ISSN: 2348-8948
Vol: 2; Issue: 5

RESEARCH ARTICLE

Computational Analysis Studies On Chalcone Derivatives As Anticonvulsant Agent

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Date Received:	Date of Accepted:	Date Published:
16th Apr2014	25th Apr2014	12th May2014

Abstract:
In the present study, twenty eight compounds from literature were docked into receptor GABA 1AZM, compound XXVII was found to be most potent followed by XXII, XX, XXIV, XIX, XXVIII showed highest moldock score or low binding energy and good hydrogen bond interaction. Further *in silico* lipophillic profile were carried out using Marvin Sketch v 5.1 and found that compound XXVII followed by others possessed the entire theoretical drug like properties. Thus provide a way to synthesize such compounds and their derivatives and evaluate them for anticonvulsant activity *in vivo.*

Keywords:

Introduction

Drugs are typically discovered by chance in a trial-and-error manner using high-throughput screening methods that use *invitro* experiments to measure the activity of a large number of compounds against a given target. This process is very expensive and time consuming. Now a days *in silico* approach allows for a faster and cheaper identification of promising drug candidates by the virtual screening of compound databases. Afterward, lab experiments (synthesis), toxicological testing, clinical trials, and so forth can be conducted to further examine the drug candidates identified by the virtual screening process. Docking methods typically use an energy-based scoring function to identify the energetically most favorable ligand conformation when bound to the target.

The general hypothesis is that lower energy scores represent better protein-ligand bindings compared to higher energy values. Therefore, molecular docking can be formulated as an optimization problem, where the task is to find the ligand-binding mode with the lowest energy. In the present study, docking simulation was performed using Molegro software [1] with GABA(PDB-ID-1AZM) as the target [2] the known chalcone derivatives were docked into a receptor's binding site. Subsequently the compounds were screened for some physicochemical properties like partition coefficient, Molecular weight, Hydrogen bond donar and acceptor prediction to evaluate their bioavailability

METHODOLOGY-

The basic target of this simulation work is to investigate the interaction of synthesized chalcones with a receptor (PDB-1AZM).The Docking simulations were performed by Molegro Software (MVD-4.2) in which we considered Chalcones as ligand against 1AZM as target protein. Ligand dataset [3] under study were docked separately into the binding site of the receptor using Molegro. The binding site was constructed which consist of all residues that have at least one atom within 3.5 Å from any atom in the co-crystallized inhibitor. This generally gives a good representation of the important residues in the binding pocket for a protein target.[4] To determine the optimal geometry of the ligand binding mode is done by iteratively evaluating a number of candidate solutions (ligand conformations) and estimating the energy of their interactions with the targets. The Highest Scoring solutions (best poses of low-energy) are returned for further analysis.

Binding affinities of compounds into GABA

Compounds were ranked after docking according to their docking scores and were visualized inside the pocket to view their fitting and closure to main residues. Molecular docking studies were revealed further insight into the nature of interactions between the compounds and active site amino acid to rationalize the obtained biological results.

CALCULATIONS OF PHYSICOCHEMICAL PROPERTIES OF COMPOUND (I-XXVIII)

Bioavailability analysis is based upon the prediction of various physicochemical properties proposed by Lipinski's Rule of Five (RO5) [5] and Ghose et al, 1999 [6] Lipophilicity, quantified as WlogP was analyzed using weighted approach with the help of logP plugins of Marvin Sketch[7]. Topological Polar Surface Area (TPSA) was calculated using Polar Surface Area plugin of Marvin Sketch[8].

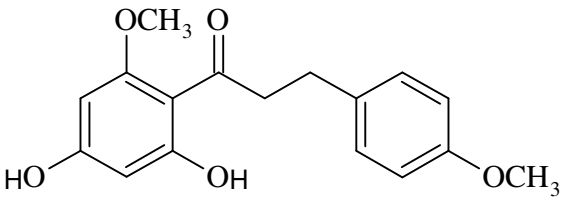
RESULTS AND DISCUSSION:

