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DESIGN AND *IN SILICO* STUDIES OF N- (α-CYANO SUBSTITUTED CINNAMOYL) NAPHTHYL HYDRAZONE DERIVATIVES

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ABSTRACT

Nafcillin is a clinically used antibacterial drug which possess 2-ethoxy-1-naphthyl substituted penicillin and some antibacterial drugs contains hydrazone moiety in their structures. The therapeutic activity of these drugs was due to the specific structural features. In view of this, it has been planned to calculate the molecular properties, bioactivity score, ADMET profile of designed novel series of N-(α-cyano substituted cinnamoyl) naphthyl hydrazones with the help of *in silico* tools such as Molinspiration and PreADMET. Molecular docking studies were also performed against FAB protein (β-ketoacyl-acyl carrier synthase III), Superoxide dismutase (SOD), PPAR ϒ (peroxisome proliferator-activated receptor gamma), Tau protein kinase, butyryl Cholinesterase enzyme by using AUTODOCK 4.0. All the derivatives obeyed Lipinski's rule, displayed moderate enzyme inhibition and kinase inhibition activities. Docking results revealed that, compound **C8** showed good binding affinity (-9.06 Kcal/Mol) against FAB protein when compared to that of standard drug nafcillin (-7.24 kcal/mol), compound **C10** exhibited better binding affinity (-10.15 Kcal/Mol) than standard drug α-tocopherol (-5.78 kcal/mol) against SOD, compound **C9** displayed good binding affinity (-10.38 Kcal/Mol)against PPAR ϒ when compared to that of the standard drug pioglitazone (-7.78 kcal/mol), compound **C3** showed better binding affinity (-9.27 Kcal/Mol) than the standard drug donepezil against tau protein (-7.56 kcal/mol). Similarly, compound **C10** exhibited better binding affinity (-10.32 Kcal/Mol) against BChE enzyme than standard drug donepezil (-9.32 kcal/mol).

Keywords: Lipinski's rule, hydrazones, i*n silico* tools, docking, binding energy

INTRODUCTION:

Over the past few decades, articles in scientific community reported that people infected with multidrug resistant bacteria can increase the resistance towards antibacterial drugs **[1].** And people facing difficulties with oxidative stress which causes various diseases like atherosclerosis, neurodegenerative diseases, cancer as well as psychological diseases **[2]**. Globally, people suffering with diabetes mellitus and alzheimer's disorders which also caused due to the imbalances in endogenous antioxidative enzymes like SOD **[3]**. So, there is a need for new drug molecules to treat multifactorial diseases.

Literature study revealed that cinnamic acid derivatives possess stimulant, carminative, antiseptic, insecticide **[4]**, antimicrobial **[5]**, antidiabetic, antiinflammatory, anticancer, antitubercular **[6]** activities. Hydrazones are the important class of organic compounds and extensive studies revealed that the lone pair on trigonally hybridized nitrogen atom of the azomethine group is responsible for the chemical and biological activities such as antimicrobial **[7]**, anticonvulsant, antidepressant, analgesic, antiinflammatory, antidiabetic, anticancer **[8]**. The topical antibacterial agent available in market with the hydrazone nuclei was nitrofurazone **[9]**. Various functional group substitutions to 2-naphthyl nuclei reported to exhibit different pharmacological actions such as antimicrobial, antiinflammatory, analgesic, antioxidant **[10]** activities. The commercially available β-lactam antibiotic with 2-naphthyl nuclei was nafcillin(https://go.drugbank.com)**.** Owing to the potentiality of cinnamic acid, 2-naphthyl and hydrazone moieties, the present study has been planned to design a novel series of N-(α-cyano substituted cinnamoyl)-2- naphthyl hydrazones to study the possible pharmacophoric contribution ofcinnamoyl, 2-naphthyl and hydrazone moieties.

