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Exploration of 24-Hydroxylase, a Vitamin D Metabolizing Enzyme through *In Silico* Screening of Some New Phenylalanine-Benzofuran-Acetamide/ Propanamide/Butanamide Hybrids: An Approach to Overcome Vitamin D Deficiency

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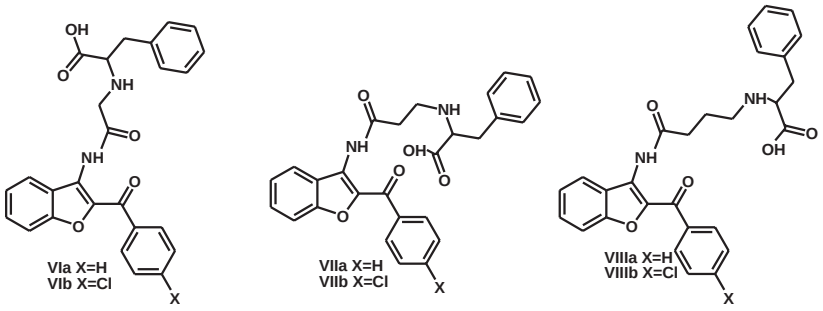
ABSTRACT Phenylalanine-benzofuran-acetamide/propanamide/butanamide hybrids **(VIa-b/VIIa-b/ VIIIa-b)** were synthesized and *in silico* screening for CYP24A1 inhibitory activity was studied. The most promising compound among all was found to be **VIa** (binding score −7.6), binds in manner very similar to the calcitriol. The carboxylate and -NH group forms two hydrogen bonds with THR394 and THR395, respectively. The ring benzofuran fits into the hydrophobic pocket and forms T-shaped π-π stacking, whereas the terminal benzyl ring forms π-sigma interaction with the ILE131 residue. These results clearly showed that these benzofuran hybrids could be a promising lead in the development of novel CYP24A1 inhibitors.



KEYWORDS CYP24A1, Vitamin D metabolism, Benzofuran, Acetamide, Propanamide, Butanamide.

INTRODUCTION

Saudi Arabian population is genuinely facing Vitamin D deficiency and related health effects. The plight is graver with the women patients.[1] Although Vitamin D has been the topic of research and discussion in the past decades, the research focused on the same has exaggerated from 2010 only.[2] Conventionally, Vitamin D deficiency has been held

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responsible for rickets leading to soft bones and skeletal deformities. However, with the advancement of research, in this area, various diseases have been associated with the deficiency of this sunshine vitamin such as cardiac diseases, obesity and metabolic syndrome, osteoporosis, fractures, hyperparathyroidism, IBS, fibromyalgia and chronic low back pain, rheumatoid arthritis, and diabetes mellitus.[3]

Vitamin D can be augmented by sun exposure and vitamins supplementation. As shown in **Figure 1**, metabolic cascade of Vitamin D involves catabolism of active form of Vitamin D (1,25-dihydroxyvitamin D3) to inactive form 1,24,25-trihydroxyvitamin D3 through 24-hydroxylase enzyme.

CYP24A1 is the cytochrome P450 component of the 24-hydroxylase enzyme which is solely responsible for its catalytic activity resulting into degradation of Vitamin D. In fact, it is also responsible for multiple-step 24-oxidation cascade from 1,25-dihydroxyvitamin D3 to calcitroic acid.[4-6] The first step of metabolic conversion involves 25-hydroxylation which takes place in the liver, whereas the second step occurs in kidney and extrarenal sites. Vitamin D binding protein serves as a carrier for transportation of active and inactive metabolites from one tissue to another. Although CYP24A1 is mainly responsible for the catabolism of active form, it works in coordination with CYP27B1 and maintains a fine-tuning mechanism to regulate exposure of active vitamin to the target tissue.[7] The inhibition of CYP24A1 can contribute to the enhancement of half-life of active Vitamin D hormone which consequently can counterbalance the deficiency of the same.

Apart from playing a central role in Vitamin D metabolism, it also serves to the clearance of various Vitamin D analogs such as doxercalciferol and maxacalcitol.[8] As Vitamin D analogs are given to the nephrological, dermatological, and cancer patients, CYP24A1 can be considered as an important drug target as its inhibitor would change the target cell concentration of Vitamin D produced in the body as well as concentration Vitamin D analogs given as xenobiotics.

Recently, some synthetic compounds such as azoles and imidazoles were found to inhibit CYP24A1 considerably. The imidazole derivatives had shown 40 times more selectivity for CYP24A1 as compared to CYP27B1.[9] Posner *et al*., in 2010, prepared a Vitamin D analog having 24(S)-NH