The ligand dataset was virtually screened with the protein targets using Molegro software and the binding energy values were analyzed for each docked conformation. Conformations having low energy and exhibited favorable hydrogen bonding with the amino acids side chain and its amide nitrogen was considered (Table 1). Binding energies of the protein-ligand interactions are important to describe how fit the ligand binds to the target macromolecule. Docking simulations of Chalcone against 1AZM protein target resulted in few best compounds that were evaluated based on the binding compatibility [docked energy (kcal/mol)] with the receptor. Ligand XXVII have higher binding affinity with the cavity present in GABA possessed the better energy (-124.31 kcal/mol) value than the others (Fig.1). From this analysis, it is evident that this compound may exhibit better interaction than other inhibitors. Besides the better interaction with the receptor, the compound should possess acceptable physical properties and chemical functionalities in order to participate in lead optimization and selection of drug discovery process. Lipinski's RO5 and Ghose et al, 1999 profiling for drug likeness were carried out for the dataset. Compounds under study had a molecular weight of less than 500 which suggested better absorption and low level of allergic reactions. Hydrogen bond donors and acceptors were less than 8. WlogP values of dataset were found to be less than 5 which predicted low level of toxicity, non-specific binding and possible oral administration [9]. but of certain compounds found to be high. **(TableII)**

Conclusion-

Protein-ligand interactions play a significant role in structural based drug discovery and designing. In the present work chalcone compounds were docked with the receptor's active sites. Compound XXVII(-124.31 kcal/mol) followed by XXII, XX, XXIV, XIX, XXVIII showed highest moldock score or low binding energy and good hydrogen bond interaction. Further *in silico* lipophillic profile were carried out using Marvin Sketch v 5.1 and found that compound XXVII followed by others possessed the entire theoretical drug like properties. Thus provide a way to synthesize such compounds and their derivatives in future.

Structure of compounds



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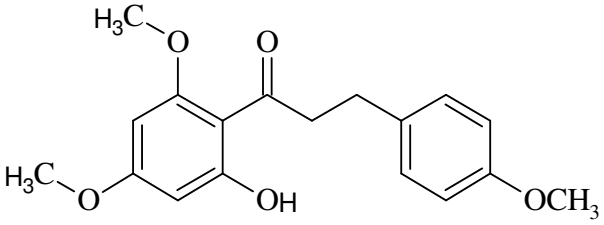

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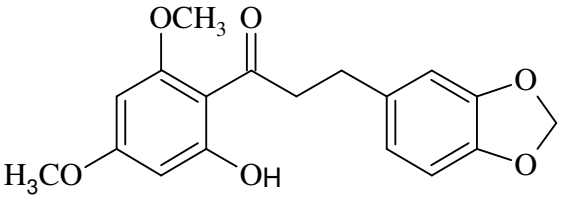

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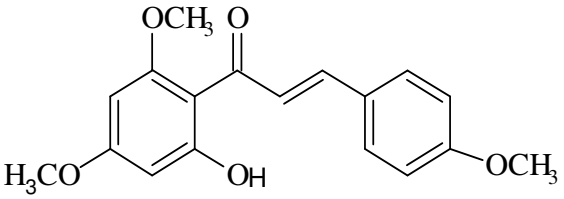

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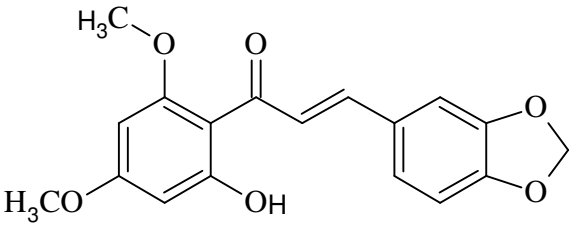

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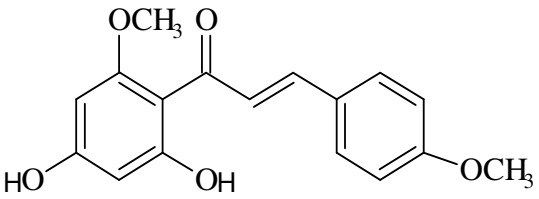

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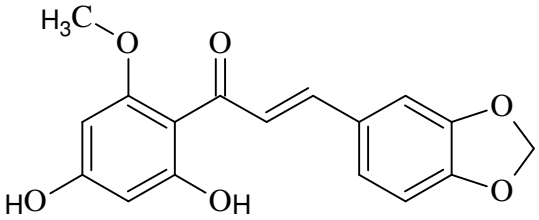

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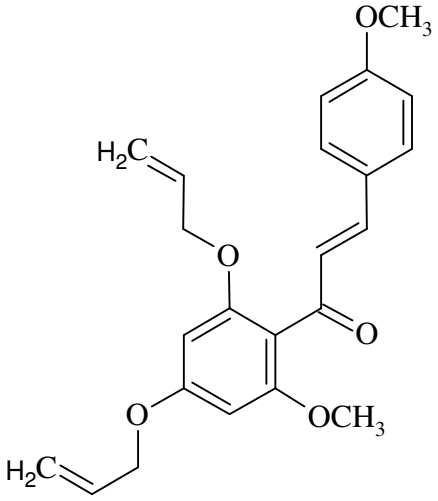

