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Establishing A Remedy Of Dyslexia From Indian Traditional Herbs By *in-silico* Methods

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Abstract: **Dyslexia is a major childhood disorder. It causes learning disability because of which several behavior flaw is noticed like stammering, faulty writing, lack of attention and seen these children more energetic than normal children of same age. Recent studies suggest association of dyslexia with multiple gene mutations. In this work, we are identifying the genes responsible for dyslexia, establishing their 3d structure by using the structural coordinates of homologous templates. Several medicinal herbs from Ayurvedic, Siddha and Unani background are found to have a cure for neurological disorders. In this work we are targeting the compounds from these herbs against the gene receptors as potential ligands for the disorder.**

Keywords: **dyslexia, medicinal herbs, homology modelling, virtual screening**

I. INTRODUCTION

Dyslexia is a language-based learning disability. Dyslexia refers to an association of symptoms, which result in people having difficulties with specific language skills, particularly reading. Dyslexia, or developmental reading disorder, is characterized by difficulty with learning to read fluently and with accurate comprehension despite normal or above-average intelligence. Students with dyslexia usually experience difficulties with other language skills such as spelling, writing, and pronouncing words. Dyslexia affects individuals throughout their lives, however, its impact can change at different stages in a person's life. It is referred to as a learning disability because dyslexia can make it very difficult for a student to succeed academically in the typical instructional environment, and in its more severe forms, will qualify a student for special education, special accommodations, or extra support services [1, 2]. Genes associated to dyslexia referred in this work are DCDC2, KIAA0319, DYX1C1, CMIP [3].

DCDC2: DOUBLECORTIN DOMAIN-CONTAINING 2

This gene encodes a doublecortin domain-containing family member. The doublecortin domain has been demonstrated to bind tubulin and enhance microtubule polymerization. This family member is thought to function in neuronal migration where it may affect the signaling of primary cilia. Mutations in this gene have been associated with reading disability (RD) type 2, also referred to as developmental dyslexia. Alternatively spliced transcript variants encoding the same protein have been found for this gene. Mutations in this gene have been associated with reading disability (Rd) also referred to as developmental dyslexia.

Changes in the DCDC2 gene are frequently found among dyslexics. Altered alleles often occur among children with riding and writing difficulties. The gene appears to have a strong linkage with the processing of speech information when writing [4, 5].

KIAA0319:

KIAA0319 is a protein which in humans is encoded by the KIAA0319 gene and its variants of the KIAA0319 gene have been associated with developmental dyslexia. Reading disability, also called dyslexia, is a major social, educational, and mental health problem associated with it. In spite of average intelligence and adequate educational opportunities, 5 to 10% of school children have been detected having substantial reading deficits. Twin have shown a substantial genetic component to this disorder, with heritable variation estimated at 50 to 70%. An NIDCD-supported investigator has identified a mutation in a gene on chromosome 6, called the KIAA0319 gene, that appears to play a key role in Specific Language Impairment. The KIAA0319 protein is expressed on the cell membrane and may be involved in neuronal migration and furthermore, KIAA0319 follows a clathrin-mediated endocytic pathway [6, 7, 8].

DYX1C1: DYSLEXIA SUSCEPTIBILITY 1 CANDIDATE 1

This gene encodes a tetratricopeptide repeat domain-containing protein. The encoded protein interacts with estrogen receptors and the heat shock proteins, Hsp70 and Hsp90. An homologous protein in rat has been shown to function in neuronal migration in the developing neocortex. A chromosomal translocation involving this gene is associated with a susceptibility to developmental dyslexia. Mutations in this gene are associated with deficits in reading and spelling. Alternative splicing results in multiple transcript variants [9, 10].

CMIP: C-MAF INDUCING PROTEIN

This gene encodes a c-Maf inducing protein that plays a role in T-cell signaling pathway. Alternatively spliced transcript variants encoding different is forms have been described for this gene. CMIP is a protein coding gene diseases associated with CMIP include speech and communication disorder specific language impairment [11].

II METHODOLOGY

Dyslexia receptor amino acid sequences were downloaded from NCBI (Table 1). Their 3d structure was modelled using swiss model.

Table 1: Dyslexia receptors with their NCBI Accession number

Gene name	Accession number
DCDC2	AAH50704.1
KIAA0319	BAA20777.3
DYX1C1	NP_570722.2
CMIP	AAH38113.1

Herbs useful in treating CNS disorders are used in this work [12, 13, 14, 15, 16]. The active compounds of the herbs used in this work are downloaded from PUBCHEM (Table 2)

Table 2: Herbs with their compounds used in this work.

Herb name	**Scientific name**	**Compounds**
Schizandra	Schisandra chinensis	Schizandrin Deonyschizandrin Gomisine
Kava kava	Piper methysticum	Kavain Caffeic Acid Dihydrokavain Methysticin Dihydromethysticin Yangonin Desmethoxyangonin Allantoin Rosmaric Acid Methyl Oleanolate Stignasterol Isoleucine Phynyalarine
Piperaceae	Piper caninum	Bornyll Caffeate
	Rheum officinale	Cinnanic Acid
	Forsythia suspensa	Pinoresinol
	Podophyllum peltatum	Pudophyllotonin
	Nardostachys jatamansi	Valeranone

The active compounds of the herbs are docked with the dyslexia receptors DCDC2, KIAA0319, DYX1C1 and CMIP in this work.

III RESULTS & DISCUSSION

Amino acid sequence of the gene responsible for Dyslexia was retrieved from Genbank/Uniprot database and their accession number was noted.

Structure modeling was done using using Swiss Model. Unknown and reference ligand were identified and virtual screening and docking studies was performed on the ligands with the receptor proteins.

