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Computational Evaluation of the Druggability and Biological Activity of Iodo-1,4-dihydropyridine Derivatives

Salma, A., El Sherbeni*, Tarek, F., El Moselhy

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Tanta University, 31527, Tanta, Egypt

Abstract Several successful antihypertensive medicines already in clinical use are derivatives of 1,4-dihydropyridine (1,4-DHP). They are considered the most potent calcium channel blockers of which, nitro-, chloro- and fluro-1,4-DHP derivatives have been extensively investigated for biological activity [1-5]. Nevertheless, iodo-1,4-DHP derivatives have not received enough attention. Our aims were to evaluate the druglikeness and bioactivity of a new series of 2- & 3-iodophenyl-2,6-dimethyl-1,4-dihydropyridine derivatives using Molispiration software, as well as to dock these derivatives into the active domain of proteins [ion channel modulator (5KMH) and nuclear receptor ligand (5EWM)] using Molegro virtual docker. The compounds 2f, 2i, 2n, 3i and 3n were found to obey Lipinski's rule and its extension and show good drug likeness, indicating good potential gastrointestinal permeability. Also, the bioactivity towards G protein–coupled receptors, ion channel, kinase, nuclear receptor and other enzyme targets was estimated for the tested compounds. The compounds 2c, 2h, 2m, 3c, 3h and 3m gave good docking scores especially against both ion channel modulator and nuclear receptor ligand, whereas, the other compounds had moderate bioactivities. In conclusion, iodo-1,4-DHP derivatives give good druglikness and *in silico* bioactivity that justify subsequent synthesis and *in vivo* testing of these compounds.

Keywords druglikeness, bioactivity, docking studies, 1,4-dihydropyridine

1. Introduction

Derivatives of 1,4-dihydropyridine (1,4-DHP) have been previously reported to have several valuable biological activities [1-5]. Their biological activities include vasodilative, antihypertensive, hepatoprotective, bronchodilator, antiatherosclerotive, antitumour, antimutagenic, antidiabetic, geroprotective and antiplatelet aggregation activity [15]. Also, it was found that 1,4-DHP derivatives can selectively modulate diverse receptors, channels and enzymes. As a result, 1,4-DHP scaffold has been proved to be a successful treatment for different diseases by a single-ligand multitarget approach [13]. Previously, nitro-, chloro- and fluoro-1,4-DHP derivatives have been screened [1-5], leading to numerous second generation commercial products [8-11] of which some have passed the clinical trials and approved for clinical use. The most important 1,4-DHP-centered clinically approved medicines are dipines [8-11], such as nimodipine, nisodipine, nitrendipine and amlodopine, successfully used as anti-hypertensive agents due to their calcium channel blocking activity.

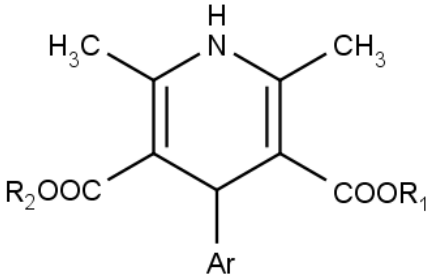
On the other hand, iodo derivatives of 1,4-DHPs were out of the focus of drug discovery; to our knowledge, no previous studies investigated the druggability and bioactivity of these derivatives. The concept of druggability is defined as the prospect to find a compound with high potency, drug-like properties, as well as measured properties concerning to undesirable side effects, metabolism and intestinal absorption. It was observed that about 30% of oral

drugs fail in development due to poor pharmacokinetics studies [18]. It is worth to note that lack of *in vivo* effectiveness of a drug candidate might be due to poor physicochemical properties of the drug candidate itself [18].
In addition, bioactivity can be predicted by studying whether the tested compounds are complementary with the binding sites on biological molecules in terms of topology, volume and physicochemical properties [20]. That's to say, it is useful to estimate the probability that molecules can bind a given protein with sufficient affinity in order to modify its activity [21]. So, computational screening of new compounds, i.e. the *in silico* prediction of druglikeness and bioactivity, has been proved to be very important in the early stage of drug discovery to subject the most suitable compounds to further optimization, and to find drug candidates for further clinical development [23].
In the current study, we investigated the druggability and *in silico* bioactivity of 2- & 3-iodophenyl-2,6-dimethyl-1,4-dihydropyridine derivatives comparable to other 1,4-DHP derivatives. Subsequently, 1,4-DHP derivatives were studied for several ligand-protein interactions to determine how the iodo-1,4-DHP derivatives would exert their blocking activity. In this study, we aim to get the required proofs rationalize the further chemical synthesis and the *in vivo* testing, leading to the development of new iodo-1,4-DHP based medicinal agents that could be superior agents in terms of efficacy and safety**.**