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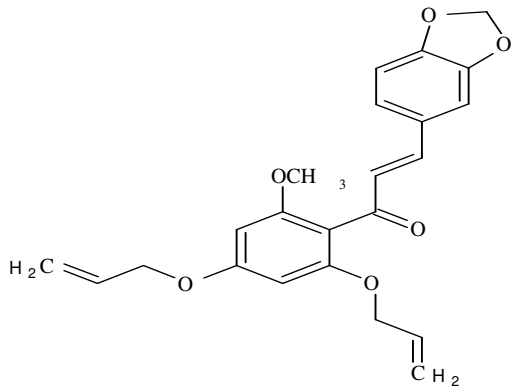

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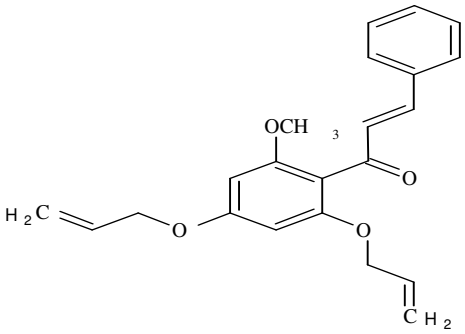

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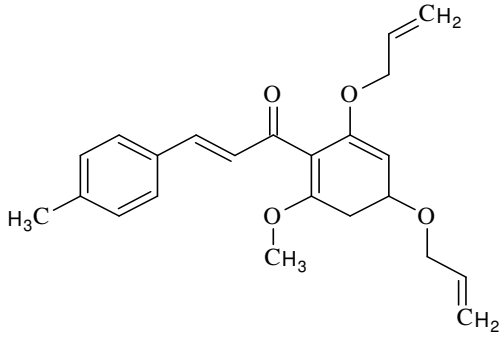

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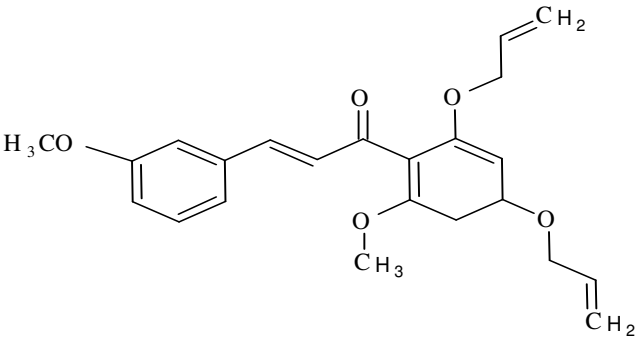

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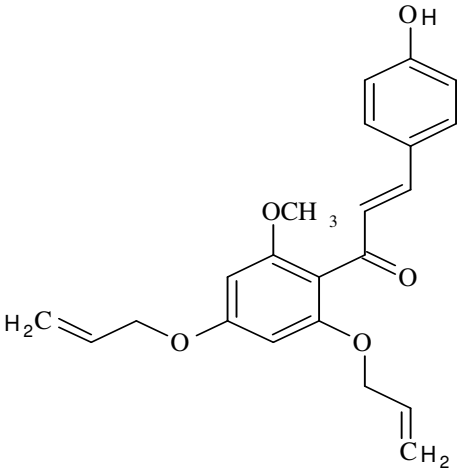

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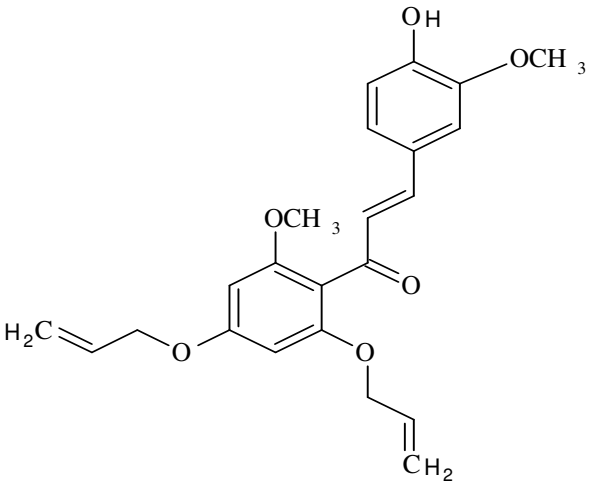