MATERIALS AND METHODS:

Molecular properties, bioactivity scores and ADMT profile

Chem Draw Ultra 12.0 was used to build the structures of title compounds. Drug likeness is a quantitative concept indicated by molecular properties which affects absorption, distribution, metabolism and excretion of compounds. Molinspiration online tool (https://www.molinspiration.com) was used for calculating molecular properties and bioactivity scores of all the title compounds. ADMT properties of title compounds were analyzed using PreADMET online tool (https://preadmet.bmdrc.kr).

Docking studies

Molecular docking is one of the drug designing methods, which predicts the favourable orientation of one molecule towards protein when bound to each other to form a stable complex. Docking studies of all the ligands were performed using AUTODOCK 4.0. In this study FAB protein (PDB: 5BNM) **[11]**, Superoxide Dismutase enzyme (PDB: 2C9V) **[12]**, PPAR ϒ (PDB: 2XKW) **[13]**, Tau protein kinase (PDB: 1J1B) **[14]** and Butyryl Cholinesterase (BChE, PBD: 6QAE) were used as targets and their X-ray crystal structures were retrieved from RCSB Protein data bank (https://www.rcsb.org**).** Discovery studio was used for visualization of results. All the title compounds along with standard drugs were docked to access their binding affinities for antibacterial, antioxidant, antidiabetic activities. Based on the BBB penetration and Log P values **[15]** only the selected compounds **C1, C3, C4, C10, C15, C16, C17** were screened for antialzheimer's activity.

RESULTS AND DISCUSSION:

The chemical structures of twenty N-(α-cyano substituted cinnamoyl) naphthyl hydrazones were generated using Chem Draw Ultra 12.0 presented in **Table 1** and the general structure was shown in **Figure 1**.

Molecular properties, Bioactivity scores, ADMET Profile:

The molecular properties and bioactivity scores of title compounds were calculated by using molinspiration and results were represented in **Table 2** and **Table 3**. The results revealed that all the derivatives followed Lipinski's rule of five and moderately active as enzyme inhibitors and kinase inhibitors, inactive as ion channel modulators, few derivatives displayed moderate protease inhibition, nuclear receptor inhibition and GPCR ligand modulator activities. Absorption and distribution properties of compounds **C1-C20** were listed in **Table 4**. Compounds **C1-C20** showed % HIA ranging from 88%-97%, $CaCO_2$ cell permeability ranges from 0.4-28, skin permeability ranges from 1.76-2.90 cm/s. All the compounds were strongly bound to plasma protein about 84% - 100%, few derivatives showed P-glycoprotein inhibition. Metabolism and toxicity profile of title compounds **C1-C20** were reported in **Table 5**. CYP450 enzymes metabolize most medications, and the most important of these enzymes are CYP2C9, CYP2C19, CYP2D6, and CYP3A4. All the derivatives except **C4** and **C8** inhibited CYP2C9 enzyme. All the title compounds except **C4, C7**and **C8**inhibited CYP2C19 enzyme, and only few compounds displayed the CYP3A4 enzyme inhibition. All the title compounds **C1-C20** showed mutagenicity by ames test.

Among all the derivatives, compound **C8, C9** possess low risk towards HERG inhibition.

Docking studies:

The binding affinities of the designed compounds and standard drugs with the selected biological targets were outlined in **Table 6**. The binding energies of compounds **C1-C20** against FAB protein, SOD and PPAR-γ ranges from -9.06 to -7.12 Kcal/mol, -10.15 to -7.07 Kcal/mol and -10.38 to -8.07 Kcal/mol respectively. The binding energies of selected compounds **C1, C3, C4, C10, C15, C16, C17** ranging from -9.27 to -7.97 Kcal/mol against 1J1B whereas the binding energies of **C10, C15** and **C16** against 6QAE were-10.32, -9.56 and -9.98 kcal/mol respectively. Among all the title compounds, compound **C8** displayed good binding affinity (-9.06 Kcal/Mol) when compared to that of standard drug naficillin (-7.68 Kcal/Mol) against 5BNM (**Figure 2** and **Figure 3)**. Among the series, compound **C10** displayed good binding affinity (-10.15 Kcal/Mol) when compared to that of standard drug α-tocopherol (-5.78 Kcal/Mol) against 2C9V (**Figure 4** and **Figure 5)**. Among all the derivatives, compound **C9** displayed good binding affinity (-10.38 Kcal/Mol) when compared to that of standard drug pioglitazone (-7.78 Kcal/Mol) against 2XKW (**Figure 6** and **Figure 7)**. Among all the title compounds, compound **C3** displayed good binding affinity (-9.127 Kcal/Mol) when compared to that of standard drug donepezil (-7.56 Kcal/Mol) against 1J1B (**Figure 8** and **Figure 9)**. Among the series, compound **C10** displayed good binding affinity when compared to that of standard drug donepezil (-9.06 Kcal/Mol) against 6QAE (**Figure 10)**.