2. Materials and Methods

2.1. The estimation of druglikeness of 1,4-dihydropyridine derivatives

A set of thirty compounds of iodo 1,4-DHPs, nefidipine, nitredipine and felodipine [1] were suggested for this work and given in Scheme 1. The physicochemical properties and bioactivity were calculated using Molinspiration software (www. Molinspiration.com).
The druglikeness was evaluated through calculating the properties that constitute Lipinski, Ghose and Veber rules using Molinspiration software (www. Molinspiration.com). Briefly, The "rule of 5" (RO5) and its completion (Ghose and Veber rules) supply a heuristic indicator for determining if a compound will be orally bioavailable. These rules have often been correlated to log P, molecular weight (MW) and number of hydrogen bond acceptors and donors in a molecule. The Lipinski`s rule (RO5) states that molecules exhibit good absorption or permeation when they have an octanol-water partition coefficient (Milog P) < 5, molecular weight (MW) < 500, number hydrogen bond donors (n OHNH) ≤ 5, number hydrogen bond acceptor (n ON) ≤ 10. The work was prolonged by Ghose et al. to setup qualifying ranges for a log P (-0.4 to 5.6) [25], molecular weight (160 to 480), and number of atoms (20 to 70). A study carried by Veber (24) on rats elucidate that molecular flexibility, topological polar surface area (PSA) and hydrogen bond count are significant determinants for oral bioavailability. Veber`s rules for good bioavailability in rats: rotatable bonds ≤ 10, topological polar surface area (PSA) ≤ 140 Å2 and total H bond donors and acceptors ≤ 12.



2-iodophenyl-			3-iodophenyl-		
Comp. No.	**R_1**	**R_2**	**Comp. No.**	**R_1**	**R_2**
2a	$CH(CH_3)_2$	$CH(CH_3)_2$	3a	$CH(CH_3)_2$	$CH(CH_3)_2$
2b	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	3b	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$
2c	$C(CH_3)_3$	$C(CH_3)_3$	3c	$C(CH_3)_3$	$C(CH_3)_3$
2d	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$	3d	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$
2e	$CH_2C_6H_5$	$CH_2C_6H_5$	3e	$CH_2C_6H_5$	$CH_2C_6H_5$

2f	CH_3	$CH(CH_3)_2$	3f	CH_3	$CH(CH_3)_2$
2g	CH_3	$CH_2CH(CH_3)_2$	3g	CH_3	$CH_2CH(CH_3)_2$
2h	CH_3	$C(CH_3)_3$	3h	CH_3	$C(CH_3)_3$
2i	CH_3	$CH_2CH_2OCH_3$	3i	CH_3	$CH_2CH_2OCH_3$
2j	CH_3	$CH_2C_6H_5$	3j	CH_3	$CH_2C_6H_5$
2k	CH_2CH_3	$CH(CH_3)_2$	3k	CH_2CH_3	$CH(CH_3)_2$
2l	CH_2CH_3	$CH_2CH(CH_3)_2$	3l	CH_2CH_3	$CH_2CH(CH_3)_2$
2m	CH_2CH_3	$C(CH_3)_3$	3m	CH_2CH_3	$C(CH_3)_3$
2n	CH_2CH_3	$CH_2CH_2OCH_3$	3n	CH_2CH_3	$CH_2CH_2OCH_3$
2o	CH_2CH_3	$CH_2C_6H_5$	3o	CH_2CH_3	$CH_2C_6H_5$

Compound	R_1	R_2	Ar
Nefidipine	CH_3	CH_3	2-nitrophenyl-
Nitredipine	CH_3	CH_2CH_3	3-nitrophenyl-
Felodipine	CH_3	CH_2CH_3	2,3-dichlorophenyl-

Scheme 1: Structures of 2-iodophenyl-1,4-dihydropyridine (2a-o) and 3-iodophenyl-1,4-dihydropyridine (3a-o), nifedipine, nitredipine and felodipine

2.2. Bioactivity Score

Bioactivity of the compounds was predicted by calculating the activity score toward G protein coupled receptors (GPCR ligand), ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor with the help of software Molinspiration score online.