Table 3: Docking analysis of the dyslexia receptors with the active compounds of the CNS herbs

COMPOUNDS docking with DCDC2 receptor	**DOCKING SCORE KCAL/MOL**	**INTERACTING AMINO ACIDS**	**NO. OF INTERACTIONS**	**DOCKING (YES/NO)**
BRONYL CAFFEATE	2612 KCAL/MOL	LEV 190	1	YES
CINNAMIC ACID	2208 KCA	THR 189	1	YES

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	L/MOL			
PINORESINOL	3784 KCAL/MOL	ARG 180	1	YES
PODOPHYLLOTOXIN	3814 KCAL/MOL	GLN 136	1	YES
VALERANONE	2208 KCAL/MOL	THR 189	1	YES
ALLANTOIN	1892 KCAL/MOL	PHE 206	1	YES
METHYSTICIN	2552 KCAL/MOL	GLU 202	1	YES
DESMETHOXYANGONIN	3100 KCAL/MOL	GLY 204 PHE 206	1 1	YES
DIHYDROKAVAIN	2538 KCAL/MOL	ARG 180 THR 178	1 1	YES
ISOLUCINE	2032 KCAL/MOL	PHE 206	1	YES
KAVAIN	2470 KCAL/MOL	THR 178	1	YES
GOMISIN	2894 KCAL/MOL	TYR 188 PHE 215	1 1	YES
ROSMARINIC ACID	3790 KCAL/MOL	THR 178	1	YES
DIHYDROMETHYSTICIN	3354 KCAL/MOL	ARG 190	1	YES
PINORESINOL	3784 KCAL/MOL	ARG 180	1	YES
STIGMASTEROL	4590 KCAL/MOL	ARG 180	1	YES
METHYLOLEANOLATE	NO DOCKING			
YANGONIN	NO DOCKING			
PHENYLALARINE	NO DOCKING			

COMPOUNDS docking with KIAA receptor	**DOCKING SCORE KCAL/MOL**	**INTERACTING AMINO ACIDS**	**NO. OF INTERACTIONS**	**DOCKING (YES/NO)**
GOMISIN	3540 KCAL/MOL	LEV 684	1	YES
METHYSTICIN	3222 KCAL/MOL	ASN 715	1	YES
ROSMARINIC ACID	4938 KCAL/MOL	ASN 715	1	YES
CINNAMIC ACID	2910 KCAL/MOL	SER 648	1	YES
PODOPHYLLOTOXIN	NO DOCKING			
ALLANTOIN	2772 KCAL/MOL	ASN 780	1	YES
SCHIZANDRIN	3930 KCA	ASN 715	1 1	YES

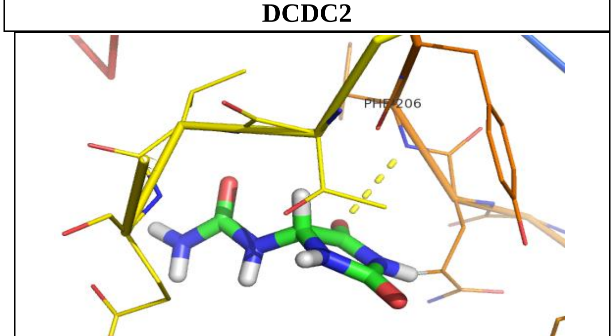
	L/MOL	SLR 795		
DESMETHOXYANGONIN	3752 KCAL/MOL	ASN 715	1	YES
BORNYLCAFFEATE	NO DOCKING			
DIHYDROMETHYSTICIN	4356 KCAL/MOL	GLN 685 ASN 715	1 2	YES
ISOLEUCINE	2794 KCAL/MOL	ASN 780 THR 779	1 1	YES
PINORESINOL	NO DOCKING			
STIGMASTEROL	NO DOCKING			
METHYLOLEANOLATE	NO DOCKING			
YANGONIN	NO DOCKING			
PHENYLALARINE	NO DOCKING			

COMPOUNDS docking with CIMP receptor	**DOCKING SCORE KCAL/MOL**	**INTERACTING AMINO ACIDS**	**NO. OF INTERACTIONS**	**DOCKING (YES/NO)**
GOMISIN	3526 KCAL/MOL	HIS 556	1	YES
METHYSTICIN	NO DOCKING			
ROSMARINIC ACID	NO DOCKING			
CINNAMIC ACID	NO DOCKING			
PODOPHYLLOTOXIN	4720 KCAL/MOL	ARG 501	1	YES
ALLANTOIN	NO DOCKING			
SCHIZANDRIN	3680 KCAL/MOL	GLU 527	1	YES
DESMETHOXYANGONIN	3754 KCAL/MOL	GLU 527	1	YES
BORNYLCAFFEATE	NO DOCKING			
DIHYDROMETHYSTICIN	4174 KCAL/MOL	ALA 526	1	YES
ISOLEUCINE	NO DOCKING			
PINORESINOL	4740 KCAL/MOL	LEU 514	1	YES
STIGMASTEROL	5100 KCAL/MOL	ARG 501	1	YES
METHYLOLEANOLATE	NO DOCKING			
YANGONIN	4040 KCAL/MOL	GLU 527	1	YES
PHENYLALANINE	3310 KCAL/MOL	LEU 540	1	YES

COMPOUNDS docking with	**DOCKING SCO**	**INTERACTING**	**NO. OF INTERACTIO**	**DOCKING**

DYX1C1 receptor	**REKCAL/MOL**	**AMINO ACIDS**	**NS**	**(YES/NO)**
DIHYDROKAVAIN	NO DOCKING			
SCHIZANDRIN	3258 KCAL/MOL	ASN 339	1	YES
METHYSTICIN	2686 KCAL/MOL	ARG 365 ASN 363	1 1	YES
VALERANONE	NO DOCKING			
METHYLOLEANOLATE	NO DOCKING			
DIHYDROMETHYSTICIN	3314 KCAL/MOL	LYS 408	1	YES
PODOPHYLLOTOXIN	3616 KCAL/MOL	ARG 371 THR 374	1 1	YES
KAVAIN	2528 KCAL/MOL	ASP 396	1	YES
DEOXYSCHIZANDRIN	NO DOCKING			
ISOLEUCINE	2046 KCAL/MOL	ARG 371	2	YES
GOMISIN	2866 KCAL/MOL	ASN 339	1	YES
YANGONIN	3202 KCAL/MOL	LYS 367	1	YES
ALLANTOIN	1980 KCAL/MOL	ARG 365	1	YES
BORNYLCAFFEATE	2500 KCAL/MOL	ARG 365	1	YES
DESMETHOXYANGONIN	2934 KCAL/MOL	LYS 349	1	YES
CINNAMIC ACID	NO DOCKING			
STIGMASTEROL	4268 KCAL/MOL	ASN 361	1	YES
PHENYLALANINE	2212 KCAL/MOL	ASP 396	2	YES
ROSMARINIC ACID	3598 KCAL/MOL	TYR 306 LYS 408 ARG 371	1 1 1	YES
PINORESINOL	3854 KCAL/MOL	LYS 322	1	YES