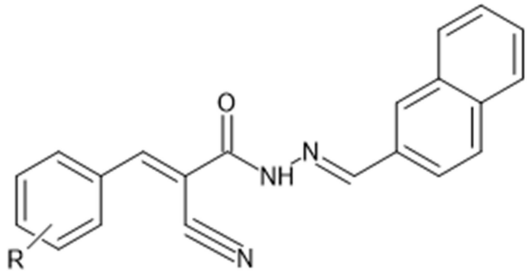

Fig 1: General structure of N- (α-cyano substituted cinnamoyl) naphthyl hydrazones

Table 1: Derivatives of N- (α-cyano substituted cinnamoyl) naphthyl hydrazones C1-C20

Compound code	R	Compound code	R	Compound code	R

C1	4- Br	C8	2-NO_2	C15	2-Cl-6-CH_3
C2	4-COOH	C9	4-$OCH_2C_6H_5$	C16	5-F-2-CH_3
C3	4-Cl	C10	3,4-Cl_2	C17	4-F-2-CH_3
C4	4-N (C_2 H_5)$_2$	C11	3,4-$(OCH_3)_2$	C18	2,3,4-$(OCH_3)_3$
C5	2-F	C12	2,3-$(OCH_3)_2$	C19	4-OH-3,5-
					(OCH3)2
C6	3-OH	C13	3-OH-4- OCH_3	C20	3-Cl-2-OH
C7	4-OCH_3	C14	4-OH-3- OCH_3		

Table 2: Molecular properties of N- (α-cyano substituted cinnamoyl) naphthyl hydrazones C1-C20

Compound code	Log p	TPSA	n atoms	mol. weight	n O N	n OH NH	n vio
C1	5.45	65.25	26	404.27	4	1	1
C2	4.55	102.5	28	369.38	6	2	0
C3	5.32	65.25	26	359.82	4	1	1
C4	5.50	68.49	30	396.49	5	1	1
C5	4.58	65.25	26	343.36	4	1	0
C6	4.14	85.48	26	341.37	5	2	0
C7	4.70	74.49	27	355.40	5	1	0
C8	4.38	111.1	28	370.37	7	1	0
C9	6.29	74.49	33	431.50	5	1	1
C10	5.93	65.25	27	394.26	4	1	1
C11	4.29	83.72	29	385.42	6	1	0
C12	4.28	83.72	29	385.42	6	1	0
C13	3.98	94.72	28	371.40	6	2	0
C14	3.98	94.72	28	371.40	6	2	0
C15	5.50	65.25	27	373.84	4	1	1
C16	5.00	65.25	27	357.39	4	1	1
C17	5.00	65.25	27	357.39	4	1	1
C18	4.29	92.96	31	415.45	7	1	0
C19	4.00	103.9	30	401.42	7	2	0
C20	4.83	85.48	27	375.81	5	2	0

Log P: logarithmic value of compound partition coefficient, TPSA: topological polar surface area, mol. weight: molecular weight n O N: number of Oxygen and Nitrogen atoms, n OH NH: number of OH and NH groups, n vio: number of violations