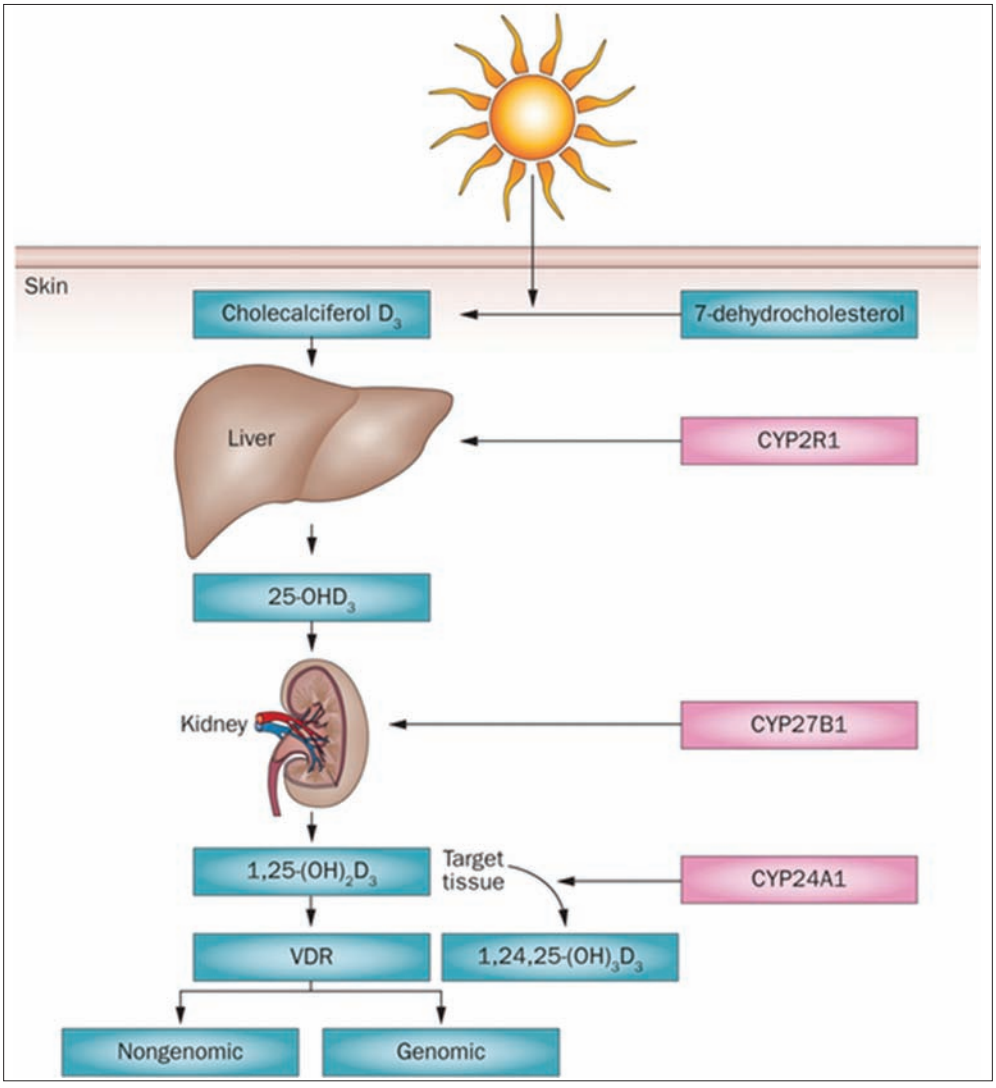


Figure 1: Metabolic cascade of Vitamin D

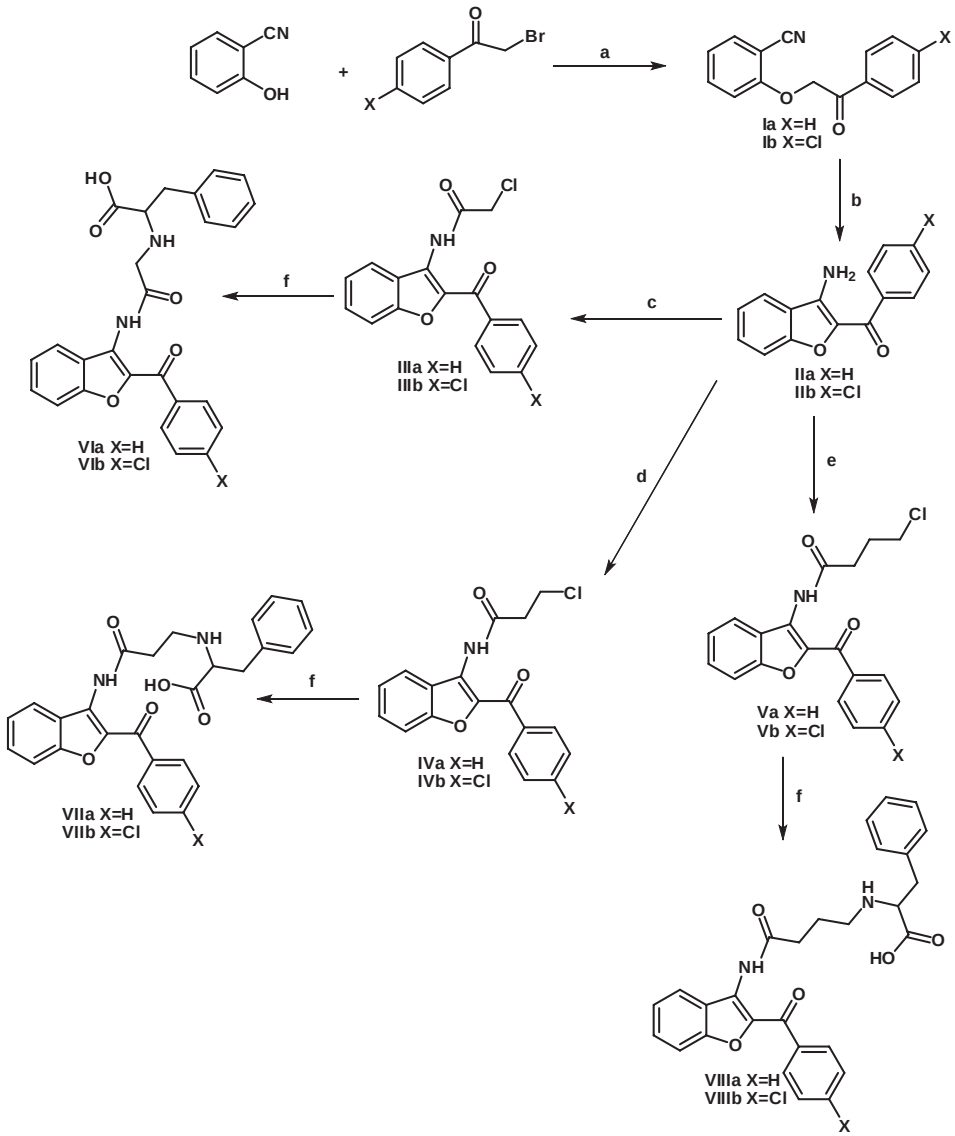
phenyl sulfoximine as side chain and reported its selectivity for CYP24A1 without any affinity to Vitamin D receptor (VDR). Another compound reported by them CTA018 had affinity for VDR as well as CYP24A1. CTA018 is under clinical trial phase II for secondary hyperparathyroidism (cytochroma).[10] Therefore, some new phenylalanine-benzofuran-acetamide/propanamide/butanamide hybrids have been synthesized and subjected to *in silico* screening in search of suitable CYP24A1 inhibitors.

