, quinazolinone, PyRx*

INTRODUCTION

Hepatocyte Nuclear Factor 4 alpha (HNF4α) protein belongs to nuclear receptor subfamily 2, group A, member (NR2A1) which is a hepatic DNA-binding protein involved in the expression of hepatic genes. It plays a major role in the development and functioning of liver, kidneys, gut and pancreatic beta cells [1]. It is also involved prominently in the regulation of gene expression that is linked to metabolic processes such as glucose and lipid homeostasis [2, 3]. Impairment of the gene expression led to gastrointestinal and metabolic diseases. HNF4α directly interacts with the proteins that are responsible for the glucose uptake and metabolism and hence HNF4α gene alterations and pathogenic mutations causes heritable form of type 2 diabetes [4]; accounts for 5% to 10% of maturity-onset diabetes of the young 1 (MODY-1) [5]. HNF4α has also been involved in inflammatory processes in internal organs such as inflammatory bowel disease. It sets out to be a novel diagnostic and prognostic biomarker in cancer therapy [6].

Due to the enormous role played by HNF4α in the human body, there is an immense interest in the scientific community to develop the small molecules that regulate the protein. HNF4α is an orphan nuclear receptor whose endogenous ligand is not known, however, later x-ray crystal structures of medium and long chain fatty acid bound ligand binding pocket sites within the HNF4α protein were developed. But these fatty acid ligands cannot completely activate or modulate the receptor activity and there is very limited evidence regarding the ligand mediated HNF4α activity. Also due to the kinetics of the ligand binding the development of small molecule ligands becomes a challenging task. Interestingly, in certain physiological situations, linoleic acid which is an endogenous ligand of HNF4α is found to be

***Corresponding Author:**

Padma Bhavani B
Centre for Pharmaceutical Sciences, Institute of Science and Technology, JNTUH, Kukatpally, Hyderabad, Telangana, India. 500085.
Contact: 040-23158666
DOI: https://doi.org/10.5281/zenodo.10408277

exchangeable from the binding site pocket of the receptor [7] which means that there is a possibility of other ligands which can be small molecules to bind to the active site of the receptor and thereby possibility of receptor activity modulation. But HNF4α ligand exchange is quite inefficient in vitro Rémy Le Guével et al identified small molecule regulators of the HNF4α based on naphthofuran scaffolds [8]. Alverine, an approved drug for the treatment of irritable bowel syndrome is found to activate HNF4α. A patent was filed by the Ligand Pharmaceuticals Incorporated [US] on the methods for and using substituted tetrahydroquinolines, phenylacetic acids and benzoic acids as HNF4α modulator compounds [9]. Nitrobenzenesulfonyl based methylbenzimidazole derivative (BIM5078) was found to be potent HNF4α antagonist identified via High-Throughput Screening. Chemically diverse collection of fragment-like activators (tryptoline and others) which modulate the HNF4α activity were discovered via Chemogenomics [10]

2. MATERIALS AND METHODS

2.1 Methodology

An adopted orphan receptor is one whose ligands have been identified in the recent years [10]. HNF4α is termed as adopted orphan receptor whose ligands are identified as free fatty acids but not having promising functional aspects. Hence, we aimed to develop small molecule ligands that can modulate the receptor. In order to achieve this, we proposed In-silico drug designing that relied on computational methods like pharmacophore based virtual screening of ligand library, molecular docking approaches that can be used to find out active molecules. In the present work, pharmacophore-based ligand lead library was generated against HNF4α that have similar steric and electronic features and further virtual screening of the obtained leads was performed to screen the molecules having best binding scores followed by ADMET studies, docking studies of the best hits. The binding interactions of the selected best hits were studied and considering the core features involved in binding, design of the novel molecules was proposed for further analysis.

2.2 Generation of Ligand Library

The crystal structure of HNF4α consists of 4 chains A, B, C, D with a total sequence length of 250 and it forms an antiparallel, three-layered α helical sandwich similar to other nuclear receptor ligand binding domains. 3D protein x-ray crystal structure was downloaded from PDB databank in PDB format (PDB Id: 1M7W). 1M7W consists of ligand binding domain with bound fatty acid in all the four chains. Using Biovia Discovery Studio the active site attributes from the largest binding site of the receptor cavity was defined (X=55.190661 60.170821 11.720768; radius=37.89). With the help of DoGSiteScorer [11] eight potential binding pockets with drug score greater than 0.5 are identified for docking considerations (fig. 1). Binding pocket amino acids are analysed using CASTp 3.0 software [12].

