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STRUCTURE-BASED DESIGN OF TAFAMIDIS ANALOGUES FOR TRANSTHYRETIN STABILIZATION: IN-SILICO STUDY

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ABSTRACT

The progressive condition known as transthyretin amyloidosis (ATTR) is brought on by the misfolding and aggregation of transthyretin (TTR), which causes organ dysfunction, particularly in the heart and peripheral nerves. Tafamidis is an oral benzoxazole derivative that inhibits the development of amyloid by stabilizing the TTR tetramer and preventing its dissociation into monomers. The pharmacokinetic, toxicological, and molecular interaction profiles of tafamidis and its derivatives were assessed in this work using an in-silico method. Protein targets from the Protein Data Bank (PDB IDs: 4HIQ and 4HIS) were used for molecular docking studies using PyRx, and ADMET characteristics were predicted using pkCSM. Tafamidis has a substantial binding affinity (-6.4 kcal/mol), according to the data, although its ADMET characteristics are limited. The 2-(3,5-dichlorophenyl)-6-(3,5-difluoro-4-hydroxyphenyl) benzo[d]oxazol-5-ol (Fig.no. 9) derivative was noteworthy for its balanced pharmacokinetic behaviour, good absorption, blood-brain barrier permeability, and similar binding affinity (~−8.3 kcal/mol). These results imply that structural alteration can preserve biological activity while improving drug-like

characteristics. Overall, our study emphasizes how crucial it is to combine ADMET prediction with molecular docking in order to optimize tafamidis derivatives in ATTR therapy.

KEYWORDS: Tafamidis, Transthyretin Amyloidosis, ADMET prediction, Structure-based drug designs, Molecular docking, In-silico study.

INTRODUCTION

The systemic disorder known as transthyretin amyloidosis (ATTR) is brought on by the misfolding of transthyretin (TTR), which makes TTR unstable and deposited. The heart and nerves are the primary organs impacted by ATTR, which can affect several systems and important organs and frequently results in increasing organ dysfunction.[3,5] Tafamidis is an oral small molecule medication that preferentially binds to TTR and kinetically prevents TTR tetramers from dissociating into monomers, which prevents TTR amyloid deposits from forming. One treatment approach for these diseases is to find small compounds that bind to and maintain the TTR tetramer, limiting its dissociation and subsequent aggregation.[1,5]

Protein misfolding, aggregation, and the accumulation of insoluble fibrils in bodily tissues and organs are the hallmarks of amyloid disorders, a broad category of illnesses. Among the numerous proteins connected to these conditions is transthyretin (TTR). The rate-limiting stage of amyloid production is tetramer dissociation into monomers.[4,6] Using in silico methods like molecular docking and ADMET prediction, recent developments in computer-aided drug design (CADD) enable quick screening and optimization of therapeutic candidates. These methods shorten the time and expense involved in finding new drugs.[7-9]

Tafamidis

Tafamidis was authorized by the US Food and Drug Administration (FDA) in 2019 to treat adult cardiomyopathy caused by either hereditary or wild-type ATTR-CM.[1] A benzoxazole derivative called tafamidis binds to transthyretin specifically, stabilizing its tetrameric structure (Fig.1.) and inhibiting the production of amyloid.[5,6] Despite the effectiveness of tafamidis, derivatives with enhanced potency, binding affinity, and pharmacokinetic characteristics still need to be developed.[6] Using the subject terms "tafamidis," "tafamidis meglumine," "Vyndaqel," and "Vyndamax," safety data pertaining to Tafamidis was gathered for a total of 19 quarters from the second quarter of 2019 to the fourth quarter of 2023 via the FAERS database.[1,10] Duplicate data and irrelevant reports were eliminated.

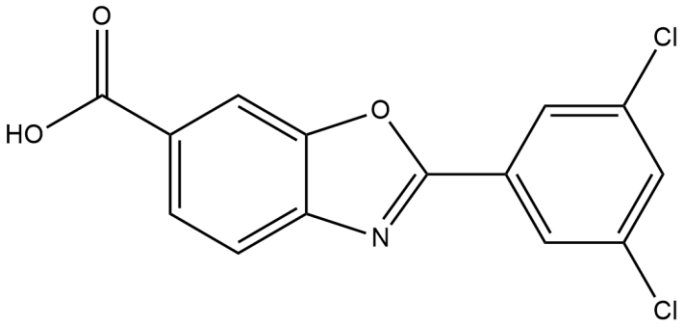


Fig.1: Structure of Tafamidis.

Mechanisms of Action

A major advancement in the treatment of ATTR is represented by tafamidis, a novel kinetic stabilizer of TTR that enhances prognosis.[1,2] Tafamidis is an oral small molecule medication that preferentially binds to TTR and kinetically prevents TTR tetramers from dissociating into monomers, which prevents TTR amyloid deposits from forming (Fig.2). Tafamidis offers patients a more effective treatment alternative, improves the disease's prognosis, and improves their quality of life.[22]