In this study, the target compounds 2-(2-(2-benzoyl/4-chlorobenzoyl)benzofuran-3-ylamino)-2-oxoethylamino)-3-phenylpropanoic acid **(VIa/b)**/2-(3-(2-(benzoyl/4-chlorobenzoyl)benzofuran-3-ylamino)-3-oxopropylamino)-3-phenylpropanoic acid (**VIIa/b**)/2-(4-(2-(benzoyl/4-chlorobenzoyl)benzofuran-3-ylamino)-4-oxobutylamino)-3-phenylpropanoic acid (**VIIIa/b**) were synthesized and *in silico* screening for CYP24A1 inhibitory activity was studied.

RESULTS AND DISCUSSION

Chemistry

Target compounds phenylalanine-benzofuran-acetamide/propanamide/butanamide hybrids (**VIa-b/VIIa-b/VIIIa-b**) were synthesized according to **Scheme 1** and their physicochemical properties and docking scores are summarized in **Tables 1** and **2**, respectively. In the first step, 2-hydroxybenzonitrile and phenacyl bromide/*p*-chlorophenacyl bromide were stirred in dimethylformamide (DMF) containing anhydrous K_2CO_3 at room temperature for 3 h to obtain the intermediate 2-(2-oxo-2-phenylethoxy) benzonitrile/2-(2-(4-chlorophenyl)-2-oxoethoxy)



Scheme 1: Synthesis of phenylalanine-benzofuran-acetamide/propanamide/butanamide hybrids (VIa-b/VIIa-b/VIIIa-b)

Reagents and conditions: a) DMF, K_2CO_3, stir, 3h; b) MeOH, MeONa, stir, 1 h; c) $ClCH_2COCl$, reflux, 30 min; d) $ClCH_2CH_2COCl$, reflux, 30 min; e) $ClCH_2CH_2CH_2COCl$, reflux, 30 min; and f) Phenylalanine, 1-butanol, K_2CO_3, KI, reflux, 10 h.

Table 1: Physicochemical properties of phenylalanine-benzofuran-acetamide/propanamide/butanamide hybrids (VIa-b, VIIa-b, and VIIIa-b)

Compound	Mol. Formula (Mol. wt.)	[a]M.P. (°C)	Yield (%)	[b]Rf value
VIa	$C_{26}H_{22}N_2O_5$ (442.46)	248–250	72	0.62
VIb	$C_{26}H_{21}ClN_2O_5$ (476.91)	286–288	74	0.64
VIIa	$C_{27}H_{24}N_2O_5$ (456.49)	308–310	71	0.62
VIIb	$C_{27}H_{23}ClN_2O_5$ (490.93)	326–328	72	0.64
VIIIa	$C_{28}H_{26}N_2O_5$ (470.52)	347–349	75	0.71
VIIIb	$C_{28}H_{25}ClN_2O_5$ (504.96)	372–374	74	0.74

[a]Melting point of the compounds at their decomposition. [b]Solvent system – Cyclohexane: Ethyl acetate (8:2)

Table 2: Docking scores of phenylalanine-benzofuran-acetamide/propanamide/butanamide hybrids (VIa-b, VIIa-b, and VIIIa-b)

S. No.	Compounds	Docking score	H-Bonding
1.	**VIa**	**−7.6**	**THR394, THR395**
2.	**VIb**	−6.6	THR395
3.	**VIIa**	−6.1	GLY499
4.	**VIIb**	−6.4	THR395
5.	**VIIIa**	**−7.2**	**GLU130**
6.	**VIIIb**	−6.6	GLU130
7.	Calcitriol	−6.3	THR394

benzonitrile (**Ia-b**). In the second step, compounds **Ia-b** were stirred with sodium methoxide in methanol for 1 h to give (3-aminobenzofuran-2-yl)(phenyl) methanone/3-aminobenzofuran-2-yl(4-chlorophenyl) methanones (**IIa-b**). The amino compounds **IIa-b** were treated with 2-chloroacetyl chloride/3-chloropropionyl chloride/4-chlorobutyryl chloride to afford *N*-(2-(benzoyl)/(4-chlorobenzoyl)benzofuran-3-yl)- 2-chloroacetamide **(IIIa-b)**, *N*-(2-(benzoyl)/(4-chlorobenzoyl)benzofuran-3-yl)-3-chloropropanamide **(IVa-b)**, and *N*-(2-(benzoyl)/(4-chlorobenzoyl)benzofuran-3-yl)- 4-chlorobutanamide **(Va-b)** respectively. In the last step, the compounds **IIIa-b/IVa-b/Va-b** were on reaction with phenylalanine in 1-butanol containing anhydrous K_2CO_3 in the presence of KI gave the target compounds **VIa-b/VIIa-b/VIIIa-b**, respectively. The compounds were confirmed by nuclear magnetic resonance (NMR), mass spectroscopy, infrared (IR), and elemental analyses.