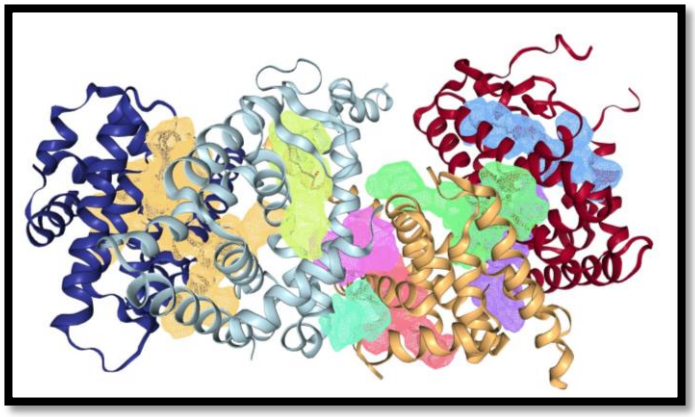
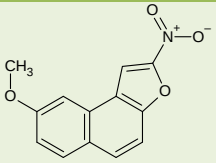
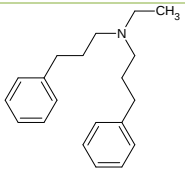
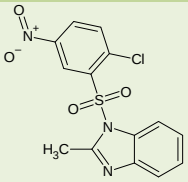


Fig 1: Eight potential drug binding pockets identified by DoGSiteScorer represented in eight different colours

HNF4α is an orphan receptor with limited reported small molecule ligands having little effect on receptor modulation. Using PyRx [13], virtual screening was performed to understand the binding affinity of the reported ligands (substituted naphthofuran, Alverine, BIM5078) with that of the receptor. However, to completely navigate the binding sites of the target, screening was performed by maximising the vina search space grid on the receptor. The binding interactions of reported molecules are studied thoroughly (Table 1) using Biovia Discovery Studio Visualiser [14]. Among them BIM5078, a nitrogen containing heterogenous molecule (1-[(2-chloro-5-nitrophenyl) sulfonyl]-2-methyl-1H-benzimidazole) is having highest affinity for HNF4α with a binding score of -8.1. After careful observation of reported molecules and their interactions hydrophobic parameters are found to play a major role in the receptor modulation (fig. 2a, 2b). It is interesting to find out the lead molecules having the same pharmacophoric fingerprint as the selected ligand BIM5078 (2c). Further screening of the obtained leads will enable to find out the feasible hits for HNF4α.

Table 1: Binding affinity scores and interactions with HNF4α of reported molecules

S. No.	Molecule	Binding score	Interactions
1	 **8-methoxy-2-nitronaphtho[2,1-b] furan**	-7.4	Conventional hydrogen bonds (LYS D:291), Hydrophobic: Pi-pi stacked: TRP D:340 Pi alkyl: ILE D:343

2	 **Alverine**	-6.6	Hydrophobic: Amide pi stacked: LEU B:186; Pi alkyl: LEU C:186; LEU C:211; LEU B:187; VAL C:208
3	 **BIM5078**	-8.1	Carbon hydrogen bonding ARG C:212, hydrophobic: pi alkyl: LEU B: 211; LEU C:211; LEU C187; VAL B:208; VAL B:190; ARG B:212

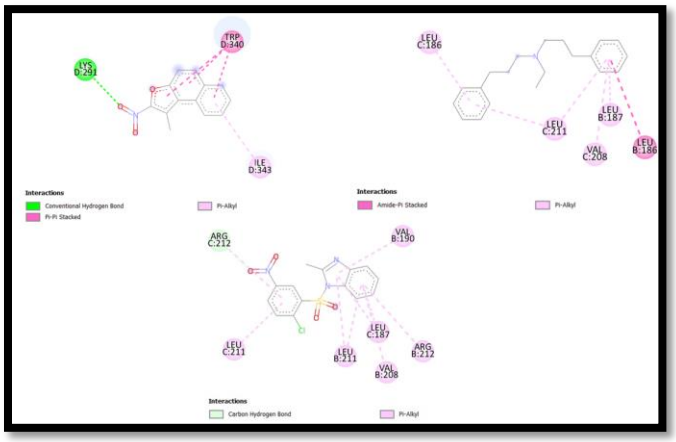


Fig: 2. Binding interactions of small molecule naphthofuran (2a), Alverine (2b), BIM5078 (2c) with HNF4α respectively.

2.2.1 Pharmacophoric Parameters:

Pharmit [15] is a search engine that facilitates virtual screening of large chemical datasets to search small molecules based on their structural and chemical similarity to another small molecule. It accepts ligand-receptor complex structure, a ligand-only structure or pharmacophore as query file. All the pharmacophore features present in the provided ligand structure will be identified by the server and if at all any receptor structure is provided, it will identify the ligand features relevant to the protein-ligand interaction using distance cutoffs between corresponding features on the receptor and ligand. The server also allows the query to be interactively edited. The ligand structure of BIM5078 is given as query file to the server which generated the pharmacophore fingerprint. As it is difficult to match all the query features, based on the binding interactions observed from the discovery visualiser (fig. 2c), the query is edited by omitting six features and the following parameters are finalised as query file (fig 3; Table 2) with the following filters applied: Mol wt <=500; Rot bonds<=10; LogP<=5; HBA<=5; HBD<=5 and number of hits per molecule as one. Pharmit also provides the energy minimization of the resulted query hits; since the input query lacks the protein-ligand complex structure optimization is not available. Hence the query file results are saved in the three-dimensional SDF file format as ligand library.