DCDC2



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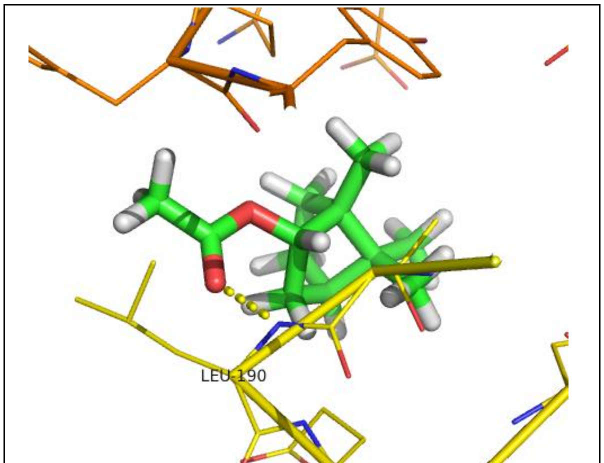

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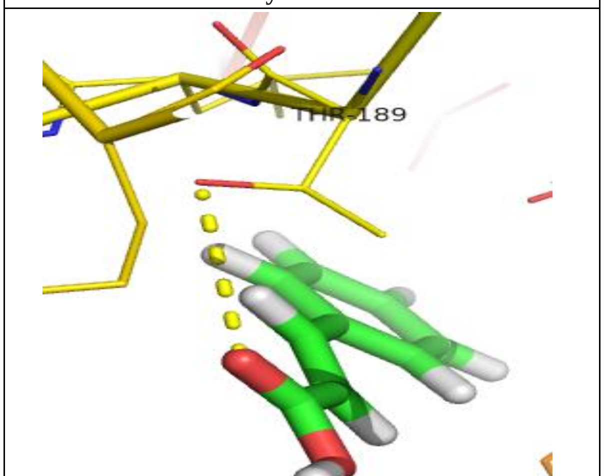

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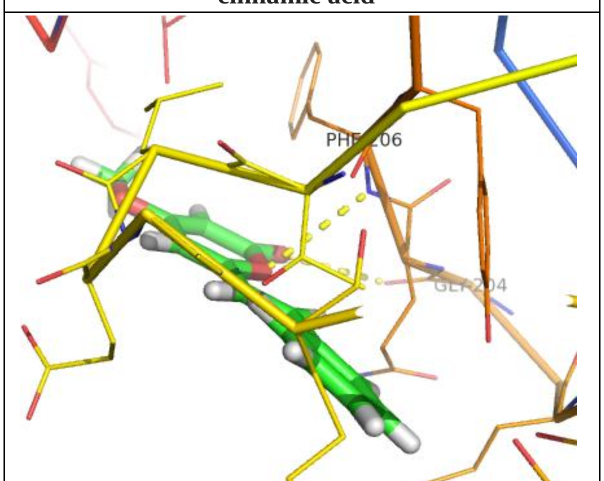

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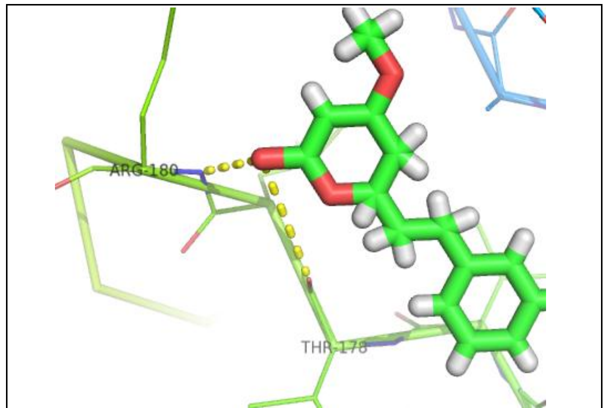

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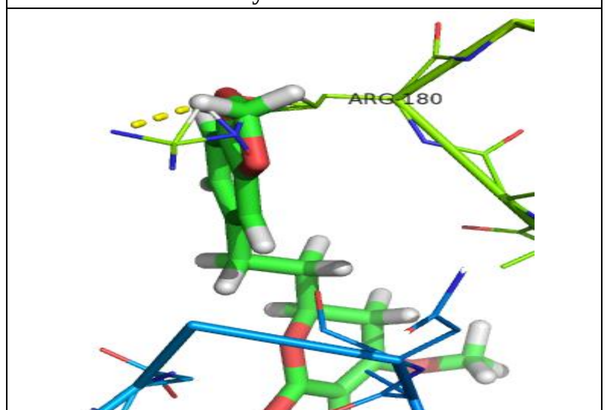

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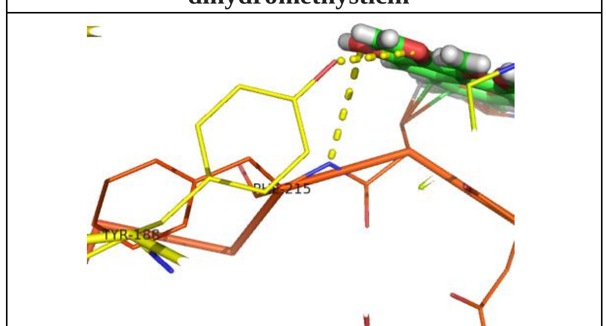