Table 3: Bioactivity scores of novel series N- (α-cyano substituted cinnamoyl) naphthyl hydrazonesC1-C20

Compound code	GPCR ligand	Ion channel	Kinase inhibition	Nuclear receptor	Protease inhibition	Enzyme inhibition
C1	-0.67	-0.71	-0.43	-0.61	-0.62	-0.40
C2	-0.52	-0.60	-0.39	-0.34	-0.45	-0.25
C3	-0.57	-0.65	-0.41	-0.52	-0.55	-0.36
C4	-0.48	-0.59	-0.34	-0.45	-0.49	-0.36
C5	-0.59	-0.64	-0.45	-0.51	-0.54	-0.36
C6	-0.54	-0.61	-0.36	-0.36	-0.51	-0.28
C7	-0.59	-0.69	-0.41	-0.50	-0.55	-0.36
C8	-0.68	-0.66	-0.54	-0.58	-0.70	-0.45
C9	-0.44	-0.51	-0.32	-0.33	-0.37	-0.24
C10	-0.54	-0.61	-0.40	-0.51	-0.53	-0.35
C11	-0.57	-0.66	-0.38	-0.49	-0.54	-0.34
C12	-0.58	-0.67	-0.42	-0.54	-0.57	-0.38
C13	-0.55	-0.64	-0.36	-0.44	-0.56	-0.31
C14	-0.55	-0.64	-0.36	-0.44	-0.56	-0.31
C15	-0.59	-0.70	-0.43	-0.52	-0.59	-0.38
C16	-0.54	-0.69	-0.37	-0.48	-0.55	-0.38
C17	-0.54	-0.69	-0.37	-0.48	-0.55	-0.38
C18	-0.56	-0.64	-0.39	-0.55	-0.55	-0.36
C19	-0.54	-0.60	-0.33	-0.43	-0.51	-0.27
C20	-0.59	-0.72	-0.35	-0.42	-0.54	-0.34

GPCR: G protein coupled receptor

Table 4: Absorption, distribution and elimination properties of title compound C1-C20

Compound code	CaCO2	MDCK	% HIA	Skin (cm/s)	BBB	% PPB	P-gp substrate
C1	23.05	0.098	97.05	-2.028	0.227	100.00	Inhibitor
C2	20.33	2.00	97.65	-2.312	0.183	93.58	NI
C3	23.22	43.83	96.79	-2.128	0.209	99.19	Inhibitor
C4	28.33	39.09	96.76	-1.905	0.134	92.99	Inhibitor
C5	21.12	1.983	96.36	-2.306	0.150	92.89	Inhibitor
C6	20.87	0.793	94.83	-2.442	0.198	90.53	NI
C7	22.53	17.44	96.35	-2.231	0.038	92.39	Inhibitor
C8	20.82	0.201	97.74	-2.140	0.112	90.97	Inhibitor
C9	32.23	1.368	97.17	-1.76	0.069	96.19	Inhibitor
C10	24.39	11.66	97.15	-2.08	0.407	100.00	Inhibitor
C11	24.21	18.06	96.43	-2.33	0.035	88.95	NI
C12	22.47	4.428	96.43	-2.31	0.218	88.86	NI
C13	21.37	8.203	94.84	-2.452	0.062	88.75	NI
C14	21.33	8.20	94.84	-2.459	0.100	88.81	NI
C15	23.02	26.05	96.87	-2.061	0.336	95.51	Inhibitor
C16	22.81	0.772	96.45	-2.254	0.192	90.86	Inhibitor
C17	23.07	8.169	96.46	-2.255	0.200	94.04	Inhibitor
C18	26.48	15.32	96.67	-2.30	0.050	88.75	NI
C19	15.41	1.977	88.07	-2.901	0.654	84.81	NI
C20	0.477	0.191	95.54	-2.42	0.477	99.76	Inhibitor