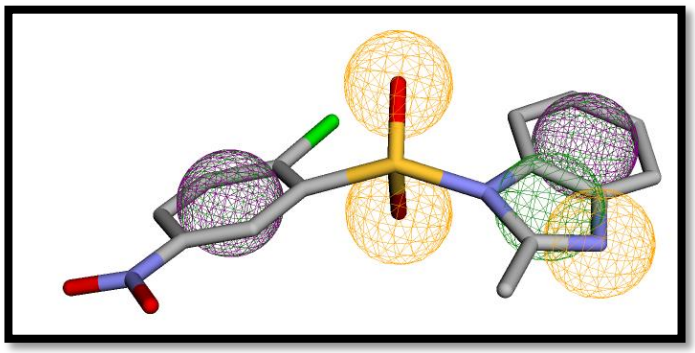


Fig 3: Pharmacophoric query parameters: Hydrogen acceptor represented as yellow spheres; purple: aromatic; green: hydrophobic

Table 2: Pharmacophore query parameters

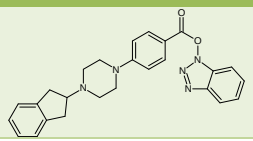
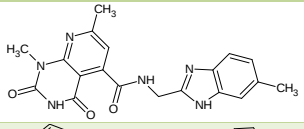
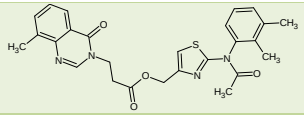
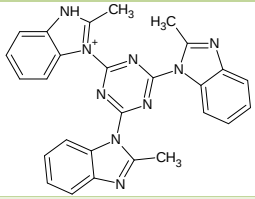
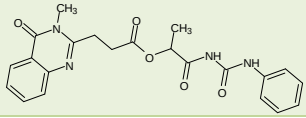
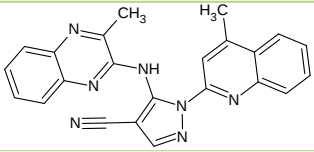
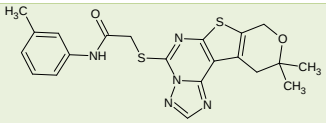
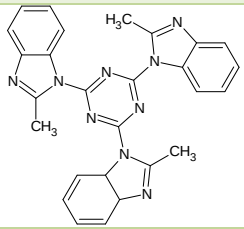
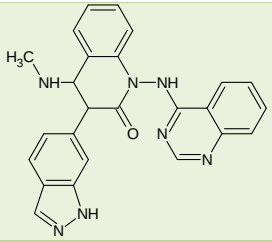
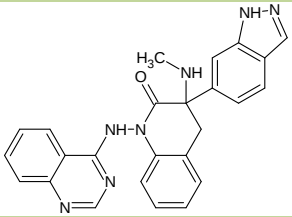
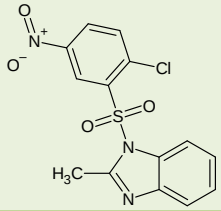
S.No.	Parameter	X	Y	Z	Radius
1	Aromatic	33.73	-15.42	-0.08	1.0
2	Aromatic	29.64	-9.99	-0.1	1.0
3	Hydrogen acceptor	31.23	-16.58	-0.3	1.0
4	Hydrogen acceptor	31.21	-12.69	-0.64	1.0
5	Hydrogen acceptor	31.85	-12.46	1.76	1.0
6	Hydrophobic	33.73	-15.42	-0.08	1.0
7	Hydrophobic	29.64	-9.99	-0.1	1.0
8	Hydrophobic	31.61	-15.5	-0.04	1.0

2.2 Docking based virtual screening (DBVS) of ligand library using PyRx

PyRx 0.8 is a user-friendly open-source software that combines the services of other open-source software like AutoDock, AutoDock Vina, and Open Babel to perform DBVS [16]. The three-dimensional SDF files of query file result of Pubchem library with 2011 structures were uploaded as input files into PyRx server for further DBVS. Binding scores are observed for the molecules and top ten hits with highest binding affinity ranks (Table 3) were

further analysed for drug likeliness, physicochemical and pharmacokinetic properties using Swiss ADME software and binding interactions using BIOVIA Discovery studio respectively. The Insilco prediction of compound toxicities by computational estimations was done by ProTox-II, a virtual lab for the prediction of toxicities of small molecules [17].