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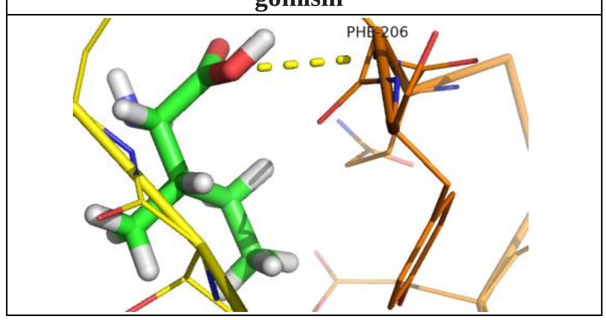

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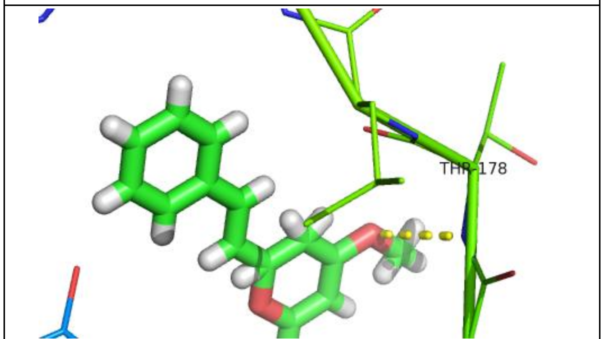
isoleucine



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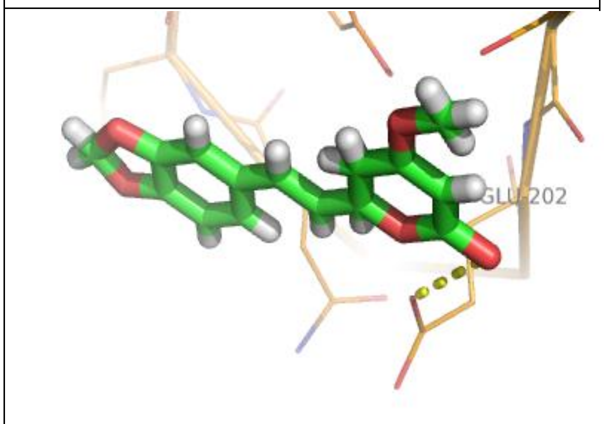

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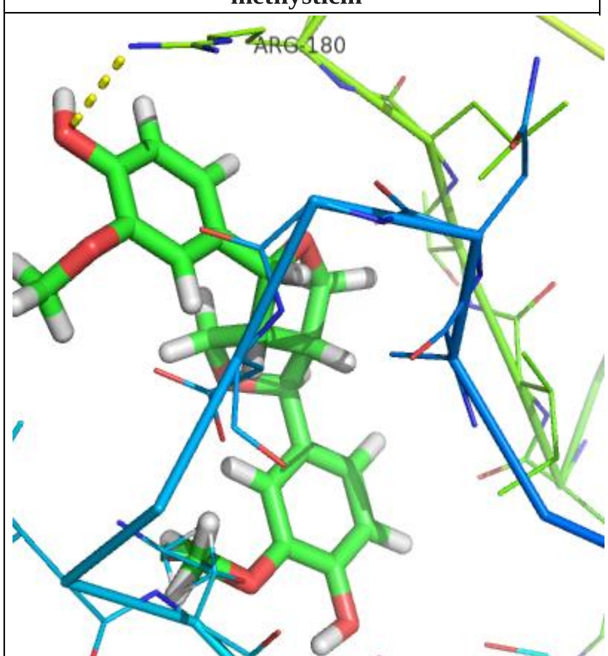

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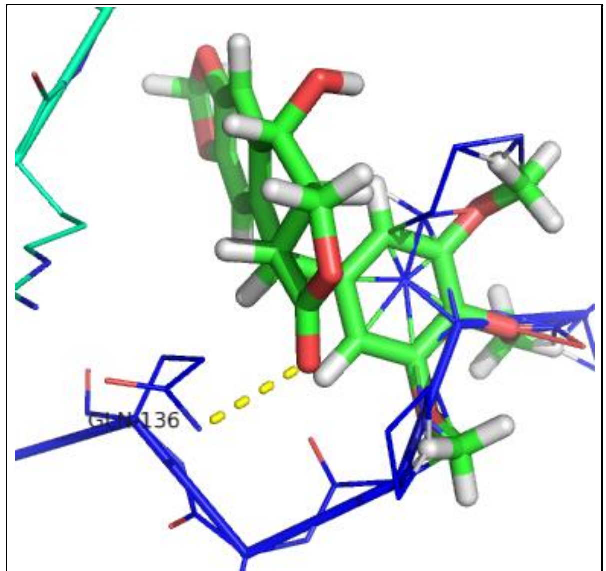

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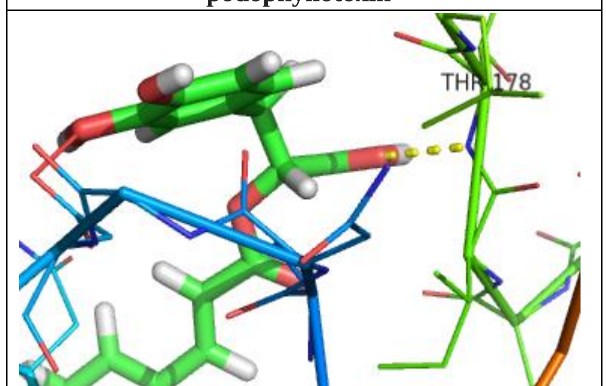