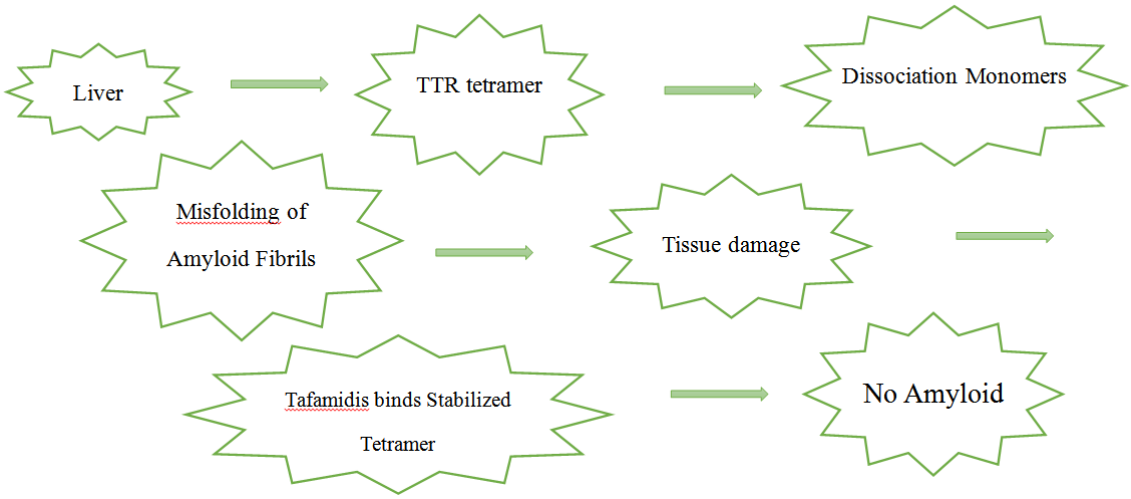


Fig. 2: Mechanisms of Action.

Pharmacokinetics

- **Absorption:** Four hours after dose, the concentration reaches its peak. Regarding high fat/calorie meal intake, there are no discernible clinically significant variations in the pharmacokinetics of tafamidis.
- **Distribution:** Tafamidis meglumine has an apparent volume of distribution (Vd) of 16 liters, while tafamidis has a Vd of 18.5 liters. TTR is the primary binding site for tafamidis. Tafamidis has a high plasma protein binding rate (>99%in-vitro).

- **Metabolism:** Clinical research has shown glucuronidation. Nevertheless, nothing is known about the metabolism of tafamidis.
- **Excretion:** The clearance of tafamidis meglumine is roughly 0.228 L/h, while the clearance of tafamidis is 0.263 L/h. The mean half-life of tafamidis is 49 hours. As a result, drug buildup following successive tafamidis doses is roughly 2.5 times higher than that following a single dose. Urine contains around 22% of the dosage, mostly as the glucuronide metabolite. Feces contain about 59% of the dose (mostly as the unmodified medication).
- **Toxicity:** Tafamidis has been used in clinical trials for up to 111 months at a dose of 80 mg without any notable side effects. A single 480 mg dose of tafamidis did not cause any side effects in healthy volunteers, with the exception of one patient experiencing moderate hordeolum. During clinical trials, two patients inadvertently consumed 160 mg of tafamidis without experiencing any negative side effects. Furthermore, there were no obvious side effects when giving dogs a very high dose of tafamidis (476 times the clinical dose of 80 mg tafamidis meglumine). Therefore, there is very little chance of overdosing in people. In the event of an overdose, however, doctors should administer routine supportive measures.[14]

Adverse Effects

- The tafamidis 20 mg, tafamidis 80 mg, and placebo groups in the 30-month ATTR-ACT study had comparable rates of side events. However, the following adverse effects are shown by data from clinical practice settings and long-term follow-up in ATTR-PN: A headache, Infection of the urinary tract, peripheral edema; upper abdominal discomfort, flatulence, diarrhea, pneumonia, influenza, acute heart failure, extremities pain, myalgia, punctate keratitis, vaginal infection.
- Laboratory problems include decreased serum thyroxine levels, elevated blood urea nitrogen and liver function tests, altered neutrophil and lymphocyte counts, and elevated prothrombin time. Treatment termination may occasionally result from renal impairment and fecal incontinence. There is only one documented instance of treatment-related pericardial effusion, making severe adverse events rare. A modest Japanese investigation found one instance of tafamidis-related sudden death. However, more thorough research has not found any tafamidis-related deaths.[14]