Table 3: Top ten DBVS hits of HNF4α (1M7W)

S. No	Pubchem ID	Structure	Binding energy (Kcal/mol
1	20655241		-12.1
2	131918667		-10.9
3	55460203		-10.8
4	153645466		-10.7
5	46670313		-10.6
6	108779266		-10.5
7	2220304		-10.5
8	71152493		-10.5
9	69462661		-10.4
10	69462666		-10.4
11	BIM5078		-8.1

3. RESULTS & DISCUSSION

3.1 DBVS Result Analysis

It is a well-known fact that nitrogenous heterocycles are an integral part of many natural drug scaffolds and synthetic molecules which possess physiological activity. From the literature search, we concluded that nitrogenous heterocycles do have a role in modulating HNF4α. Hence considering the nitrogenous scaffold and highest binding affinity score of BIM5078, the pharmacophore fingerprint of BIM5078 is selected for ligand library generation. A total of 5,153 hit molecules are obtained after screening of different databases which include CHEMBL32(138), ChemDiv (162), ChemSpace (760), MCULE (540), MolPort (526), PubChem (2011), LabNetwork (161), ZINC (855). PubChem molecules which are 2011 in number are further selected for DBVS and binding affinity scores were noted. Top ten hit molecules are selected for binding interaction studies. PubChem ID:20655241is having highest binding affinity (-12.1Kcal/mol) with HNF4α followed by PubChem ID:131918667 (-10.9 Kcal/mol) comparatively much better than BIM 5078 reference molecule. But the molecule PubChem ID:131918667 showed unfavourable donor-donor bond interaction with LYS 291 amino acid in the B chain. Also, PubChem ID: 2220304 showed unfavourable acceptor-acceptor interactions with ASP 289 amino acid in the D chain (Table 4). Unfavourable donor-donor and unfavourable acceptor-acceptor interactions will reduce the stability of the compound activity and thereby reduces the stability of the complex because they indicate the repulsion between two molecules or atoms [18].

Table 4: Binding interactions of the top ten hits with HNF4α

Pubchem ID	Binding Interactions
20655241	Conventional hydrogen bonds: THR B:334; ARG A:303; Pi-Alkyl bond: ILE A:343; PRO B:333; LEU A:332; Pi-Pi stacked: TRP A:340; Pi-Pi T shape: HIS A:214; Pi Anion: ASP A: 287; Pi cation: ARG B:258;
131918667	Conventional hydrogen bonds: THR A:334; ARG A:258; HIS B:214; Alkyl bond: TRP B:340; Unfavourable donor-donor bond: LYS B: 291; Pi-Alkyl bond: PRO A:333; ILE B:284; LEU B:332; ALA B:213;290; Pi Anion: ASP B: 287; Pi cation: LYS B:291; Carbon-hydrogen: ARG B:212;
55460203	Conventional hydrogen bonds: THR D:334; ARG C:303; ARG D:258; Pi-Alkyl bond: ILE C:343; PRO D:333; LEU C:332; Pi-Pi stacked: TRP C:340; Pi-Pi T shape: HIS C:214; Pi Anion: ASP C: 287; Pi cation: LYS C:291; Carbon-hydrogen: ASP C:289; SER D:337;
153645466	Conventional hydrogen bonds: LYS D:291; Pi-Alkyl bond: ILE D:343; PRO D:333; LEU C:332; Pi-Pi stacked: TRP D:340; Pi-Sigma: GLN C:341;
46670313	Conventional hydrogen bonds: ASP C:287; HIS C:214; THR D:334; ARG D:258; LYS C:291; Pi-Alkyl bond: ILE C:343; PRO D:333; LEU C:332; Pi-Pi stacked: TRP C:340; Carbon-hydrogen: ALA C:213; SER C:337;
108779266	Pi-Alkyl bond: ALA B:215; LEU B:186; LEU C:211; VAL C:190; VAL B:208; LEU C:187; LEU C:186; ARG B:212; LEU B:211; Amide-pi stack: LEU C:186;
2220304	Conventional hydrogen bonds: THR C:334; HIS D:214; LYS D:291; Unfavourable acceptor-acceptor: ASP D: 289; Pi-Alkyl bond: PRO C:333; ILE D:284; LEU D:332; Pi cation: ARG C:258; Pi-sulphur: TRP D:340;
71152493	Pi-Alkyl bond: LYS D:291; Pi cation: LYS D:291; ARGC:258; Pi-Donor hydrogen bond: TRP D:340;
69462661	Conventional hydrogen bonds: TRP D:340; LEU D:365; Pi-Alkyl bond: ILE D:343; Pi-Pi stacked: TRP D:340; Pi cation: ARG C:258; LYS D:291; Carbon-hydrogen: ASP D:287; ALA D:213; ARG D:212
69462666	Conventional hydrogen bonds: TRP D:340; Pi-Alkyl bond: ILE D:343; LYS D:291; Pi-Pi stacked: TRP D:340; Pi cation: ARG C:258; LYS D:291; Carbon-hydrogen: ALA D:213; GLU D:217