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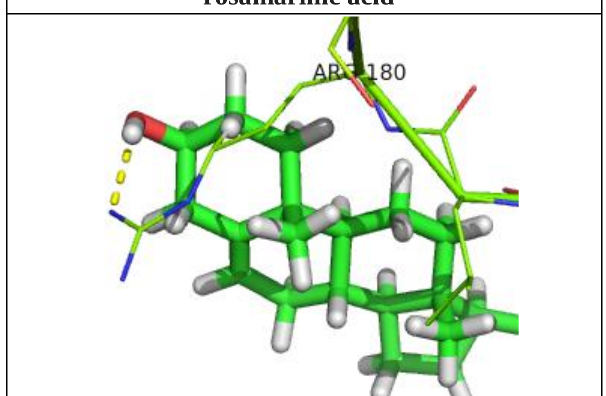

stigmasterol

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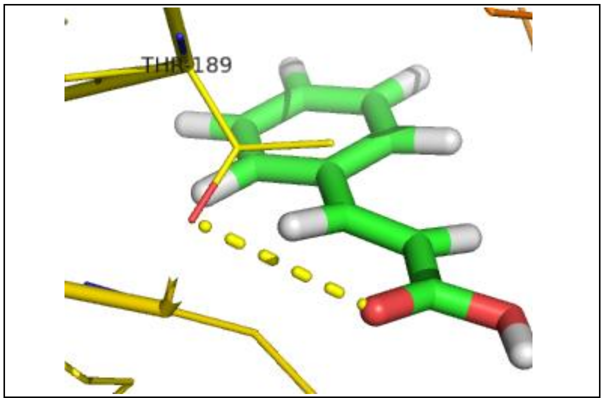

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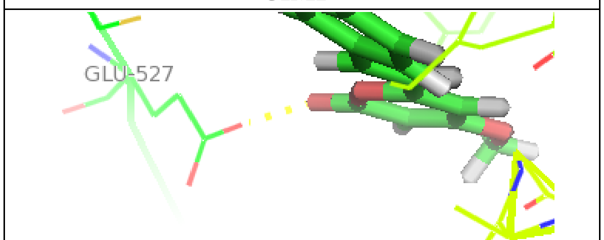
CIMP



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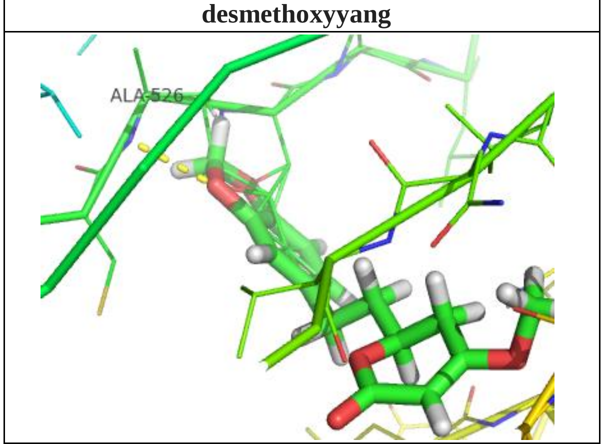

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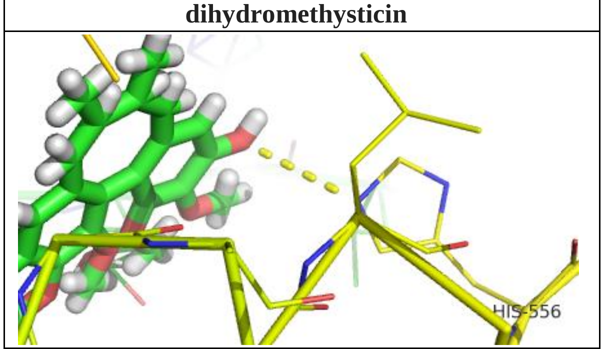

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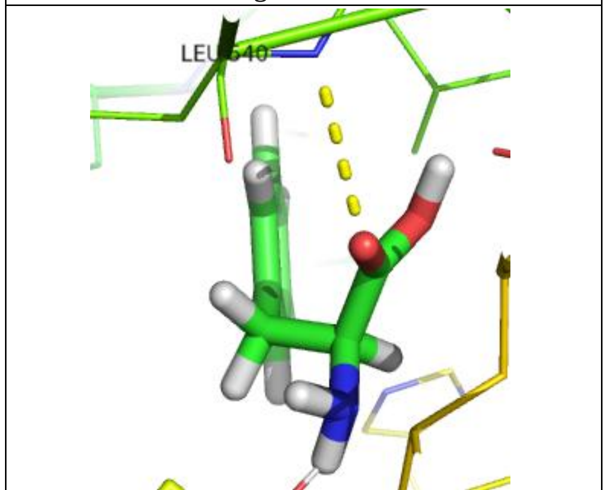

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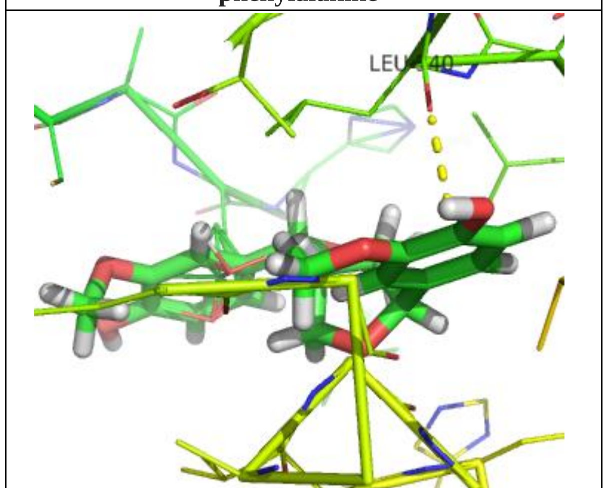

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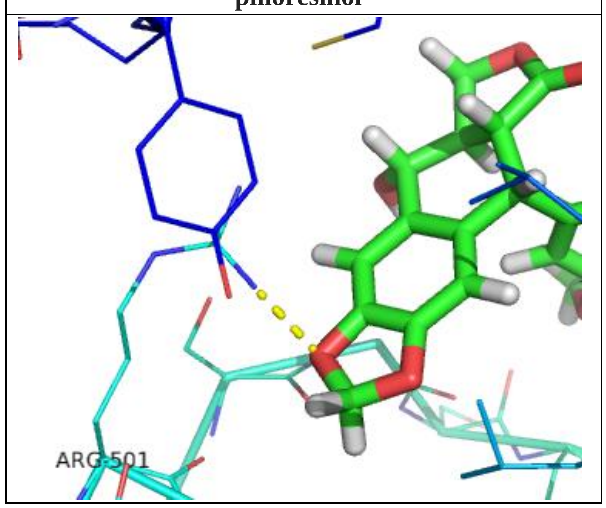