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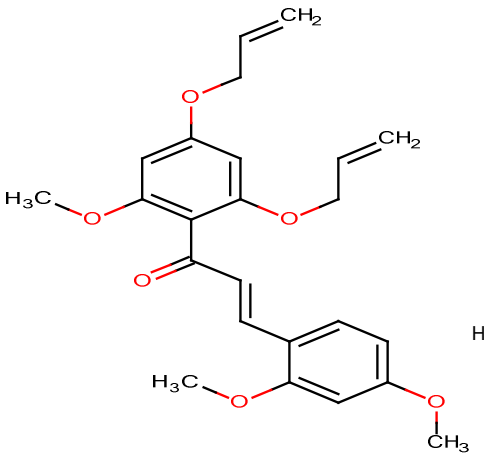

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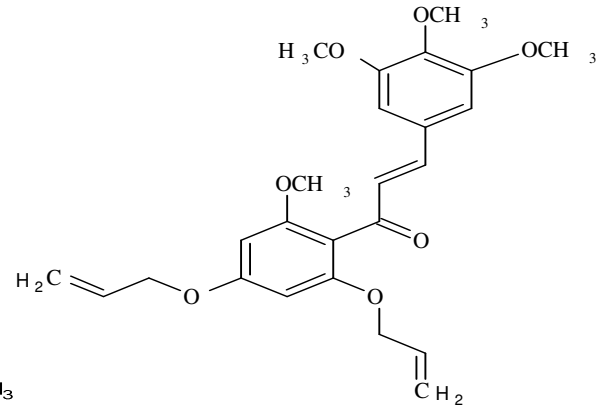

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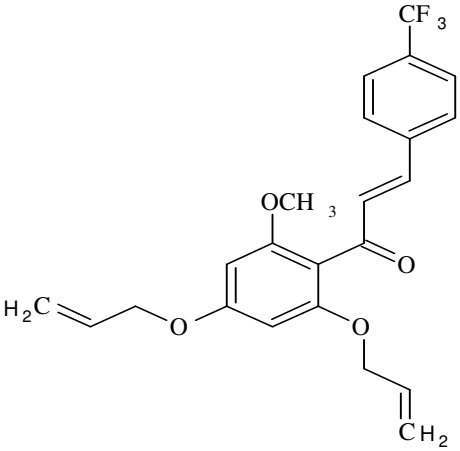

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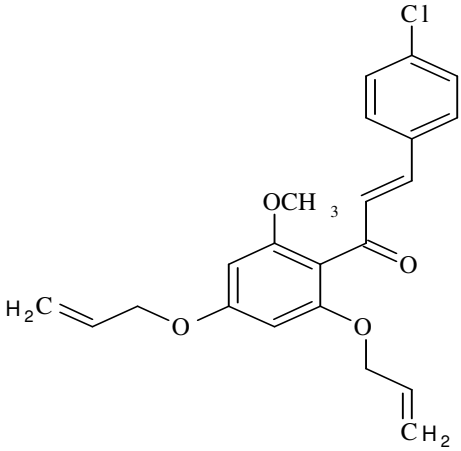

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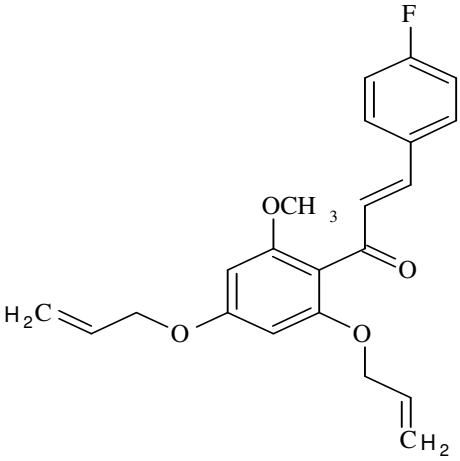

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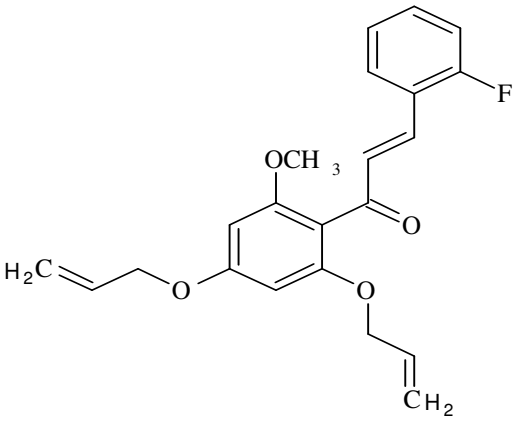