$CaCO_2$: Model of intestinal epithelial barrier, MDCK: Madin-Darby Canine Kidney monolayers, %HIA: percentage of Human Intestinal Absorption, BBB: Blood Brain Barrier, %PPB: Plasma Protein Binding, P-gp: P-glycoprotein, NI: non inhibitor

Table 5: Metabolism and toxicity of title compounds C1-C20

Compound	CYP2C19 inhibition	CYP2C9 inhibition	CYP2D6 inhibition	CYP3A4 inhibition	Ames test	HERG inhibition
C1	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C2	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C3	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C4	NI	NI	NI	NI	Mutagen	Medium risk
C5	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C6	Inhibitor	Inhibitor	NI	NI	Mutagen	High risk
C7	Inhibitor	NI	NI	NI	Mutagen	Medium risk
C8	NI	NI	NI	NI	Mutagen	Low risk
C9	Inhibitor	Inhibitor	NI	Inhibitor	Mutagen	Low risk
C10	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C11	Inhibitor	Inhibitor	NI	Inhibitor	Mutagen	Medium risk
C12	Inhibitor	Inhibitor	NI	Inhibitor	Mutagen	Medium risk
C13	Inhibitor	Inhibitor	NI	Inhibitor	Mutagen	High risk
C14	Inhibitor	Inhibitor	NI	Inhibitor	Mutagen	High risk
C15	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C16	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C17	Inhibitor	Inhibitor	NI	NI	Mutagen	Medium risk
C18	Inhibitor	Inhibitor	NI	Inhibitor	Mutagen	Medium risk
C19	Inhibitor	Inhibitor	NI	Inhibitor	Mutagen	High risk
C20	Inhibitor	Inhibitor	NI	NI	Mutagen	High risk

NI: Non inhibitor, Ames test: simple model for compound mutagenesis, HERG inhibition: the human-a-go-go-Related Gene codes for alpha sub unit of K^+ channel

Table 6: Docking results of novel series C1-C20 against target proteins

Compound	Binding energy (Kcal/mol)	

	5BNM	2C9V	2XKW	1J1B	6QAE
C1	-8.2	-7.76	-10.01	-9.01	-7.62
C2	-7.12	-8.02	-8.91	-	-
C3	-8.14	-8.53	-9.94	-9.27	-7.63
C4	-7.33	-7.46	-9.45	-7.97	-4.74
C5	-7.96	-7.94	-8.94	-	-
C6	-8.78	-9.06	-9.29	-	-
C7	-7.87	-7.25	-9.26	-	-
C8	-9.06	-8.51	-9.62	-	-
C9	-8.27	-8.69	-10.38	-	-
C10	-8.83	-10.15	-9.88	-8.33	-10.32
C11	-7.45	-7.87	-8.55	-	-
C12	-8.15	-7.07	-8.07	-	-
C13	-8.83	-8.49	-8.95	-	-
C14	-8.36	-7.96	-9.33	-	-
C15	-8.98	-8.60	-9.10	-8.08	-9.56
C16	-8.90	-8.88	-8.99	-8.19	-9.98
C17	-8.44	-9.15	-9.69	-8.20	-9.24
C18	-7.73	-7.15	-8.85	-	-
C19	-8.39	-7.63	-9.05	-	-
C20	-8.56	-8.88	-9.42	-	-
Ciprofloxacin	-5.29	-	-	-	-
Nafcillin	-7.68	-	-	-	-
α-tocopherol	-	-5.78	-	-	-
Pioglitazone	-	-	-7.78	-	-
Donepezil	-	-	-	-7.56	-9.32

Ciprofloxacin, nafcillin, alpha tocopherol, pioglitazone, donepezil - standard drugs