Docking studies

In our effort to identify promising CYP24A1 inhibitors, we studied the molecular interactions of the reference ligand calcitriol with CYP24A1. AutoDock (ADT) 4.2 with Lamarckian genetic algorithm-implemented program suite was used to identify the appropriate binding modes and conformation of the ligand molecule. Once the orientation and conformation of ligand within the binding site were optimized by docking simulation, the best scoring pose was further relaxed and then analyzed to identify the most relevant interactions. The crystal structure of CYP24A1 (PDB ID: 3K9V, resolution: 2.5 Å) was retrieved from the RCSB protein data bank (PDB) for molecular modeling studies. The pocket comprising Ile131, Trp134, Met148, Met245, Met246, Phe249, Ala326, Glu329, Thr330, Val391, Thr394, Thr 395 Gly499, and Ile500 residues in the CYP24A1 was identified as the active site.[11] Calcitriol was found to occupy the catalytic center of CYP24A1 where the cocrystallized native crystal heme occupies. The hydroxyl group of calcitriol forms a hydrogen bond with THR394. The octahydroindene ring positioned near the hydrophobic pocket and formed π interactions with PHE104 and PHE393 whereas the alkyl side chain aligned near to the LEU79 and formed a π-alkyl interaction. These binding interactions are consistent with previous reports and gave insight into structure optimization in a further study. Based on these observations, benzofuranone was designed as promising CYP24A1 inhibitors. Molecular docking studies of the designed molecules also revealed that they fit into the active site and form hydrogen bonds with the active sites. The binding free energy of all the compounds (**VIa-b, VIIa-b,** and **VIIIa-b)** was in the range of −6.1–−7.6 kcal/mol as compared to calcitriol with -6.3 kcal/mol, indicating enough affinity between ligands and protein [**Figures 2-8, Table 2**]. The most promising compound **VIa** (binding score − 7.6) binds in manner very similar to the calcitriol [**Figures 2 and 8**]. The carboxylate and -NH group forms two hydrogen bonds with THR394 and THR395, respectively. The ring benzofuran fits into the hydrophobic pocket and forms T-shaped π-π stacking, whereas the terminal benzyl ring forms π-sigma interaction with the ILE131 residue. These results clearly showed that these benzofuran derivatives could be promising lead in the development of novel CYP24A1 inhibitors. **Figure 9** shows the 3D overlay of all the compounds along with calcitriol at the active site of CYP24A1 (PDB ID 3KNV). **Figure 10** displays the 2D binding interactions of heme at the active site of CYP24A1 (PDB ID 3K9V).

EXPERIMENTAL SECTION

Chemistry

All the solvents and reagents used were of laboratory grade and obtained from various suppliers. The progress of the reactions was observed by thin-layer chromatography (TLC) on silica gel G pre-coated plates using cyclohexane:ethyl acetate (8:2) as solvent system. Iodine chamber was used for the visualization of the TLC spots. The melting points (°C) of the synthesized compounds

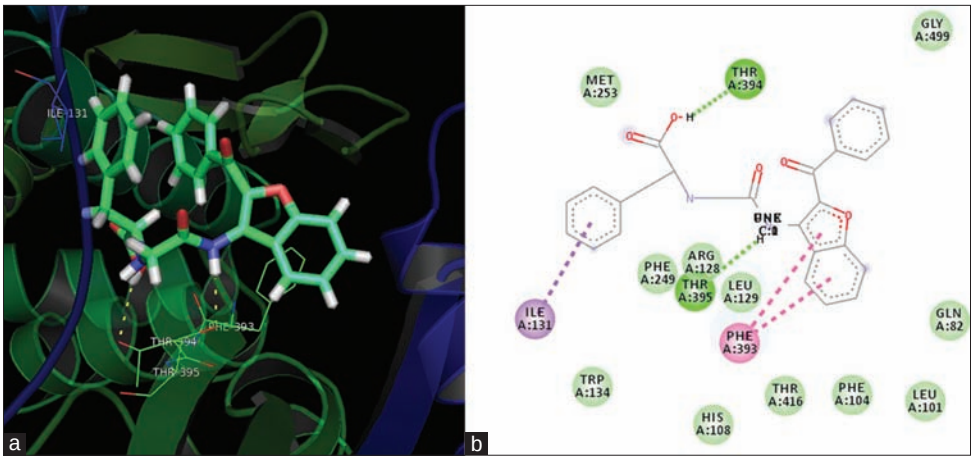


Figure 2: (a) Docking pose of compound VIa at the active site of CYP24A1 (PDB ID 3K9V) showing two hydrogen bonding. (b) 2D binding interactions of compound VIa