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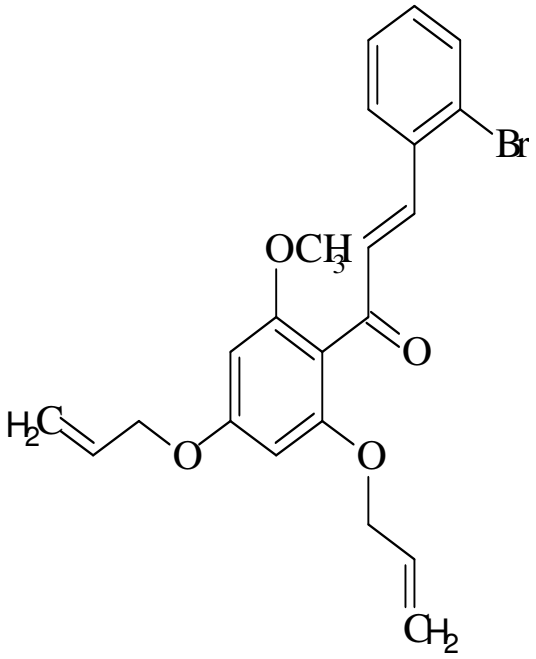

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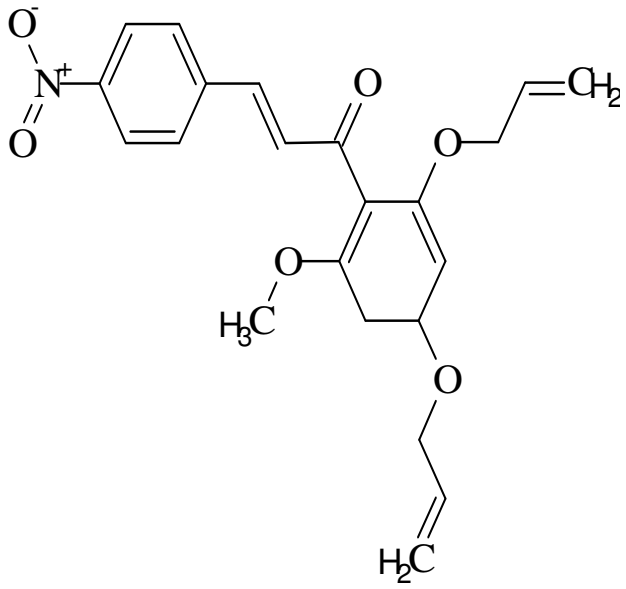

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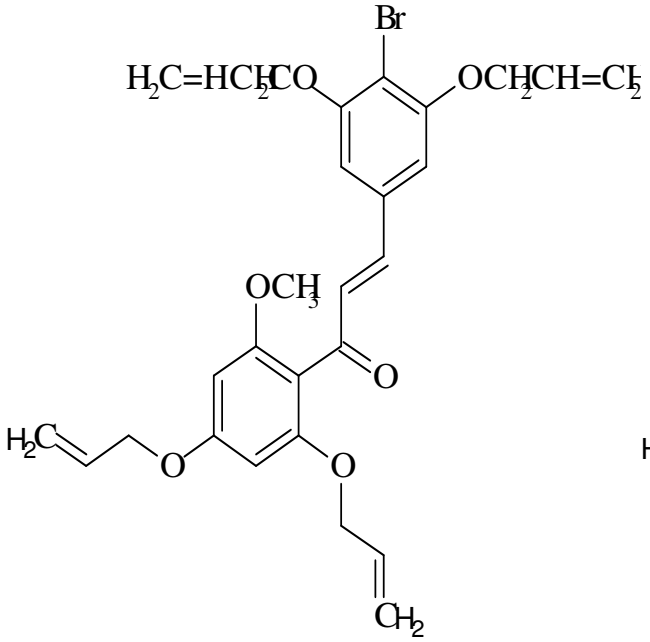

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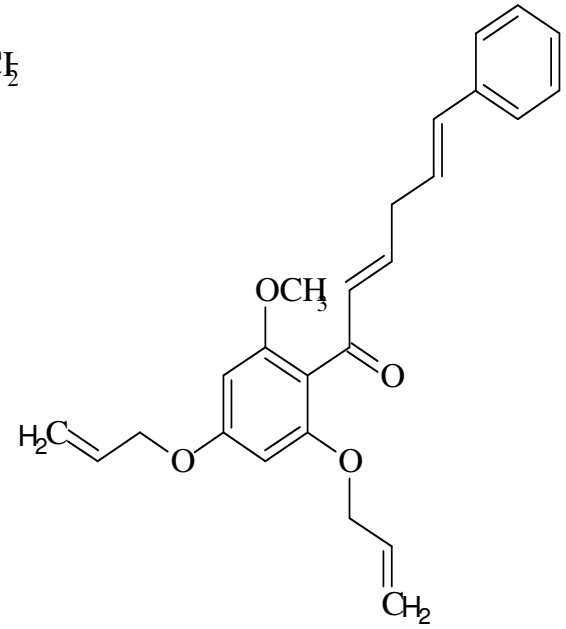