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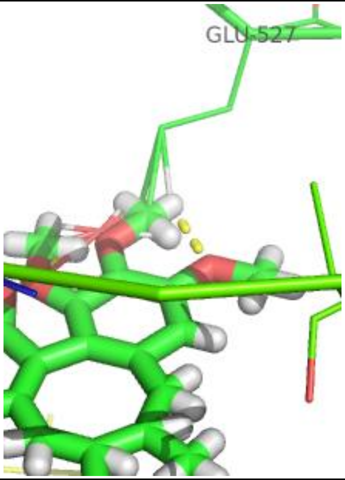
podophyllotoxin



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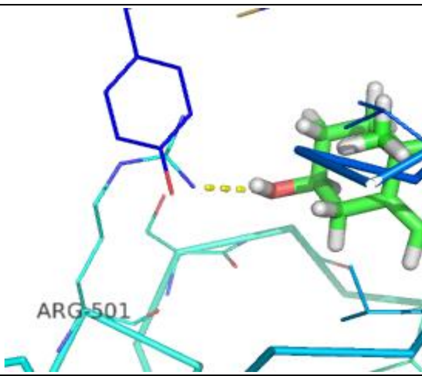

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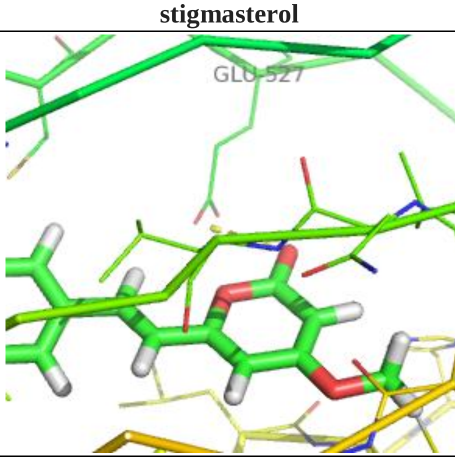

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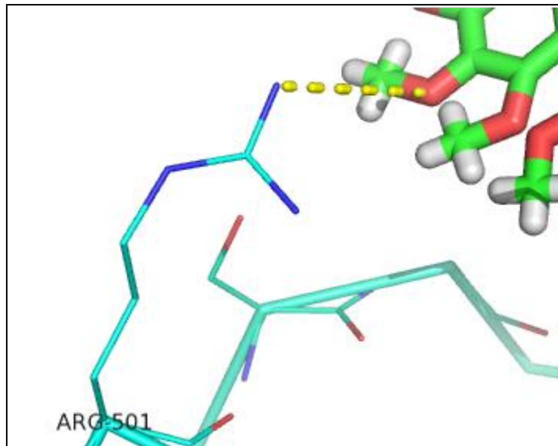
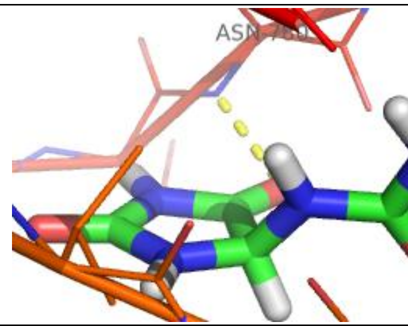


deoxyschizandrin

KIAA



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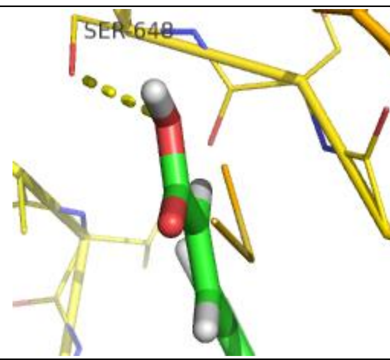

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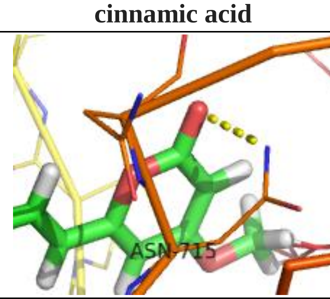

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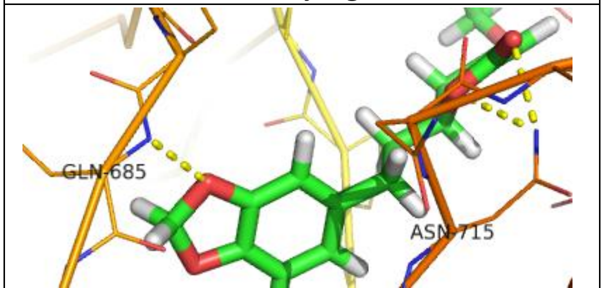

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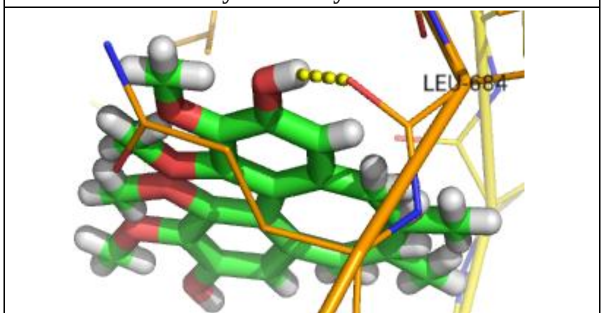

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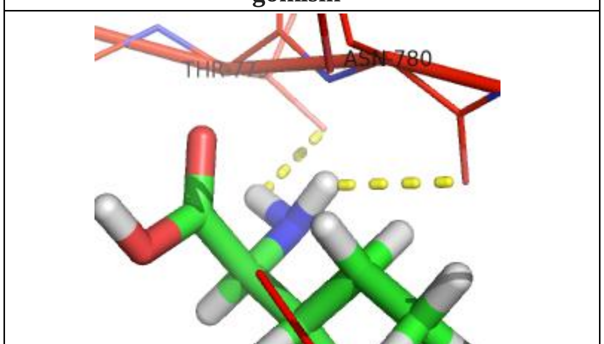