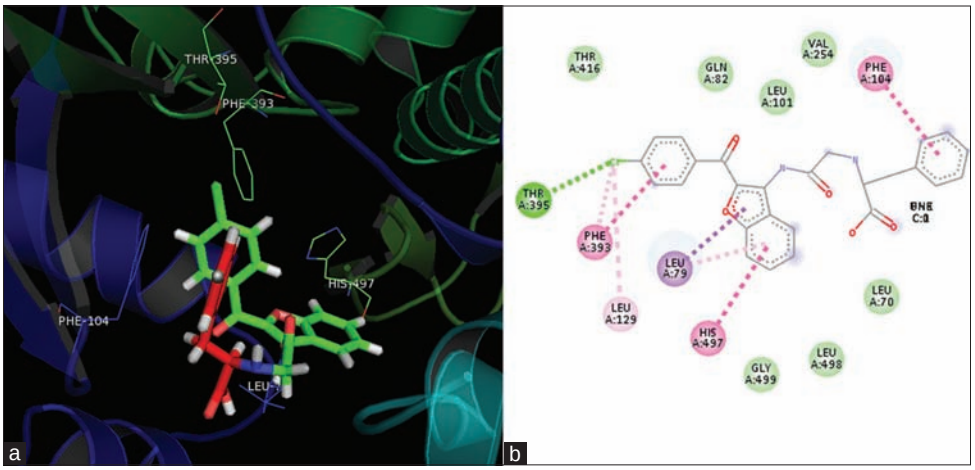


Figure 3: (a) Docking pose of compound VIb at the active site of CYP24A1 (PDB ID 3K9V) showing one hydrogen bonding. (b) 2D binding interactions of compound VIb

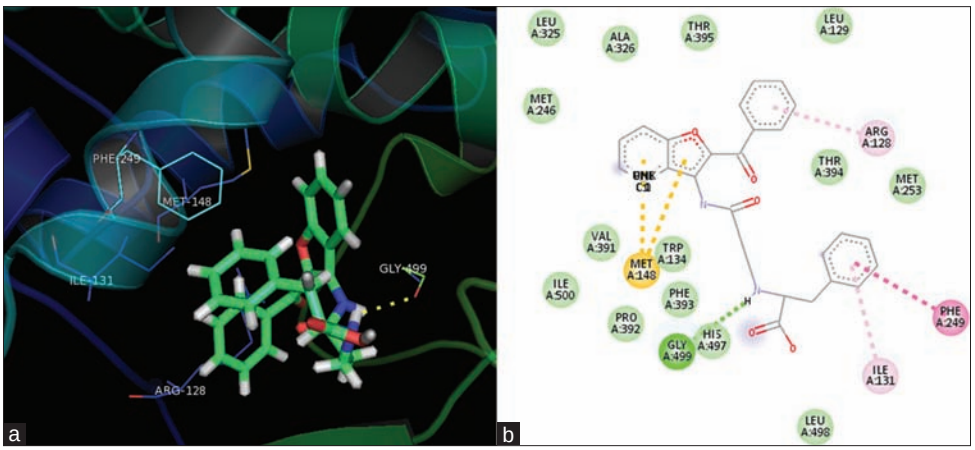


Figure 4: (a) Docking pose of compound VIIa at the active site of CYP24A1 (PDB ID 3K9V) showing one hydrogen bonding. (b) 2D binding interactions of compound VIIa

were measured on a Gallenkamp melting point apparatus (Sanyo Gallenkamp, South Borough, United Kingdom) in open glass capillaries and are uncorrected.^{1}H-NMR spectra were recorded on a BRUCKER-PLUS NMR (Billerica, MA, USA) operating at 500 MHz in deuterated dimethyl sulfoxide-d_6. Chemical shifts were reported in parts per million (ppm, δ) and the signals were described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were recorded on a Shimadzu GCMS-QP 5000 instrument (Shimadzu, Tokyo, Japan). Elemental analyses (C, H, and N) were conducted with a PerkinElmer-series-II analyzer and all analyses were found

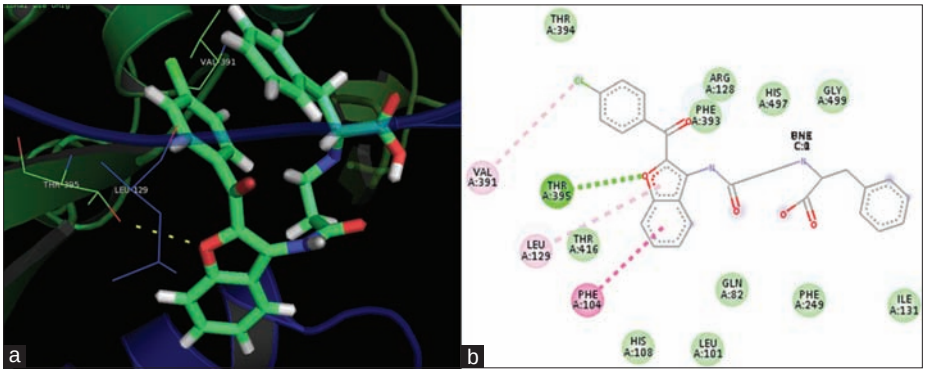


Figure 5: (a) Docking pose of compound VIIb at the active site of CYP24A1 (PDB ID 3K9V) showing one hydrogen bonding. (b) 2D binding interactions of compound VIIb