MATERIAL METHOD

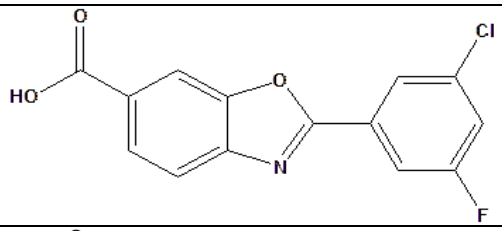
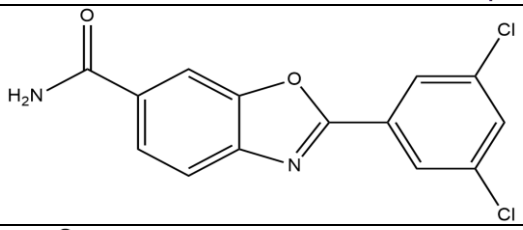
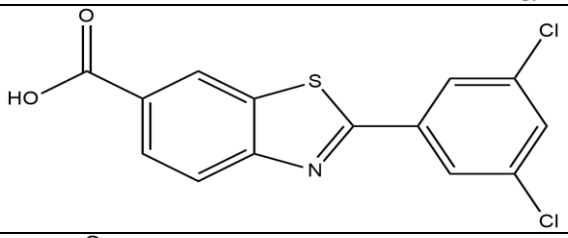
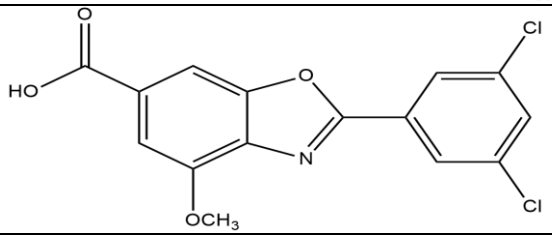
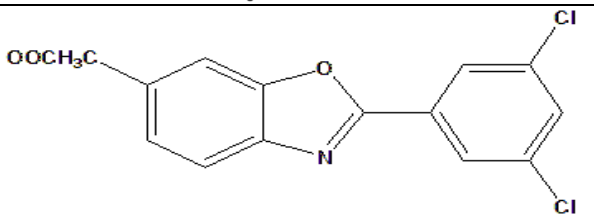
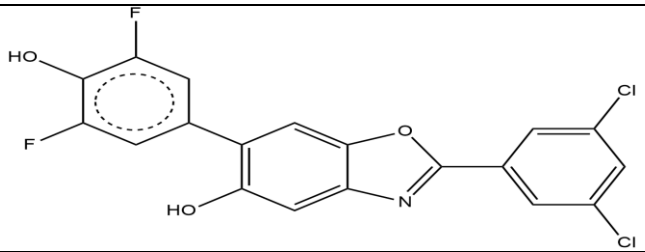
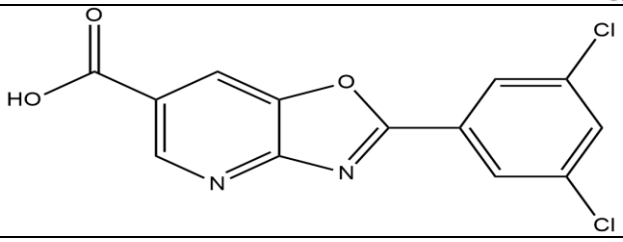
Tafamidis complexes were obtained from the Protein Data Bank ID 4HIQ and 4HIS were the corresponding PDB codes. We examined the behaviour of Tafamidis in the body and its possible toxicity using the pkCSM program. Using this approach, we examined and forecasted ADMET characteristics, which are essential for comprehending how the medication functions in humans. By examining its absorption properties, such as how it is absorbed in the intestine and how soluble it is in water, Tafamidis capacity to enter the bloodstream was calculated. To understand how Tafamidis spreads throughout the body we examined distribution parameters like: Blood-brain barrier permeability, permeability of the central nervous system, Volume of dispersion, fraction unbound in plasma.

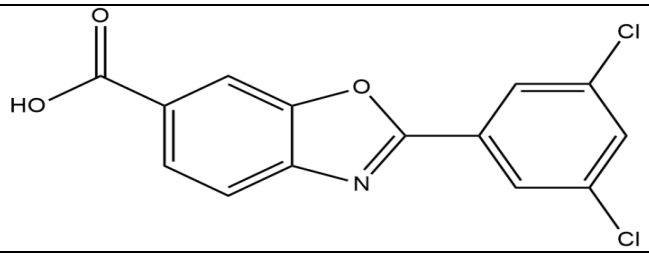
Additionally, we examined Tafamidis interactions with cytochrome P450 enzymes, which are crucial for drug breakdown. We specifically examined the following: substrate or inhibitory activity toward enzymes such as CYP3A4; inhibitory activity toward enzymes such as CYP2D6; substrate or inhibitory activity toward CYP1A2; and substrate or inhibitory activity toward enzymes such as CYP2C9.

Tafamidis elimination profile was evaluated utilizing excretion-related metrics such clearance and renal OCT2 substrate status. Additionally, we assessed Tafamidis toxicological by forecasting their toxicity, hepatotoxicity, and AMES mutagenicity. the maximum dosage that they could withstand. The safety profile of the medication candidate Tafamidis is revealed by these metrics. To investigate how Tafamidis bind to the target protein, we conducted molecular docking studies using PyRx. The Tafamidis structure was imported into the software. The macromolecular target was loaded. To guarantee accurate docking, we erected a grid cage around the spot. The docking simulation was executed. I obtained the interaction poses and binding affinities. The results were exported for additional analysis.

Designed Derivatives

Table no.1.

Sr. no.	Name of the ligand	Structure of the ligand	Binding affinity Kcal/mol
1	2-(3-chloro-5-fluorophenyl) benzo[d]oxazole-6-carboxylic acid		-6.1 Kcal/mol
2	2-(3,5-dichlorophenyl) benzo[d]oxazole-6-carboxamide		-6.9 Kcal/mol
3.	2-(3,5 dichlorophenyl) benzo[d]thiazole-6-carboxylic acid		-6.2 Kcal/mol
4	2-(3,5 dichlorophenyl)-4-methoxybenzo[d]oxazole-6-carboxylic acid		-6.8 Kcal/mol
5.	Methanedione compound with 2-(3,5dichlorophenyl)-6-methyl benzo[d]oxazole (1:1)		-6.2 Kcal/mol
6.	2-(3,5-dichlorophenyl)-6-(3,5-difluoro-4-hydroxyphenyl) benzo[d]oxazol-5-ol		-8.3 Kcal/mol
7.	2-(3,5-dichorophenyl) oxazolo [4,5-b] pyridine-6-carboxylic acid		-6.4 Kcal/mol

	Standard drug: - Tafamidis		-6.4 Kcal/mol

ADMET study

Table no.2.