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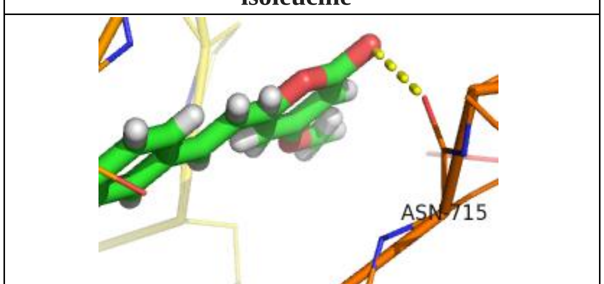

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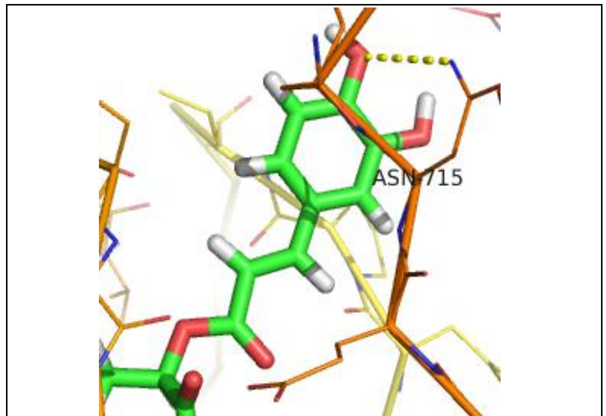

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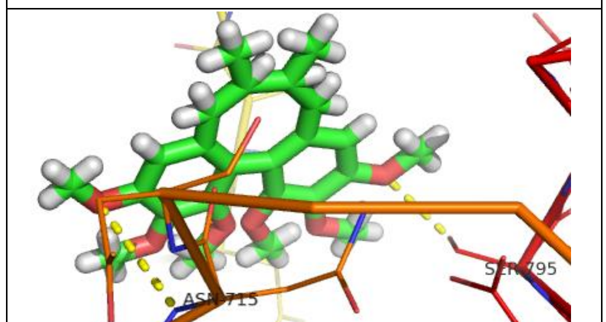
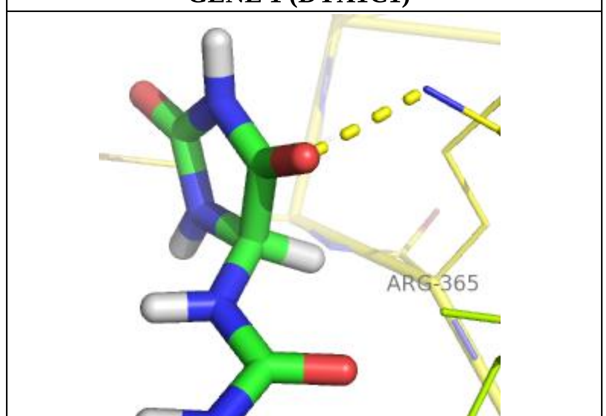


schizandrin

DYSLEXIA SUSCEPTIBILITY 1 CANDIDATE GENE 1 (DYX1C1)



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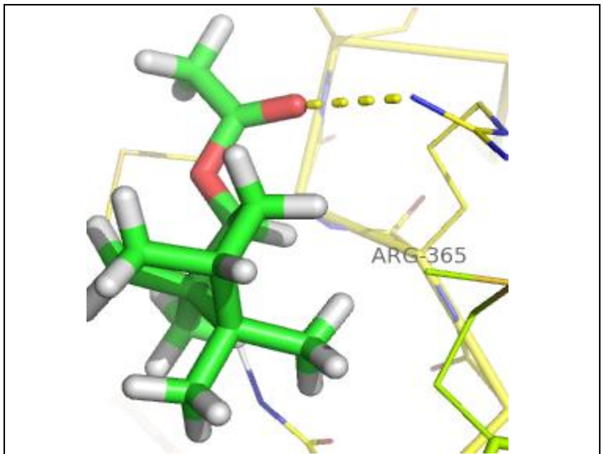

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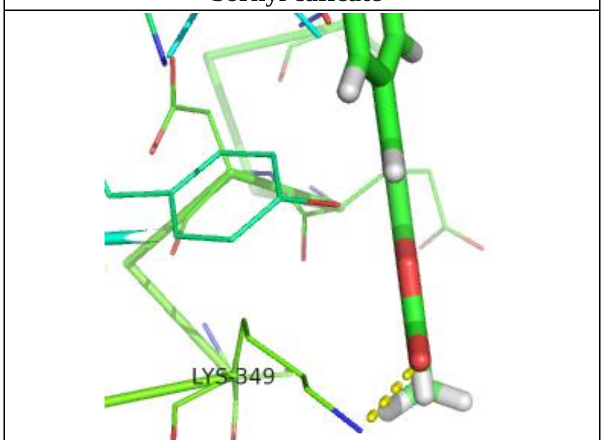

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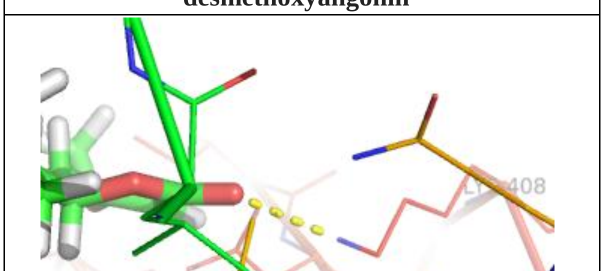

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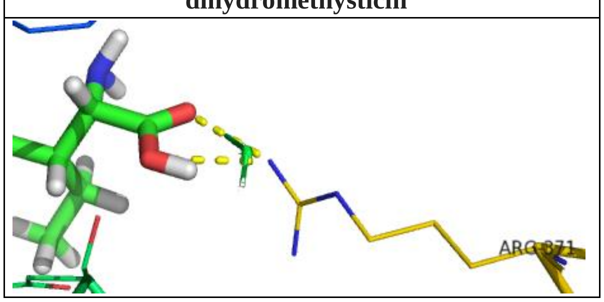