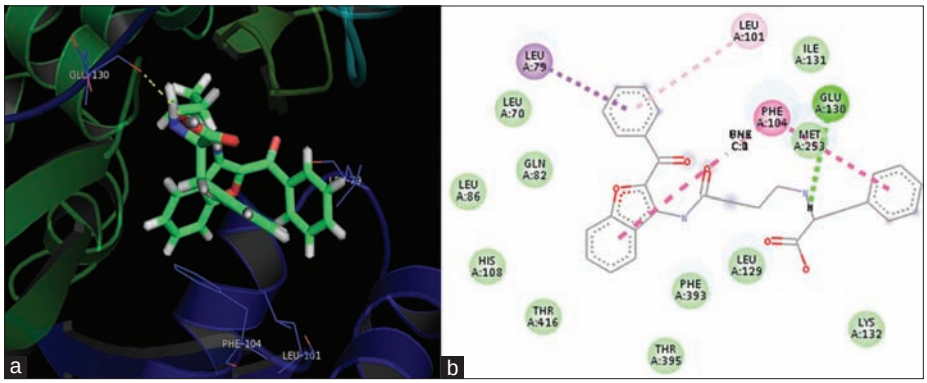


Figure 6: (a) Docking pose of compound VIIIa at the active site of CYP24A1 (PDB ID 3K9V) showing one hydrogen bonding. (b) 2D binding interactions of compound VIIIa

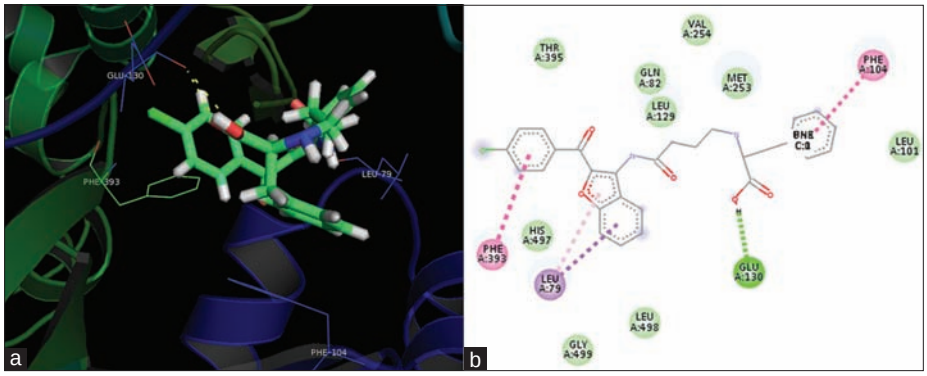


Figure 7: (a) Docking pose of compound VIIIb at the active site of CYP24A1 (PDB ID 3K9V) showing one hydrogen bonding. (b) 2D binding interactions of compound VIIIb

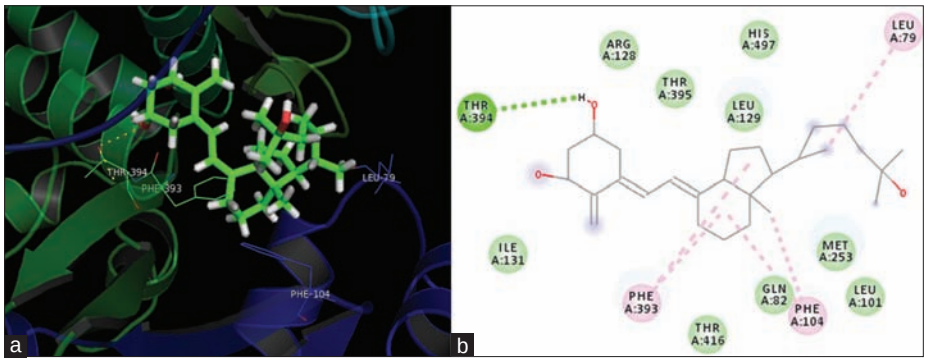


Figure 8: (a) Docking pose of calcitriol at the active site of CYP24A1 (PDB ID 3KNV) showing one hydrogen bonding. (b) 2D binding interactions of calcitriol

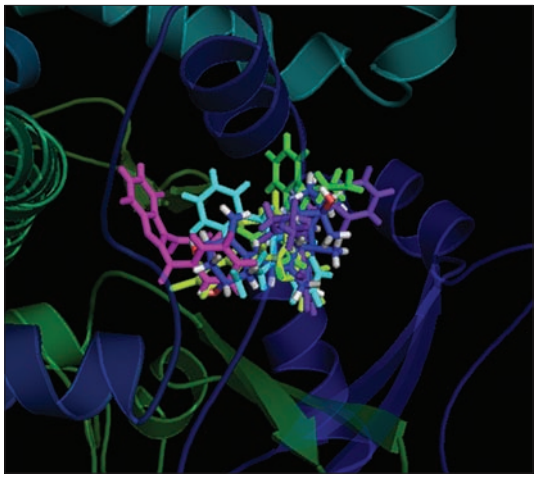


Figure 9: 3D overlay of all the compounds along with calcitriol at the active site of CYP24A1 (PDB ID 3KNV)

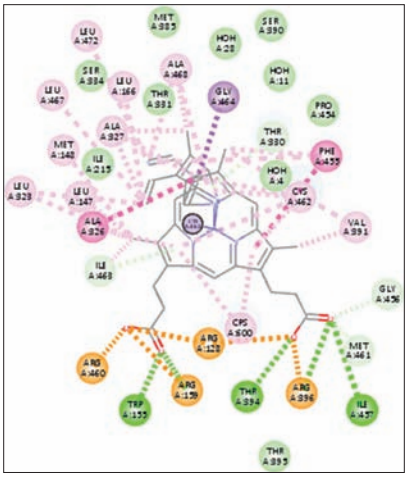


Figure 10: 2D binding interactions of heme at the active site of CYP24A1 (PDB ID 3K9V)

to be consistent with theoretical values unless indicated (within 0.4%). IR spectra were recorded in a PerkinElmer FT-IR spectrophotometer 1000 (PerkinElmer, Waltham, MA, USA) by making KBr pellets.