2.3. Molecular Docking Studies

Three-dimensional crystal structures of the selected proteins were downloaded from Protein Data Bank (PDB) (http://www.rcsb.org/): ion channel modulator (5KMH) and nuclear receptor ligand (5EWM). All PDB's proteins were loaded in the Molegro virtual docker V6.0 (MVD) with elimination of all water molecules and cofactors. Standard Molegro algorithm was applied for setting up the input structures.

The structures of ligands were drawn and energy minimized using Marvin Sketch V5.1.3 [26], then saved as Mol2 file format. For docking, these compounds were allowed to interact with the proposed proteins utilizing Molegro Virtual Docker V6.0 (MVD), in order to identify the most active conformer.

Flexible ligand models were applied for docking and post docking geometry optimizations using Molegro Virtual Docker V6.0 (MVD). This program uses a grid-based scheme for energies of individual atoms, allowing a rapid computation of the interaction energy of the protein-ligand complex as the interaction between the ligand and the grid.

A docking sphere (20 Å radius) was set on the binding sites of each protein structure in order to allow various orientations of each ligand to be searched in the binding cavities. Molecular docking scores of the poses were then compared to each other and to nifedipine.

3. Results and Discussion

3.1. Evaluation of Druglikeness

Druglikeness can be concluded as a balance between molecular properties and structure features of molecules which influence their absorption, distribution, metabolism, and excretion (ADME) in human body and finally determine how druglike they are. Molecular properties such as bioavailability and membrane permeability are always related with some basic molecular descriptors such as logP (partition coefficient), molecular weight (MW) [30], topological polar surface area (TPSA), or hydrogen bond acceptors and donors counts in a molecule.

The lipophilicity is potentially connected to toxicity, which is in harmony with the observation that lipophilic binding is non-specific, whereas polar binding is linked to specificity and therefore selectivity.

The results from **Table1** and **Table 2** reveal that the compounds 2f, 2i, 2n, 3i and 3n obeyed the rules and showed good druglikeness score. The logP value of a compound is a well-established measure of the compound's hydrophilicity. It has been shown that our compounds have a reasonable probability of good absorption, their logP

value ranged between 3.99 to 4.93 that is not exceed 5.0. Topoligical polar surface area (TPSA) is a very useful parameter for the prediction of drug transport properties. The tested compounds were found to have topological polar surface area (TPSA) below 140 $Å^2$. Number of rotatable bond is important for conformational changes of molecules under study and ultimately for the binding of receptors or channels. The compounds possess lower range of number of rotatable bonds [8-11] $\leq$ 10 therefore they exhibit low conformational flexibility except the compounds 4 and 19 have number of rotatable bonds = 11.

Table 1: Druglikeness of 2-iodo derivatives with reference (nifedipine, nitrendipine and felodipine)

Comp. No.	miLogP	TPSA	n.A.	MW	nON	nOHON	n.V.	nrotb	vol.
2a	5.67	64.64	27	483.35	5	1	1	7	370.21
2b	6.44	64.64	29	511.40	5	1	2	9	403.82
2c	6.57	64.64	29	511.40	5	1	2	7	402.69
2d	3.79	83.11	29	515.34	7	1	1	11	388.61
2e	7.39	64.64	35	579.43	5	1	2	9	446.74
2f	4.93	64.64	25	455.29	5	1	0	6	336.82
2g	5.32	64.64	26	469.32	5	1	1	7	353.63
2h	5.38	64.64	26	469.32	5	1	1	6	353.06
2i	3.99	73.87	26	471.29	6	1	0	8	346.02
2j	5.79	64.64	29	503.34	**5**	1	2	**7**	375.08
2k	5.31	64.64	26	469.32	5	1	1	7	353.63
2l	5.69	64.64	27	483.35	5	1	1	8	370.43
2m	5.76	64.64	27	483.35	5	1	1	7	369.86
2n	4.37	73.87	27	485.32	6	1	0	9	362.83
2o	6.17	64.64	30	517.36	**5**	1	2	8	391.89
Nifedipine	3.07	110.46	25	346.34	8	1	0	6	302.78
Nitrendipine	3.70	110.46	26	362.38	8	1	0	7	325.82
Felodipine	4.56	64.64	25	386.27	5	1	0	6	329.56

Notes: Milog P: partition coefficient; TPSA: Topological polar surface area; n.A.:number of atoms; MW: molecular weight; nON: number of hydrogen acceptor; nOHNH: number of hydrogen donor, n.V.: number of violation of five Lipinsky rules; nrotb: number of rotatable bonds and vol: volume of molecule.