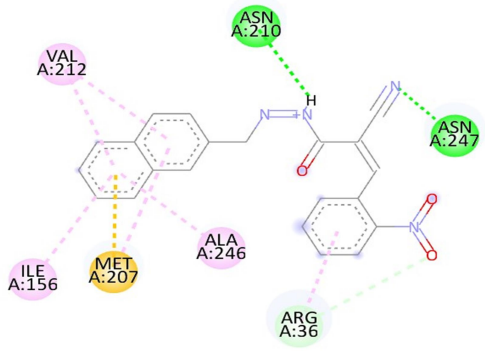

Fig 2- 2d view of docking interactions of C8 against 5BNM

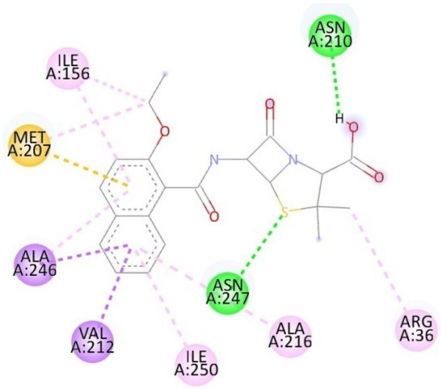

Fig 3- 2d view of docking interactions of nafcillin against 5BNM

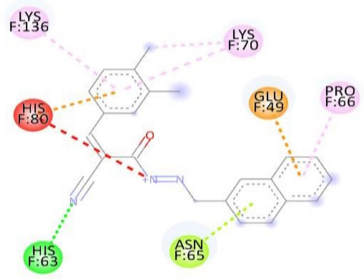

Fig 4- 2d view of docking interactions of C10 against 2C9V

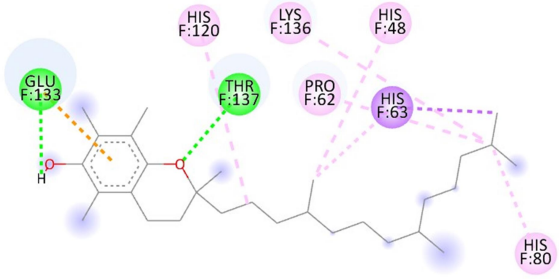

Fig 5- 2d view of docking interactions of α-tocopherol against 2C9V

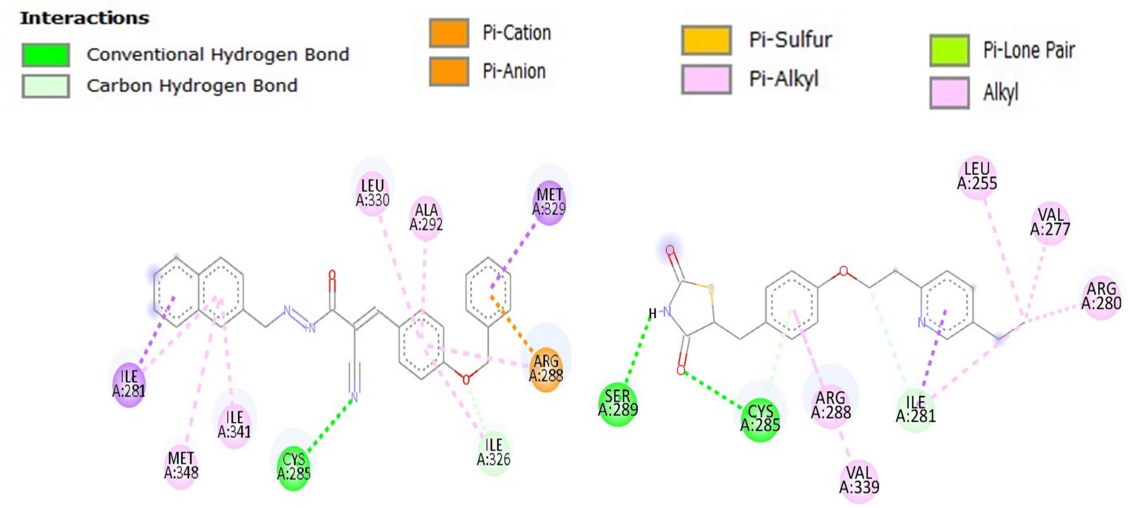

Fig 6- 2d view of docking interactions of C9 against 2XKW **Fig 7- 2d view of docking interactions of pioglitazone against 2XKW**