		Tafamidis	**2-(3-chloro-5-fluorophenyl) benzo[d]oxazole-6-carboxylic acid**	**2-(3,5-dichlorophenyl) benzo[d]oxazole-6-carboxamide**
Property	**Model Name**	**Predicted Value**	**Predicted Value**	**Predicted Value**
Absorption	Water solubility	-5.162	-3.923	-5.073
Absorption	Caco2 permeability	0.776	1.058	1.007
Absorption	Intestinal absorption (human)	91.556	92.225	92.871
Absorption	Skin Permeability	-2.747	-2.727	-2.94
Absorption	P-glycoprotein substrate	Yes	No	Yes
Absorption	P-glycoprotein I inhibitor	No	No	No
Absorption	P-glycoprotein II inhibitor	No	No	No
Distribution	VDss (human)	-1.043	-0.421	-0.596
Distribution	Fraction unbound (human)	0.103	0.199	0.102
Distribution	BBB permeability	-0.006	-0.261	-0.343
Distribution	CNS permeability	-1.648	-1.989	-1.733
Metabolism	CYP2D6 substrate	No	No	No
Metabolism	CYP3A4 substrate	No	Yes	No
Metabolism	CYP1A2 inhibitor	Yes	Yes	Yes
Metabolism	CYP2C19 inhibitor	Yes	No	Yes
Metabolism	CYP2C9 inhibitor	No	No	No
Metabolism	CYP2D6 inhibitor	No	No	No
Metabolism	CYP3A4 inhibitor	No	Yes	No
Excretion	Total Clearance	0.043	0.028	-0.156
Excretion	Renal OCT2 substrate	No	No	No
Toxicity	AMES toxicity	No	No	Yes
Toxicity	Max. tolerated dose (human)	1.083	0.62	1.165
Toxicity	hERG I inhibitor	No	No	No
Toxicity	hERG II inhibitor	No	No	No
Toxicity	Oral Rat Acute Toxicity (LD50)	2.853	2.744	2.803
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	1.452	1.045	1.576
Toxicity	Hepatotoxicity	Yes	Yes	Yes
Toxicity	Skin Sensitisation	No	No	No
Toxicity	T. Pyriformis toxicity	1.384	0.412	1.819
Toxicity	Minnow toxicity	0.381	-0.125	0.513

		2-(3,5 dichlorophenyl) benzo[d]thiazole-6-carboxylic acid	2-(3,5 dichlorophenyl)-4-methoxybenzo[d]oxazole-6-carboxylic acid	Methanedione compound with 2-(3,5dichlorophenyl)-6-methyl benzo[d]oxazole (1:1)	2-(3,5-dichlorophenyl)-6-(3,5-difluoro-4-hydroxyphenyl) benzo[d]oxazol-5-ol	2-(3,5-dichorophenyl) oxazolo [4,5-b] pyridine-6-carboxylic acid
Property	**Model Name**	**Predicted Value**	**Predicted Value**	**Predicted Value**	**Predicted Value**	**Predicted Value**
Absorption	Water solubility	-5.541	-5.247	-5.705	-3.819	-3.145
Absorption	Caco2 permeability	1.416	0.791	1.413	0.961	1.286
Absorption	Intestinal absorption (human)	90.823	91.553	95.079	88.439	92.269
Absorption	Skin Permeability	-2.711	-2.822	-2.847	-2.735	-2.729
Absorption	P-glycoprotein substrate	Yes	Yes	Yes	Yes	No
Absorption	P-glycoprotein I inhibitor	No	No	No	No	No
Absorption	P-glycoprotein II inhibitor	No	No	No	Yes	No
Distribution	VDss (human)	-0.977	-1.168	-0.72	-0.697	-0.234
Distribution	Fraction unbound (human)	0.086	0.102	0.058	0.283	0.212
Distribution	BBB permeability	0.138	-0.632	0.067	0.151	-0.929
Distribution	CNS permeability	-1.538	-1.813	-1.489	-1.502	-2.954
Metabolism	CYP2D6 substrate	No	No	No	No	No
Metabolism	CYP3A4 substrate	Yes	Yes	Yes	Yes	No
Metabolism	CYP1A2 inhibitor	Yes	Yes	Yes	Yes	No
Metabolism	CYP2C19 inhibitor	Yes	Yes	Yes	Yes	No
Metabolism	CYP2C9 inhibitor	No	No	No	Yes	No
Metabolism	CYP2D6 inhibitor	No	No	No	No	No
Metabolism	CYP3A4 inhibitor	No	No	No	Yes	No
Excretion	Total Clearance	0.19	0.242	-0.349	-0.08	0.183
Excretion	Renal OCT2 substrate	No	No	No	No	No
Toxicity	AMES toxicity	No	No	No	Yes	No
Toxicity	Max. tolerated dose (human)	1.096	0.962	1.1	0.702	0.321
Toxicity	hERG I inhibitor	No	No	No	No	No
Toxicity	hERG II inhibitor	No	No	No	Yes	No
Toxicity	Oral Rat Acute Toxicity (LD50)	2.941	2.834	2.723	2.179	2.334
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	1.354	1.444	1.466	0.112	0.701
Toxicity	Hepatotoxicity	No	Yes	No	Yes	Yes