The ligand binding domain (LBD) of human HNF4α consists of amino acid residues from 140–382. All the obtained hits showed conventional hydrogen bonding, hydrophobic interactions (pi-pi stacking/pi-alkyl etc) within the LBD of HNF4α (Table 4). Although the binding interactions doesn't exactly match with the binding interactions of endogenous ligand (free fatty acid) of HNF4α and BIM 5078, all the interactions are within the LBD site with docking scores greater than them. This indicates that the obtained hits show greater binding affinity with the sites other than fatty acid binding site although within the LBD. The quinoline and quinoxaline core of PubChem Id: 108779266 occupies the same hydrophobic pocket as that of benzimidazole core of BIM 5078.

3.2 Insilco ADMET property and Toxicity Analysis

Assessment of absorption, distribution, metabolism and excretion (ADME) properties is an essential step in the drug development process which can be done by using valid computer models as an alternative to experiments. Here in this case, SwissADME web tool [19] is used to predict models for physicochemical properties, pharmacokinetics, drug-likeness and synthetic chemistry accessibility. All the hits showed molecular weight ranging from 378 to 490 g/mol. General acceptable range is between 341.0 and 437.5 g/mol [20]. All the hit molecules showed drug likeliness (Table 5). ProTox-II webserver (TOX PREDICTION) is used for the prediction of toxicity of selected hits after omitting PubChem molecules 131918667 and 2220304. The molecules with PubChem IDs 55460203 and 46670313 have comparatively higher predicted LD50 (mg/Kg) values 1000 and 1250 respectively with toxicity profile as inactive in all aspects (Table 6). Hence considering the synthetic accessibility and Insilco toxicity predictions, PubChem molecules with IDs 55460203 and 46670313 are considered for further analysis.

Table 5: Predicted pharmacokinetic property profile of top ten hits

Pubchem ID	20655241	131918667	55460203	153645466	46670313	108779266	2220304	71152493	69462661	69462666
Mol Wt	439.51	378.38	490.57	472.52	422.43	391.43	439.55	473.53	435.48	435.48
Num. heavy atoms	33	28	35	36	31	30	30	36	33	33
Num. arom. heavy atoms	21	19	21	33	16	25	18	24	25	25
Num. rotatable bonds	5	4	9	3	10	3	5	3	4	4
Num. H-bond acceptors	5	5	6	5	6	5	5	6	5	5
Num. H-bond donors	0	3	0	1	2	1	1	0	3	3
Log P o/w (iLOGP)	3.96	1.51	4.18	-0.45	3.13	3.48	3.32	3.76	2.14	2.53
Water Solubility (Log S)	-5.82	-3.07	-5.01	-6.95	-3.50	-5.85	-5.14	-5.86	-5.07	-5.29
GI absorption	High	High	Low	High	High	High	Low	High	High	High
Drug likeliness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Synthetic accesibility	3.61	2.79	3.94	3.47	3.66	3.62	3.68	5.06	4.09	3.88

Table 6: Predicted toxicity profile of top ten hits

Pubchem ID	20655241	55460203	153645466	46670313	108779266	71152493	69462661	69462666
Predicted LD50 (mg/Kg)	2500	1000	500	1250	500	826	2000	800
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Active	Inactive	Active	Inactive
Carcinogenicity	Active	Inactive	Active	Inactive	Active	Active	Active	Active
Immunotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Mutagenicity	Active	Inactive	Active	Inactive	Active	Active	Active	Inactive
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive

4. Proposed Design of Novel Analogues

Nitrogen-based heterocycles occupy more than 75% of drugs approved by the FDA [21]. All the obtained hit molecules contain various nitrogenous heterocyclic scaffolds like benzotriazole,

piperazine, benzimidazole, pyridopyrimidine, quinazolinone, thiazole, triazine, quinoline, quinoxaline, triazolo pyrimidine, indazole, quinazoline, dihydroquinoline. Quinazolinone derivatives play a prominent role as potent pharmacophoric units and greatly helps in the design and development of a wide range of bioactive compounds owing to their versatile nature [22]. They have important role as anticancer [23], anti-inflammatory [24], anti-cholinesterase [25], DHFR inhibitory [26] and antimicrobial [27] agents. Quinazolinone-sulphonyl urea-based derivatives showed reduced glucose levels [28]. Based on the binding interaction studies, ADMET and PROTOX properties PubChem molecule 55460203 and 46670313 are considered as basic molecules for designing new drug like molecules. These molecules showed maximum interactions with the target and have quinazolinone ring in common (fig. 4&5).