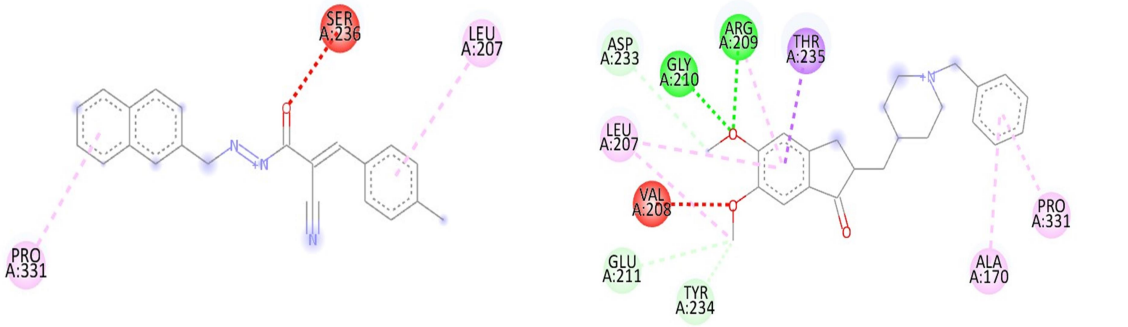

Fig 8- 2d view of docking interactions of C3 against 1J1B **Fig 9- 2d view of docking interactions of donepezil against 1J1B**

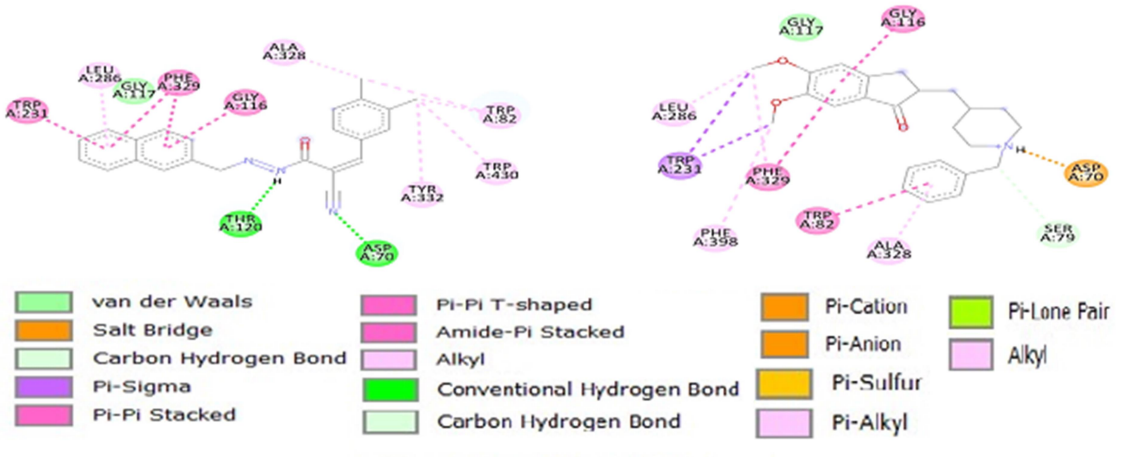

Fig 10- 2d view of docking interactions of C10 and donepezil against 6QAE

CONCLUSION:

A novel series of N-(α-cyano substituted cinnamoyl)-2- naphthyl hydrazones were designed, and various properties were predicted using *in silico* tools and docking studies were performed against FAB protein, SOD, PPAR ϒ, Tau protein kinase, BChE enzyme. From the study, it was found that all the title compounds obeyed Lipinski's rule indicating good oral bioavailability. Docking studies revealed that among the series, compound **C8** with nitro group substitution was predicted to have good antibacterial activity, **C10** with 3,4-dichloro substitution was predicted to have good antioxidant and antialzheimer's activities, **C9** with 4-benzyloxy substitution was predicted to possess good antidiabetic activity.

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