Toxicity	Skin Sensitisation	No	No	No	No	No
Toxicity	T. Pyriformis toxicity	1.453	1.134	1.747	0.286	0.314
Toxicity	Minnow toxicity	0.102	0.334	0.153	-1.847	-1.44

RESULTS AND DISCUSSION

Absorption

According to reports, tafamidis has variable permeability and low solubility. Since the commercially available tafamidis meglumine is produced as a powder that is encapsulated in gelatin, it is thought to be released quickly once it reaches the duodenum, enabling the dissolution and absorption process to begin right away. The stomach is the dose-accepting compartment and upstream driver of intestinal absorption in the ADAM (Advanced Dissolution, Absorption, and Metabolism) model, which was used to describe the absorption process.[13] According to reports, tafamidis is quickly absorbed and reaches its maximal concentration two hours after oral treatment. Tafamidis has a typical half-life of roughly 59 hours and is primarily bound to proteins (>99.5%) in the plasma[11] (Table no.2).

Distribution

Following oral tafamidis treatment to healthy volunteers, the apparent volume of distribution was observed to be 16 L (0.2 L/kg for an 80 kg patient). The Sawada equation was used to calculate the volume of distribution at steady state (Vss) for a complete PBPK distribution model, taking into account distribution in the following tissues: adipose, bone, brain, gut, pancreas, heart, kidney, liver, lung, muscle, skin, and spleen (Table no.2). Assuming that drug distribution in rats is similar to that in humans, partition coefficients between each tissue and plasma (Kp) were derived from rat PK research on tafamidis distribution, with the exception of bone, pancreas, muscle, and skin. As previously mentioned[12], the Rodgers and Rowland model was used to predict Kp for bone, pancreas, muscle, and skin.

Metabolism and Excretion

Tafamidis is mainly broken down via UGT-mediated glucuronidation, which is mostly carried out by UGT1A1, UGT1A3, and UGT1A9. As indicated in drug-prescribing information, metabolism was characterized using a holistic metric of oral clearance, 0.263 L/h. Unfortunately, no intrinsic clearance values or contributions of each of the enzymes can be discovered in the publically available literature.[11,12] Because it lacks the mechanistic scalability provided by intrinsic clearance data, the model is also unsuitable for populations with altered UGT abundance (i.e., certain disorders, including liver cirrhosis) or for

evaluating drug-drug interactions. A significant portion of pharmacologically inactive tafamidis metabolite is anticipated to be eliminated with bile, according to material submitted to the FDA; this route of elimination is not taken into consideration by the proposed model because there is insufficient information to mechanistically define such a mechanism [13] (Table no.2).

Molecular Docking

Docking tests utilizing PyRx software revealed strong interactions between Tafamidis and proteins. The binding affinity of the parent Tafamidis was around -6.4 kcal/mol. With docking scores of -8.3 kcal/mol, some derivatives, such as 2-(3,5-dichlorophenyl)-6-(3,5-difluoro-4-hydroxyphenyl) benzo[d]oxazol-5-ol (Fig.no.9), exhibited greater interactions (Table no.1). These substances interacted with the active site. They did, however, have several problems with ADMET features.[15,16] However, a derivative that substitutes 6-fluoro for 6-chloro stood out. Its binding affinity was -6.1 kcal/mol (Table no.1). Additionally, this molecule demonstrated permeability and absorption. It might effectively cross the blood-brain barrier. It had a balanced metabolic profile.[17] It is therefore a strong contender. The substance acts better in the body when fluorine is substituted, according to the study. It continues to communicate with the target. IDH enzymes are significantly inhibited by tafamidis. Studies verified this. The docking results facilitate the creation of improved versions. Analogues may result from this.[17]