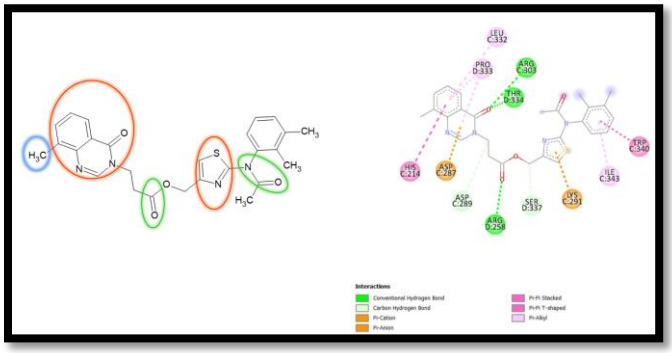


Fig 4: Structural assessment to consider basic scaffolds and their interactions to design new analogues. Left: Basic scaffold-Quinazolinone circled in red/aromatic/heterocyclic (hydrophobic interactions) side chain linked with conventional hydrogen bonding interactions represented in green and alkyl groups in blue. Right: 2D visualisation of PubChem ID 55460203

Quinazolinone ring with alkyl group substituents showed active hydrophobic interactions besides amide groups. Carboxylic side chains showed conventional hydrogen bonding. Moving along with these parameters fig. 6 depicts a novel strategy of designing new leads with good synthetic feasibility and probable drug likeliness.

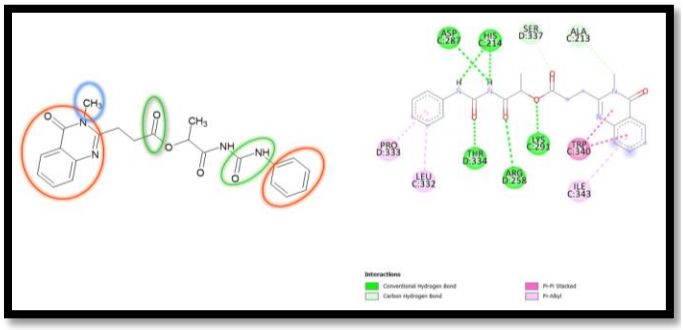


Fig 5: Structural assessment to consider basic scaffolds and their interactions to design new analogues. Left: Basic scaffold-Quinazolinone circled in red/aromatic/heterocyclic (hydrophobic interactions) side chain linked with conventional hydrogen bonding interactions represented in green and alkyl groups in blue. Right: 2D visualisation of PubChem ID 46670313

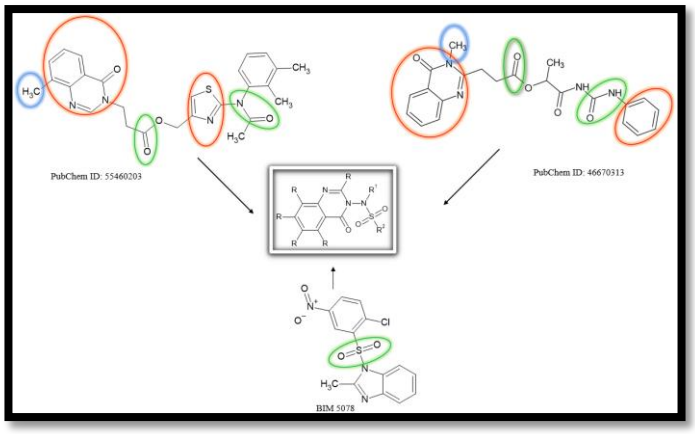


Fig 6: Proposed design strategy based on the hits selected from DBVS against HNF4α. R=R1= Alkyl/Aromatic; R2= Heterocyclics (Aromatics/Non-Aromatics)

The proposed strategy aimed to combine the important functional groups present in both the hits that are involved in the key interactions with the target, keeping intact the core quinazolinone moiety as such. It aimed to reduce the molecular weight to the accepted range at the same time number of rotatable bonds for further synthetic feasibility. The chemical structure and functionality of the sulfonyl group helps in forming key hydrogen bonding interactions with the active site amino acid residues of biological targets [29]. Hence sulfonyl group forms an important therapeutic agent in the drug discovery domain. Quinazolinone sulfonyl group hybrids showed potent anti-hyperglycaemic activity [30, 31]. BIM5078 consists of sulfonyl group which is retained in the novel pharmacophore. Hydrophobic interactions are the key interactions that play a prominent role in the protein-ligand complex. They are more frequent interactions and are considered as driving factor in high-efficiency ligands to form drug-receptor interactions [32]. Alkyl and aromatic substituents of both the hits participated in hydrophobic interactions (aromatic-aromatic; pi-pi stacked, pi-pi alkyl, pi-pi T shaped). It was found that HNF4α is found to interact with ligands like lauric acid/myristic acid, BIM5078, PubChem molecules 55460203 and 46670313 mainly in the form of hydrophobic interactions. Hence all possible alkyl/aromatic substituents are proposed at all possible positions around quinazolinone core.