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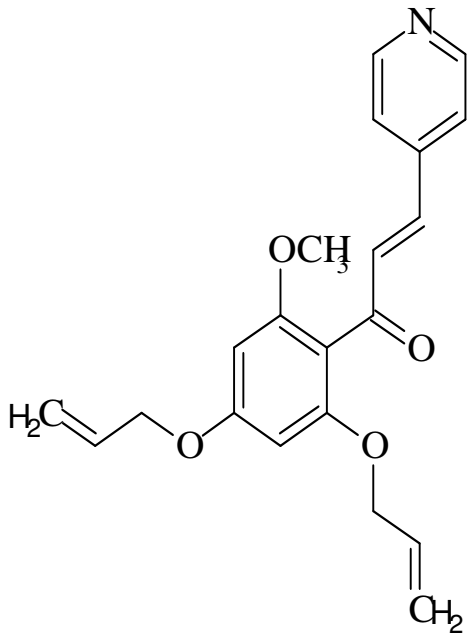

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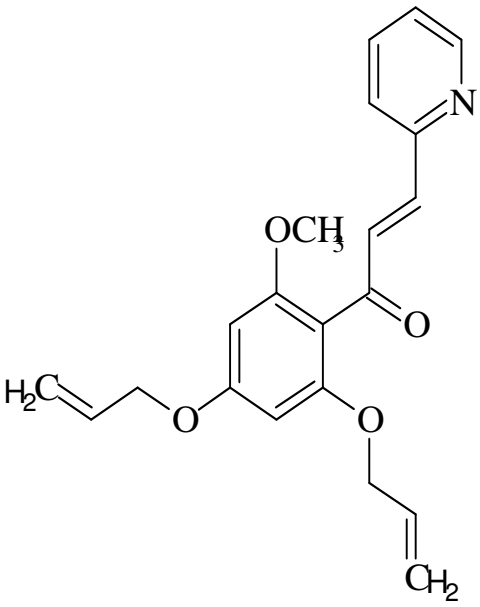

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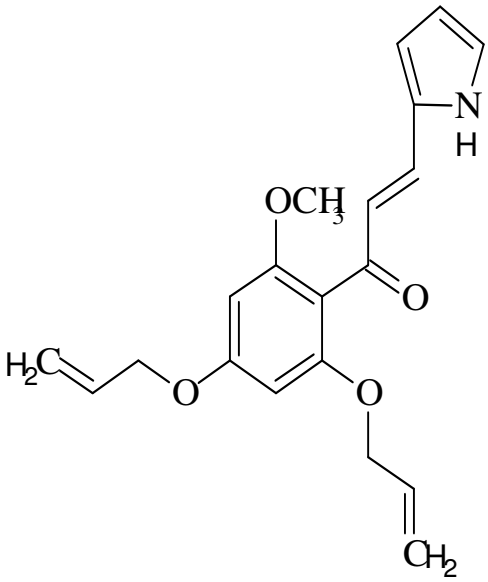

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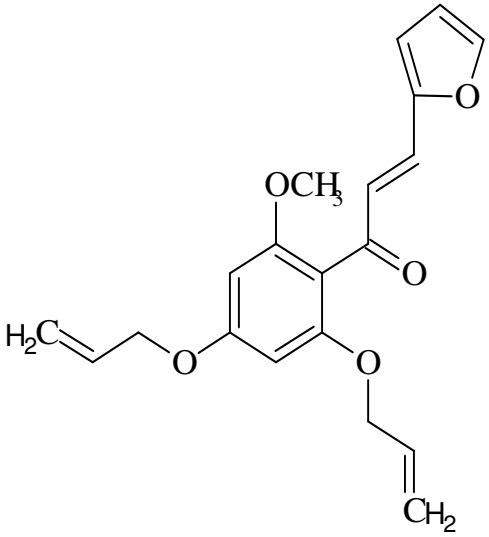