- **Standard Drug: Tafamidis**

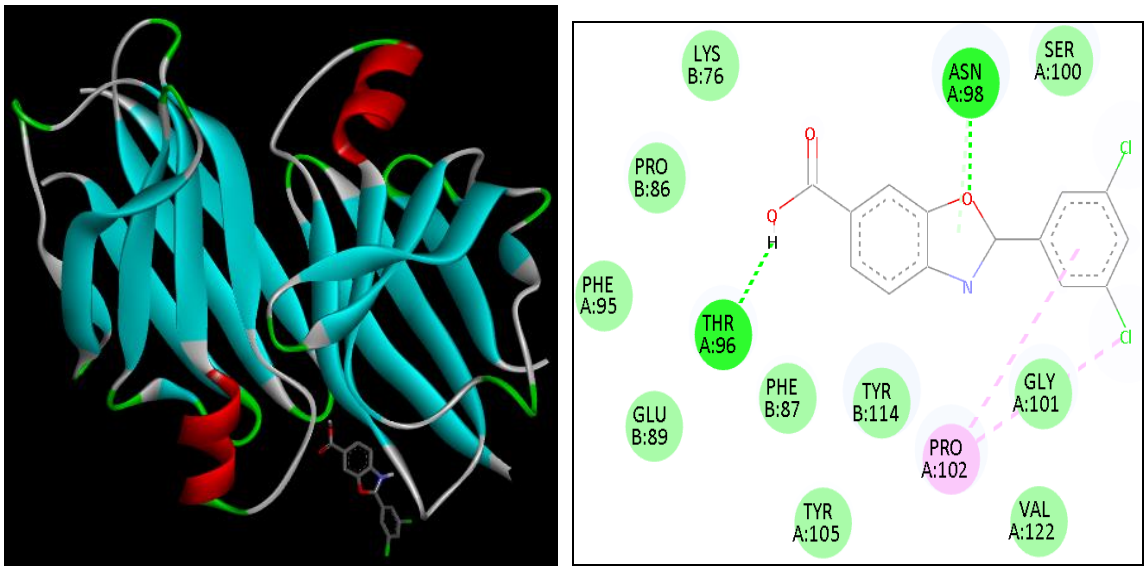


Fig.3 Interaction of Tafamidis with 8AWW.

- **Compound A1: 2-(3-chloro-5-fluorophenyl) benzo[d]oxazole-6-carboxylic acid**

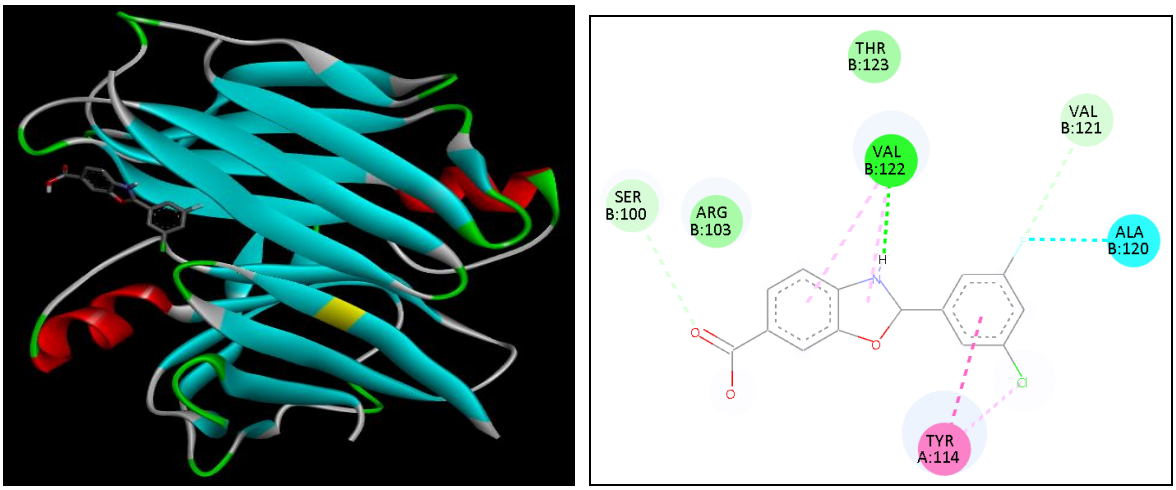


Fig.4 Interaction of compound A1 with 8AWW.

- **Compound A2: 2-(3,5-dichlorophenyl) benzo[d]oxazole-6-carboxamide**

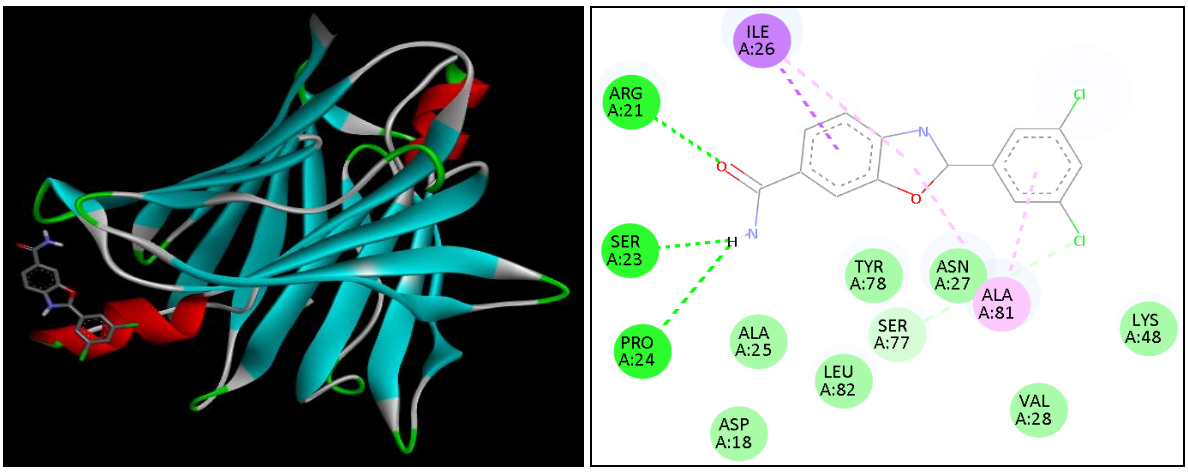


Fig.5 Interaction of compound A2 with 8AWW.