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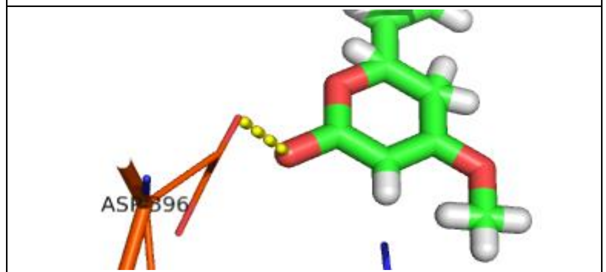

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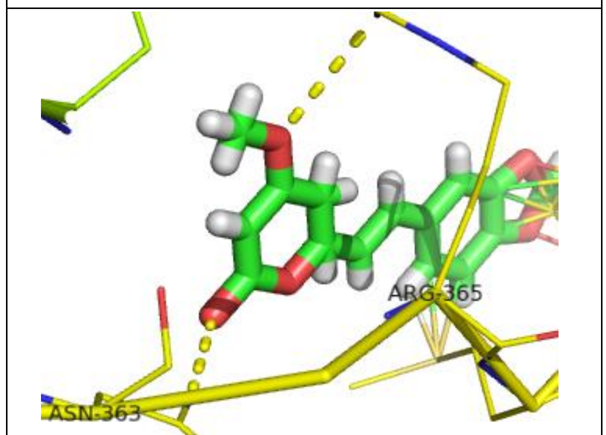

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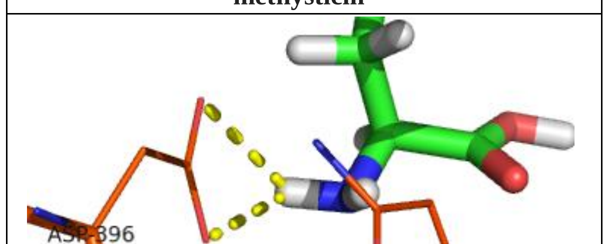
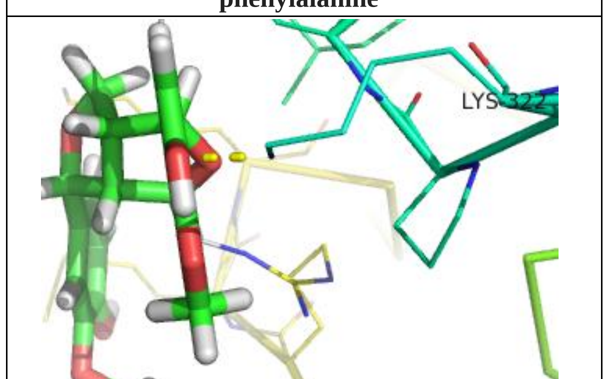
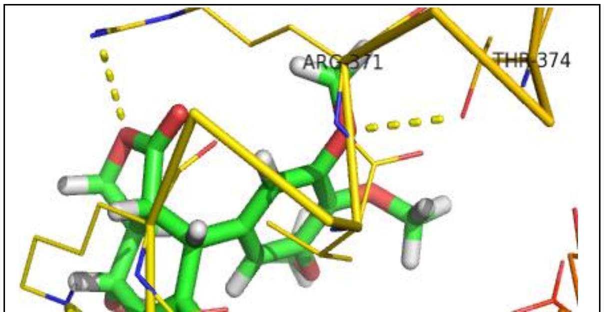


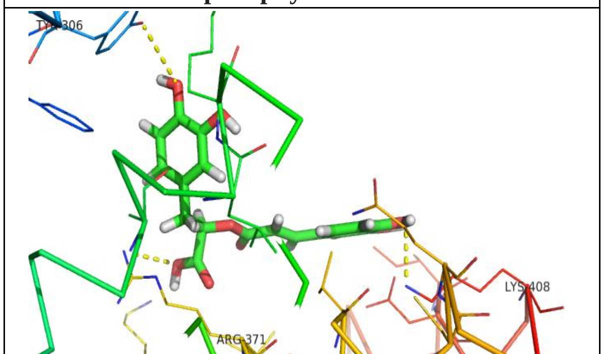
phenylalanine



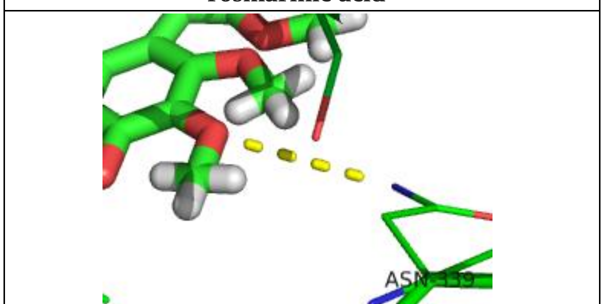
pinoresinol



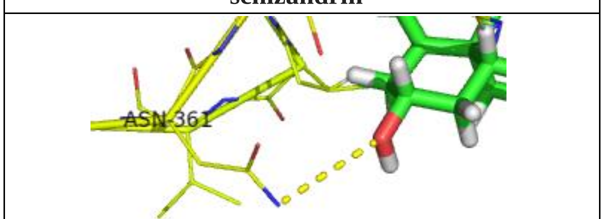
podophyllotoxin



rosmarinic acid



schizandrin



stigmasterol

Fig. 1: Docking images of the dyslexia receptors with the active compounds of the CNS herbs

It is seen that DCDC2 best interacts with desmethoxyangonin, dihydrokavain and gomisin.

It is seen that KIAA best docks with schizandrin, dihydromethysticin and isoleucine.

It is seen that CMIP docks with gomisin, podophyllotoxin, schizandrin, desmethoxyangonin, pinoresinol, stigmasterol, yangonin and phenylalanine.

It is seen that DYX1C1 docks best with methysticin, podophyllotoxin, isoleucine, phenylalanine and rosmarinic acid and has a good docking score and interaction with desmethoxyangonin.

IV CONCLUTION

It is seen that the compound desmethoxyangonin docks with all the receptors and has good interaction with all the receptors and hence selected as best ligand for dyslexia receptor proteins.

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