N-(2-(benzoyl)/(4-chlorobenzoyl)benzofuran-3-yl)- 2-chloroacetamide **(IIIa-b)**, *N*-(2-(benzoyl)/(4-chlorobenzoyl)benzofuran-3-yl)-3-chloropropanamide **(IVa-b)**, and *N*-(2-(benzoyl)/(4-chlorobenzoyl)benzofuran-3-yl)- 4-chlorobutanamide **(Va-b)** were prepared following the reported methods.[12-16]

General synthetic method for2-(2-(2-(benzoyl/4-chlorobenzoyl)benzofuran-3-ylamino)-2-oxoethylamino)-3-phenylpropanoic acid (VIa/b)/2-(3-(2-(benzoyl/4-chlorobenzoyl)benzofuran-3-ylamino)-3-oxopropylamino)-3-phenylpropanoic acid(VIIa/b)/2-(4-(2-(benzoyl/4-chlorobenzoyl)benzofuran-3-ylamino)-4-oxobutylamino)-3-phenylpropanoic acid (VIIIa/b)

A mixture of **IIIa/IIIb/IVa/IVb/Va/Vb** (1 mmol) and phenylalanine (1 mmol) was refluxed in 1-butanol containing anhydrous K_2CO_3 in the presence of catalyst KI for 10 h. The reaction mixture was then poured into ice water to give the solid product which was filtered and recrystallized from ethanol to obtain pure product (**VIa-VIIIb**).[17]

2-(2-(2-Benzoylbenzofuran-3-ylamino)-2-oxoethylamino)-3-phenylpropanoic acid (VIa)

IR (cm^{-1}) KBr: 3460 (amide NH_{str}), 1670 (amide $C=O_{str}$), 1710 (benzoyl $C=O_{str}$), 1715 (carboxylic acid $C=O_{str}$), 2981 (carboxylic acid OH_{str}), 3332 (amineNH_{str}); ^{1}H NMR ($CDCl_3$): (δ, ppm) 12.52 (s, 1H, COOH), 10.02 (s, 1H, CONH), 2.02 (s, 1H, NH), 7.28–7.90 (m/br, 14H, Ar-H and protons of benzofuran), 3.43 (d, 2H, $COCH_2$), 3.87 (t, 1H, CHNH of phenylalanine), 3.03, 3.28 (m, 2H, $C_6H_5CH_2$ of phenylalanine); mass (m/z) 442.16 (M^+), 443.17 (M^++1), 444.20 (M^++2); analysis (calc. %/found %): C 70.58 (70.36) H 5.01 (5.09) N 6.33 (6.49) O 18.08 (18.06).

2-(2-(2-(4-Chlorobenzoyl)benzofuran-3-ylamino)-2-oxoethylamino)-3-phenylpropanoic acid (VIb)

IR (cm^{-1}) KBr: 3468 (amide NH_{str}), 1674 (amide $C=O_{str}$), 1712 (benzoyl $C=O_{str}$), 1718 (carboxylic acid $C=O_{str}$), 2989 (carboxylic acid OH_{str}), 3336 (amineNH_{str}), 780 (C-Cl_{str}); ^{1}H NMR ($CDCl_3$): (δ, ppm) 12.52 (s, 1H, COOH), 10.02 (s, 1H, CONH), 2.02 (s, 1H, NH), 7.27–7.89 (m/br, 13H, Ar-H and protons of benzofuran), 3.44 (d, 2H, $COCH_2$), 3.88 (t, 1H, CHNH of phenylalanine), 3.04, 3.29 (m, 2H, $C_6H_5CH_2$ of phenylalanine); mass (m/z) 476.12 (M^+), 477.15 (M^++1), 478.13 (M^++2); analysis (calc. %/found %): C 65.48 (65.67) H 4.44 (4.47) Cl 7.43 (7.23) N 5.87 (5.68) O 16.77 (16.95).

2-(3-(2-(Benzoylbenzofuran-3-ylamino)-3-oxopropylamino)-3-phenylpropanoic acid (VIIa)

IR (cm^{-1}) KBr: 3462 (amide NH_{str}), 1673 (amide $C=O_{str}$), 1712 (benzoyl $C=O_{str}$), 1718 (carboxylic acid $C=O_{str}$), 2985 (carboxylic acid OH_{str}), 3335 (phenylalanine amine NH_{str}); ^{1}H NMR ($CDCl_3$): (δ, ppm) 12.55 (s, 1H, COOH), 10.03 (s, 1H, CONH), 2.01 (s, 1H, NH of phenylalanine), 7.30–7.89 (m/br, 14H, Ar-H and protons of benzofuran), 2.32 (t, 2H, $COCH_2$), 2.82 (t, 2H, CH_2 β to CO), 3.04, 3.29 (m, 2H, $C_6H_5CH_2$ of phenylalanine); mass (m/z) 456.16 (M^+), 457.17 (M^++1), 458.19 (M^++2); analysis (calc. %/found %): C 71.04 (71.26) H 5.30 (5.19) N 6.14 (6.29) O 17.52 (17.26).