- **Compound A3: 2-(3,5 dichlorophenyl) benzo[d]thiazole-6-carboxylic acid**

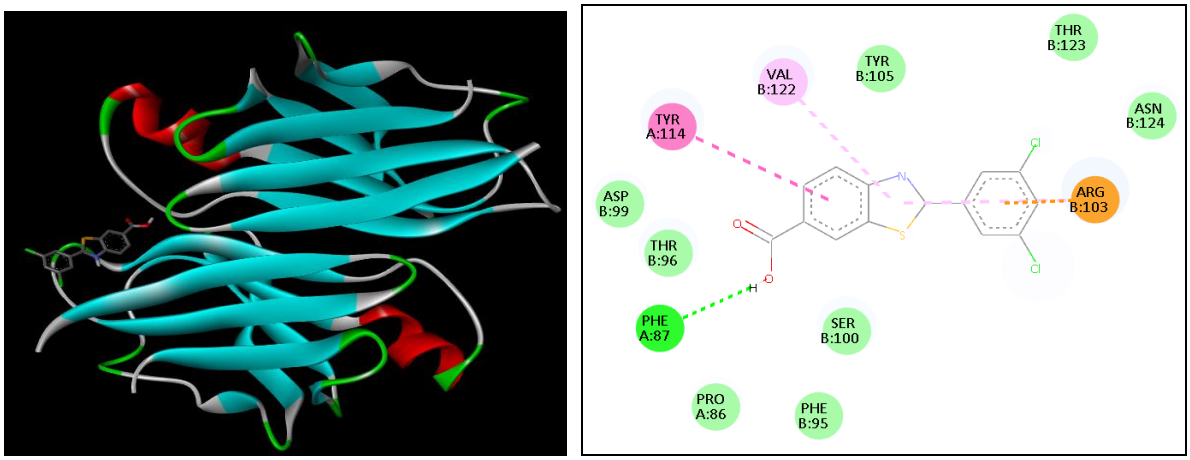


Fig.6 Interaction of compound A3 with 8AWW.

- **Compound A4: 2-(3,5 dichlorophenyl)-4-methoxybenzo[d]oxazole-6-carboxylic acid**

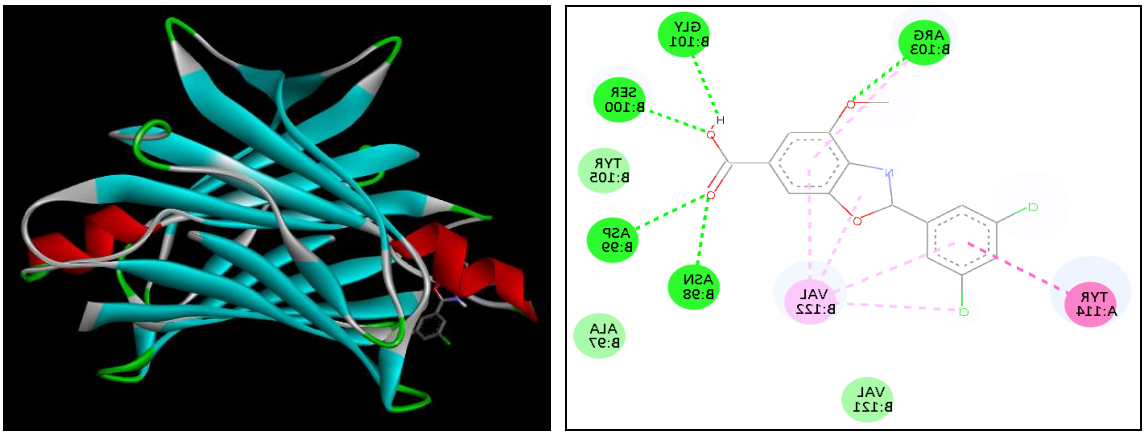


Fig.7 Interaction of compound A4 with 8AWW.

- **Compound A5: Methanedione compound with 2-(3,5dichlorophenyl)-6-methyl benzo[d]oxazole**

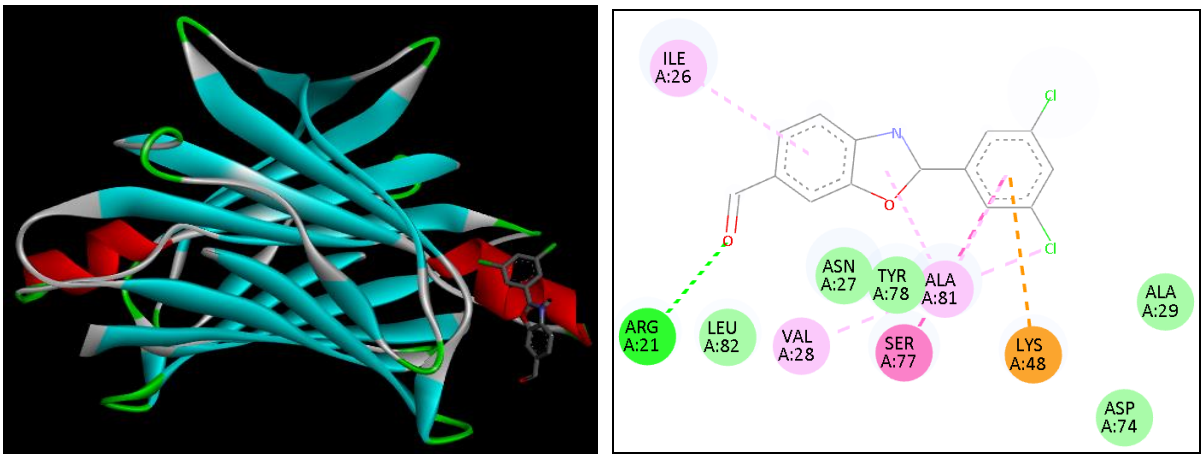


Fig.8: Interaction of compound A5 with 8AWW.