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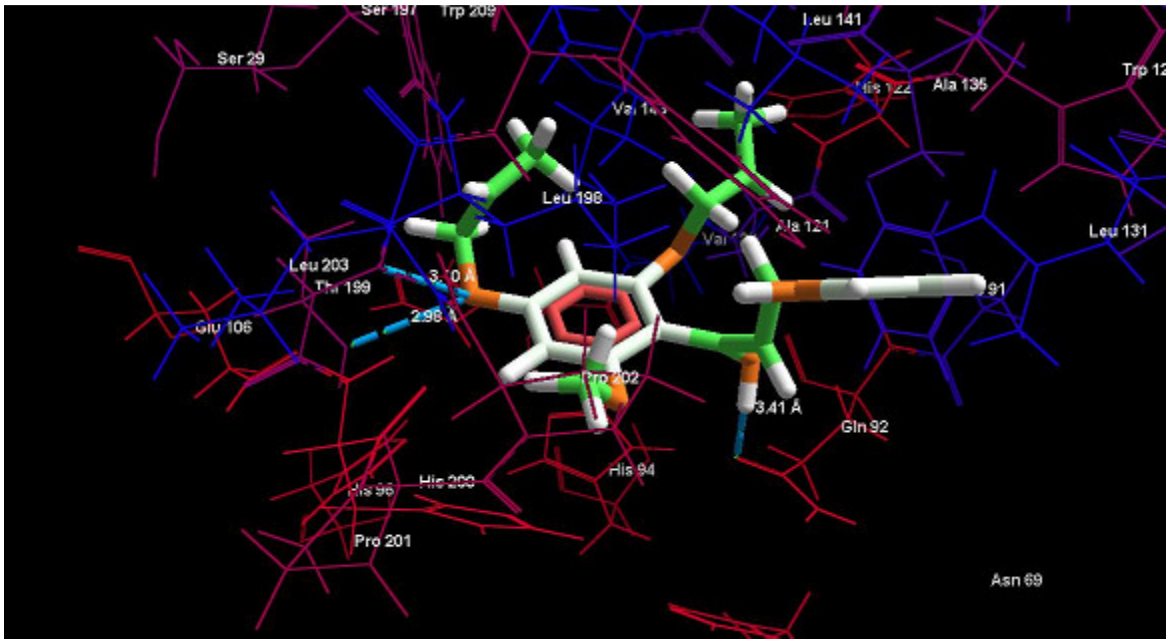
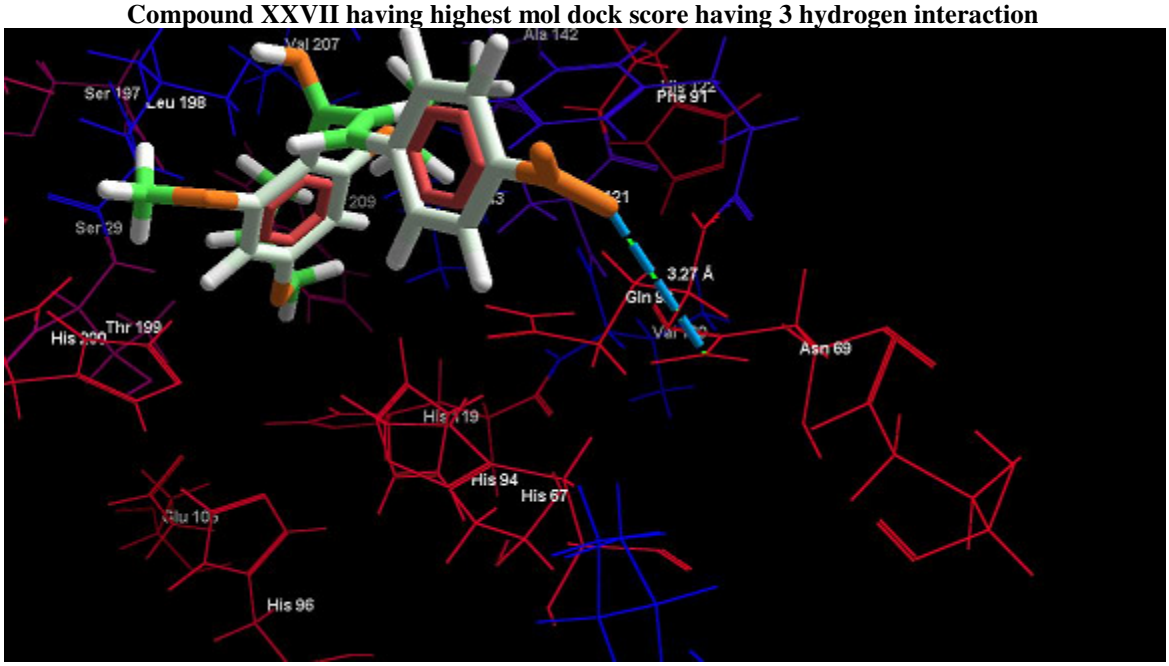


Compound XXVII having highest mol dock score having 3 hydrogen interaction



Compound XXII having good mol dock score but least number of interactions.