CONCLUSION

HNF4α protein is a transcription factor mainly expressed in the epithelial tissues of liver, gut, pancreas and kidney. It has prominent role in controlling a variety of activities particular to that specific gene. It is primarily an adopted orphan with endogenous ligand as free fatty acid. Small molecule modulators in place of free fatty acids may help in modulating the activity of HNF4α further. Quinazolinone moiety containing novel molecules based on the hits obtained from the pharmacophore based virtual screening were proposed. Further biological evaluation of the selected two hit molecules (PubChem IDs 55460203 and 46670313) against HNF4α also helps in determining its activity.

REFERENCES

[1] Sirano Dhe-Paganon, Karen Duda, Melanie Iwamoto, Young-In Chi, Steven E Shoelson, S. Crystal structure of the hnf4 alpha ligand domain in complex with endogenous fatty acid ligand. The Journal of biological chemistry, 2002; 277(41): 37973-6.

[2] Alice Kiselyuk, Seung-Hee Lee, Suzette Farber-Katz, et al. HNF4α antagonists discovered by a high-throughput screen for modulators of the human insulin promoter. Chemistry & biology, 2012; 19(7): 806-18.

[3] Seung-Hee Lee, Sonalee Athavankar, Tom Cohen et al. Identification of Alverine and Benfluorex as HNF4α Activators. ACS Chem. Biol., 2013; 8: 1730−1736.

[4] Isabelle Meijer, Sabine Willems, Xiaomin Ni, et al. Chemical Starting Matter for HNF4α Ligand Discovery and Chemogenomics. International Journal of Molecular Sciences, 2020; 21: 7895.

[5] Laura S. Hoffman; Tamaryn J. Fox; Catherine Anastasopoulou; Ishwarlal Jialal. Maturity Onset Diabetes in the Young. StatPearls Treasure Island (FL): StatPearls Publishing; 2023.

[6] Duo-Duo Lv, Ling-Yun Zhou & Hong Tang. Hepatocyte nuclear factor 4α and cancer-related cell signalling pathways: a promising insight into cancer treatment. Exp Mol Med, 2021, 53: 8–18.

[7] Xiaohui Yuan, Tuong Chi Ta, Min Lin, et al. Identification of an Endogenous Ligand Bound to a Native Orphan Nuclear Receptor. PLOS ONE, 2009, 4(5): e5609.

[8] Remy Le Guevel, Frederik Oger, Aurelien Lecorgne, et al. Identification of small molecule regulators of the nuclear receptor HNF4α based on naphthofuran scaffolds. Bioorg. Med. Chem., 2009, 17: 7021–7030.

[9] Pierre Michellys, Jyun-Hung ChenHoyt MeyerDonald Karanewsky. Substituted tetrahydroquinolines, phenylacetic acids and benzoic acids as hepatocyte nuclear factor 4 (hnf-4) modulator compounds" WO-2005016255-A2 / 2005-02-24, 2005.

[10] Yanhong Shi. Orphan nuclear receptors in drug discovery. Drug Discovery Today, 2007, 12(11-12): 440-445.

[11] Katrin Schöning-Stierand, Konrad Diedrich, Christiane Ehrt et al. ProteinsPlus: a comprehensive collection of web-based molecular modeling tools. Nucleic Acids Research, 2022, 50: W611-W615.

[12] Wei Tian, Chang Chen, Xue Lei et al. CASTp 3.0: computed atlas of surface topography of proteins. Nucleic Acids Research, 2018, 46(W1): W363–W367.

[13] Sargis Dallakyan, Arthur J Olson. Small-Molecule Library Screening by Docking with PyRx. AJ. Methods Mol Biol., 2015, 1263:243-50.

[14] BIOVIA, Dassault Systèmes, 2021 [BIOVIA DISCOVERY STUDIO Visualizer], [v21.1.0.20298], San Diego: Dassault Systèmes.

[15] Jocelyn Sunseri, David Ryan Koes. Pharmit: interactive exploration of chemical space, Nucleic Acids Research, 2016, 44(W1): W442–W448.

[16] Sree Karani K, Sailu Sarvagalla, Mohane Selvaraj C. Docking-Based Virtual Screening Using PyRx Tool: Autophagy Target Vps34 as a Case Study. Molecular Docking for Computer-Aided Drug Design, 2021, 22: (463-477).