- **Compound A6: 2-(3,5-dichlorophenyl)-6-(3,5-difluoro-4-hydroxyphenyl) benzo[d] oxazol-5-ol**

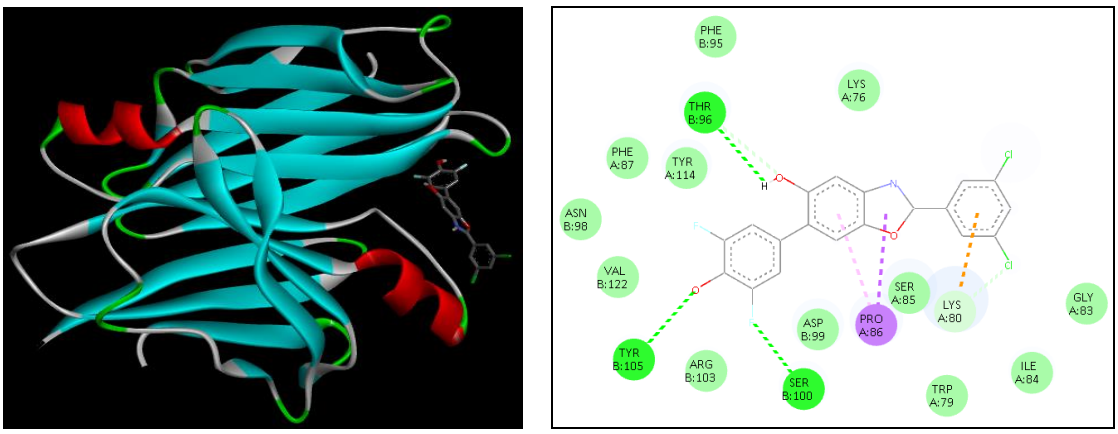


Fig. 9: Interaction of compound A3 with 8AWW.

- **Compound A7: 2-(3,5-dichorophenyl) oxazolo [4,5-b] pyridine-6-carboxylic acid**

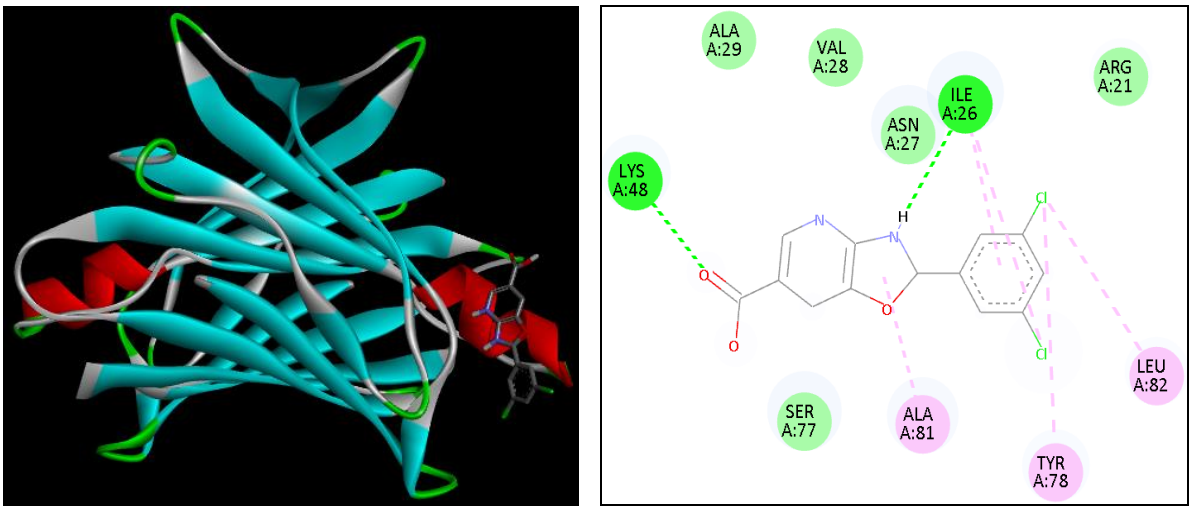


Fig.10: Interaction of compound A7 with 8AWW.

CONCLUSION

Tafamidis is an efficient transthyretin stabilizer with a good safety profile and a high binding affinity, according to this study. Its favourable pharmacokinetic characteristics, such as strong protein binding, a moderate distribution, and a safe toxicity profile, were validated by in silico analysis. Certain structural changes can further enhance therapeutic performance, according to molecular docking studies. The 6-fluoro substituted counterpart stood out among the assessed derivatives because of its balanced ADMET profile, strong absorption, and sustained binding affinity. Despite the fact that some derivatives exhibited greater binding, their therapeutic potential is diminished by their pharmacokinetic constraints. Therefore, for medication development to be effective, both binding affinity and ADMET characteristics must be optimized.

In conclusion, an effective and economical method for creating better tafamidis derivatives is the combination of computational methods like molecular docking and ADMET prediction. These discoveries could aid in the creation of safer and more effective medications to treat transthyretin amyloidosis.

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