Table I-showing Docking Results of Compounds I- XXVIII

COMPOUND NO.	Mol Dock Score	No. of interactions	Amino acid Residue	Distance	COMPOUND NO.	Mol Dock Score	No. of interactions	Amino acid Residue	Distance
I	-96.078	2	Thr 139 Thr 199	2.60 2.80	IX	-93.82	4	Thr 199 Thr 199 Thr 199 Thr 199	3.25 3.25 3.00 3.00
II	-112.53	2	Thr 199 Thr 199	2.95 2.63	X	-110.75	3	Gln 92 Thr 199 Thr 199	2.71 3.36 3.07
III	-105.216	2	Thr 199 Thr 199	2.33 2.72	XI	-72.092	5	His 200 His 200 His 200 Thr 199 Thr 199	3.34 3.25 3.21 2.67 2.66
IV	-92.49	3	Gln 92 Thr 199 Thr 199	3.14 2.84 2.66	XII	-98.19	3	His 67 Thr 199 Thr 199	3.40 3.12 2.95
V	-101.24	3	Thr 199 Thr 199 Gln 92	3.23 3.10 3.11	XIII	-101.29	2	Thr 199 Thr 199	3.14 3.20
VI	-105.09	4	His 200 Gln 92 Thr 199 Thr 199	2.90 2.86 2.85 3.08	XIV	-85.57	5	His 200 Thr 199 Thr 199 His 119 Leu 131	3.10 2.77 3.18 3.29 3.22
VII	-111.18	4	Thr 199 Thr 199 His 200 Gln 92	2.98 3.03 2.85 2.75	XV	-100.55	1	Thr 199	3.12
VIII	-90.45	2	Thr 199 Thr 199	3.06 2.53					

COMPOUND NO.	Mol Dock Score	No. of interactions	Amino acid Residue	Distance	COMPOUND NO.	Mol Dock Score	No. of interactions	Amino acid Residue	Distance
XVI	-96.28	4	Thr 199 Thr 199 Thr 199 His 200	3.03 3.10 3.05 3.23	XXIII	-81.098	1	Thr 199	3.57
XVII	-102.67	1	His 119	3.52	XXIV	-112.15	3	Gln 92 Thr 199 Thr 199	2.39 3.29 3.54
XVIII	-103.26	1	His 199	3.57	XXV	-103.11	3	Gln 92 Thr 199 Thr 199	3.16 3.38 3.15
XIX	-114.069	3	Gln 92 Thr 199 Thr 199	2.50 3.02 3.08	XXVI	-107.34	4	His 200 His 200 Thr 199 Thr 199	3.10 3.29 2.60 3.12
XX	-114.02	2	Thr 199 Thr 199	3.15 3.41	XXVII	-124.31	3	Gln 92 Thr 199 Thr 199	3.41 3.10 2.98
XXI	-100.80	2	Gln 92 Thr 199	2.67 3.10	XXVIII	-109.15	3	Gln 92 Thr 199 Thr 199	3.31 3.12 2.94
XXII	-114.88	1	Asn 69	3.27					

*Compound XXVIIexhibited high binding energy (Mol dock score) with 3 number of hydrogen interaction

Table II- *in silico* bioavailability analysis of Chalcones

Compound No.	HD	HA	WlogP	MW	TPSA
I	2	5	3.54	302.11	75.99
II	1	5	3.68	316.34	64.99
III	1	6	3.46	330.1	74.22
IV	1	5	3.76	314.1	64.99
V	1	6	3.54	328.09	74.22
VI	2	5	3.62	300.09	75.99
VII	2	6	3.40	314.07	85.22
VIII	0	5	4.72	380.16	53.99
IX	0	6	4.50	394.14	63.22
X	0	4	4.88	350.15	44.76
XI	0	4	5.39	364.16	44.76
XII	0	5	4.72	380.16	53.99
XIII	1	5	4.58	366.14	64.99
XIV	1	6	4.42	396.15	74.22
XV	0	5	4.72	380.16	53.99
XVI	0	7	4.41	440.18	72.45
XVII	0	4	5.76	418.13	44.76
XVIII	0	5	5.48	384.11	44.76
XIX	0	4	5.02	368.14	44.76
XX	0	4	5.02	368.14	44.76
XXI	0	4	5.65	428.06	44.76
XXII	0	6	4.82	395.40	90.58
XXIII	0	6	6.80	540.11	63.22
XXIV	0	4	5.85	390.18	44.76
XXV	0	5	3.66	351.14	57.65
XXVI	0	5	3.90	351.14	57.65
XXVII	1	4	3.88	339.14	60.55
XXVIII	0	4	3.94	340.13	57.90

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