2-(3-(2-(4-Chlorobenzoyl)benzofuran-3-ylamino)-3-oxopropylamino)-3-phenylpropanoic acid (VIIb)

IR (cm^{-1}) KBr: 3464 (amide NH_{str}), 1675 (amide $C=O_{str}$), 1718 (benzoyl $C=O_{str}$), 1720 (carboxylic acid $C=O_{str}$), 2980 (carboxylic acid OH_{str}), 3330 (phenylalanine amine NH_{str}), 777 (C-Cl_{str});^{1}H NMR ($CDCl_3$): (δ, ppm) 12.56 (s, 1H, COOH), 10.00 (s, 1H, CONH), 2.02 (s, 1H, NH of phenylalanine), 7.31–7.95 (m/br, 13H, Ar-H and protons of benzofuran), 2.31 (t, 2H, $COCH_2$), 2.83 (t, 2H, CH_2 β to CO), 3.03, 3.30 (m, 2H, $C_6H_5CH_2$ of phenylalanine); Mass (m/z) 490.14 (M^+), 491.16 (M^++1), 492.18 (M^++2); analysis (calc. %/found %): C 66.06 (66.26) H 4.72 (4.89) Cl 7.22 (7.34) N 5.71 (5.49) O 16.29 (16.02).

2-(4-(2-(Benzoylbenzofuran-3-ylamino)-4-oxobutylamino)-3-phenylpropanoic acid (VIIIa)

IR (cm^{-1}) KBr: 3466 (amide NH_{str}), 1674 (amide $C=O_{str}$), 1708 (benzoyl $C=O_{str}$), 1716 (carboxylic acid $C=O_{str}$), 2982

(carboxylic acid OH_{str}), 3333 (phenylalanine amine NH_{str}); ^1H NMR ($CDCl_3$): (δ, ppm) 12.56 (s, 1H, COOH), 10.01 (s, 1H, CONH), 2.01 (s, 1H, NH of phenylalanine), 7.30–7.90 (m/br, 14H, Ar-H and protons of benzofuran), 2.34 (t, 2H, $COCH_2$), 1.69 (p, 2H, CH_2 β to CO), 2.54 (t, 2H, CH_2 γ to CO),3.03, 3.29 (m, 2H, $C_6H_5CH_2$ of phenylalanine); mass (m/z) 470.18 (M^+), 471.17 (M^++1), 472.18 (M^++2); analysis (calc. %/found %): C 71.47 (71.36) H 5.57 (5.42) N 5.95 (6.05) O 17.00 (17.17).

2-(4-(2-(4-Chlorobenzoyl)benzofuran-3-ylamino)-4-oxobutylamino)-3-phenylpropanoic acid (VIIIb)

IR (cm^{-1}) KBr: 3467 (amide NH_{str}), 1676 (amide $C=O_{str}$), 1716 (benzoyl $C=O_{str}$), 1719 (carboxylic acid $C=O_{str}$), 2987 (carboxylic acid OH_{str}), 3334 (phenylalanine amine NH_{str}), 786 (C-Cl_{str}); ^1H NMR ($CDCl_3$): (δ, ppm) 12.57 (s, 1H, COOH), 10.02 (s, 1H, CONH), 2.02 (s, 1H, NH of phenylalanine), 7.29–7.91 (m/br, 13H, Ar-H and protons of benzofuran), 2.33 (t, 2H, $COCH_2$), 1.70 (p, 2H, CH_2 β to CO), 2.55 (t, 2H, CH_2 γ to CO),3.04, 3.30 (m, 2H, $C_6H_5CH_2$ of phenylalanine); mass (m/z) 504.16 (M^+), 505.17 (M^++1), 506.17 (M^++2); analysis (calc. %/found %): C 66.60 (66.43) H 4.99 (5.23) Cl 7.02 (7.25) N 5.55 (5.48) O 15.84 (15.61).

Docking studies

Molecular docking studies were performed using ADT 4.2 to identify appropriate binding modes and conformation of the ligand molecules. The crystal structure of CYP24A1 (PDB code: 3K9V, resolution-2.5 Å) was retrieved from the PDB and used for molecular modeling studies. The structures of all the compounds (**VIa-b, VIIa-b,** and **VIIIa-b**) were sketched using Chemdraw ultra 13.0 and converted into 3D structures using HyperChem Pro 8.0 Software (www.hyper.com). ADT tools version 1.5.6 (www.autodock.scrips.edu) was used to prepare molecular docking. The active site of CYP24A1 protein was predicted by the sitemap, with the following residues: ILE131, TRP134, MET148, MET245, MET246, PHE249, ALA326, GLU329, THR330, VAL391, THR394, THR 395 GLY499, and ILE500 in the active site, which are similar to the template active site residues reported previously.[11] Using this, the grid box size was set to a dimension of 5.13 × −21.85 × 25.68 in x, y, z coordinates to cover the active site of the protease while virtual screening was performed by ADT 4.2.5.1. The best binding conformation was selected from the docking log (.dlg) file for each ligand and further interaction analysis was done using PyMol and Discovery Studio Visualizer 4.0.

CONCLUSION

Some new phenylalanine-benzofuran-acetamide/propanamide/butanamide hybrids (**VIa-b**, **VIIa-b,** and **VIIIa-b**) were synthesized in good yield, characterized and *in silico* screening for CYP24A1 inhibitory activity was done. **VIa** (binding score −7.6) was found to be the most promising compound among all binds in similar manner to the natural ligand, calcitriol. The outcomes clearly displayed that these benzofuran hybrids could be a promising lead in the development of novel CYP24A1 inhibitors.

CONFLICTS OF INTEREST

The author confirms that the content of this article has no conflicts of interest.

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