[17] Priyanka Banerjee, Andreas O Eckert, Anna K Schrey, and Robert Preissner. ProTox-II: a webserver for the prediction of toxicity of chemicals.Nucleic Acids Res. 2018.

[18] Ida Musfiroh, Alia Resti Azura, Driyanti Rahayu. Prediction of Asiatic Acid Derivatives Affnity Against SARS-CoV-2 Main Protease Using Molecular Docking, Pharmaceutical Sciences, 2020, (7): 57-64.

[19] Antoine Daina, Olivier Michielin, Vincent Zoete. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep., 2017, 7, 42717.

[20] Gbolahan O. Oduselu, Rufus Afolabi, Ibitayo Ademuwagun, et al. Structure-based pharmacophore modeling, virtual screening, and molecular dynamics simulation studies for identification of Plasmodium falciparum 5-aminolevulinate synthase inhibitors, Sec. Infectious Diseases: Pathogenesis and Therapy, 2023, 9: 2022.

[21] Nagaraju Kerru, Lalitha Gummidi, Suresh Maddila et al. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications, Molecules, 2020, 25(8): 1909.

[22] Mohamed M. Khalifa, Helmy M. Sakr, Albaraa Ibrahim et al. Design and synthesis of new benzylidene-quinazolinone hybrids as potential anti-diabetic agents: In vitro α-glucosidase inhibition, and docking studies. Journal of Molecular Structure, 2022, 1250 (2): 131768.

[23] Aram Faraji, Rasoul Motahari, Zaman Hasanvand et al. Quinazolin-4 (3H)-one based agents bearing thiadiazole-urea: Synthesis and evaluation of anti-proliferative and antiangiogenic activity, Bioorganic Chemistry, 2021, 108: 104553.

[24] Zayed, M. F. and M. H. Hassan. Synthesis and biological evaluation studies of novel quinazolinone derivatives as antibacterial and anti-inflammatory agents." Saudi Pharmaceutical Journal, 2014, 22(2): 157-162.

[25] Muhammad Sarfraz, Nargis Sultana and Muhammad I. Tariq. Synthesis, in silico pharmacokinetic profile and anti-cholinesterase activity of quinazolin-4 (3h)-one derivatives, Rev. Roum. Chim, 2018, 63(11): 1035-1041.

[26] Sarah T Al-Rashood, Ihsan A Aboldahab, Mahmoud N Nagi, et al. Synthesis, dihydrofolate reductase inhibition, antitumor testing, and molecular modeling study of some new 4 (3H)-quinazolinone analogs, Bioorganic & Medicinal Chemistry, 2006, 14(24): 8608-8621.

[27] Ghadamali Khodarahmi, Elham Jafari, Gholamhossein Hakimelahi et al. Synthesis of some new quinazolinone derivatives and evaluation of their antimicrobial activities. Iranian Journal of Pharmaceutical Research, 2012, 11(3): 789.

[28] Mohamed K Ibrahim, Ibrahim H Eissa, Mohamed S Alesawy et al. Design, synthesis, molecular modeling and anti-hyperglycemic evaluation of quinazolin-4 (3H)-one derivatives as potential PPARγ and SUR agonists. Bioorganic & Medicinal Chemistry, 2017, 25(17): 4723-4744.

[29] X Chen, S Hussain, S Parveen, et al. Sulfonyl Group-Containing Compounds in the Design of Potential Drugs for the Treatment of Diabetes and Its Complications. Current Medicinal Chemistry, 2012, 19(21): 3578 – 3604.

[30] Aiten M Soliman, Heba M Karam, Mai H Mekkawy and Mostafa M Ghorab. Antioxidant activity of novel quinazolinones bearing sulfonamide: Potential radiomodulatory effects on liver tissues via NF-κB/ PON1 pathway. European Journal of Medicinal Chemistry, 2020, 197: 112333.

[31] Mohammed K Ibrahim, Abd-Elghany, A, El-Helby et al. Modeling, Synthesis and Antihyperglycemic Activity of Novel Quinazolinones Containing Sulfonylurea Moiety. J. Biol. Pharm. Sci. 2009 7(1) 40-51.

[32] Renato Ferreira de Freitas and Matthieu Schapira. A systematic analysis of atomic protein–ligand interactions in the PDB. Med. Chemm.Commun., 2017, 8(10): 1970-1981.

How to cite this article:

Authors Name. Padma Bhavani B. IDENTIFICATION AND DESIGN OF SMALL MOLECULE HNF4α MODULATORS BY PHARMACOPHORE BASED VIRTUAL SCREENING APPROACH. J Pharm Res 2023; 12(06): 56-63
DOI: https://doi.org/10.5281/zenodo.10408277

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nils