In addition, the compounds 2f, 2i, 2n, 3i and 3n have molecular weights (MW) ranged between 455.29 – 485.32 that is below 500, number of hydrogen bond donors (nOHNH) are less than 5 and also hydrogen bond acceptors (nON) are 5-7 that is below 10. Finally, all compounds have number of atoms ranged 25-30 that is within 20-70. The results were compared with standards nifedipine, nitrendipine and felodipine as shown in **Table1** and **Table 2**. From the results reveal that the compounds 2f, 2i, 2n, 3i and 3n obeyed Lipinski and its extension rules and may be orally bioactive.

Table 2: Druglikeness of 3-iodo derivatives with reference (nifedipine, nitrendipine and felodipine)

Comp. No.	miLogP	TPSA	n.A.	MW	n ON	nOHNH	n.V.	nrotb	vol.
3a	6.17	64.64	27	483.35	5	1	1	7	370.21
3b	6.94	64.64	29	511.40	5	1	2	9	403.82
3c	7.06	64.64	29	511.40	5	1	2	7	402.69
3d	4.29	83.11	29	515.34	7	1	1	11	388.61
3e	7.88	64.64	35	579.43	5	1	2	9	446.74
3f	5.43	64.64	25	455.29	5	1	1	6	336.82
3g	5.82	64.64	26	469.32	5	1	1	7	353.63
3h	5.88	64.64	26	469.32	5	1	1	6	353.06
3i	4.49	73.87	26	471.29	6	1	0	8	346.02
3j	6.29	64.64	29	503.34	**5**	1	2	**7**	375.08
3k	5.81	64.64	26	469.32	5	1	1	7	353.63
3l	6.19	64.64	27	483.35	5	1	1	8	370.43

3m	6.25	64.64	27	483.35	5	1	1	7	369.86
3n	4.87	73.87	27	485.32	6	1	0	9	362.83
3o	6.66	64.64	30	517.36	**5**	1	2	8	391.89
nifedipine	3.07	110.46	25	346.34	8	1	0	6	302.78
nitrendipine	3.70	110.46	26	362.38	8	1	0	7	325.82
felodipine	4.56	64.64	25	386.27	5	1	0	6	329.56

Notes: Milog P: partition coefficient; TPSA: Topological polar surface area; n.A.:number of atoms; MW: molecular weight; n ON: number of hydrogen acceptor; nONH: number of hydrogen donor, n.V.: number of violation of five Lipinski rules; n.rotb: number of rotatable bonds and vol volume of molecule.

3.2. Bioactivity Score

The previous results show that some of target compounds have physicochemical properties within the acceptable criteria. Thus, these parameters serve as a guide for further screening of the 1,4-DHPs as : [G-protein-coupled receptors ligand (GPCRL); Ion channel modulator (ICM); Kinase inhibitor (KI); Nuclear receptor ligand (NRL); Protease inhibitor (PI)]. So, by using Molinspiration software "online test", the bioactivity of all compounds were estimated and represented in **Table 3** and **Table 4**.

Furthermore, the drugs in the protease and GPCR-peptidic tribes are characterized by significantly higher average molecular weight, while those in the ion channel family have lower average molecular weight. Drugs in the GPCR-lipid, GPCR peptidic and nuclear hormone receptor (NHR) families have significantly higher cLogP. In addition, drugs in the GPCR-peptidic and protease families have more acceptors, while those in NHR families have fewer acceptors.

Taking into consideration, the bioactivity scores (0.0 to 5.0) may refer to significant biological activities, if the bioactivity scores (-5.0 to 0.0) it is moderately active and finally if the bioactivity scores (< -5.0) it is inactive.

On these observation, the results in **Table 3** and **Table 4** demonstrated that both 2-iodo derivatives (2a-o) and 3-iodo derivatives (3a-o) may be more active comparing with standards (nifedipine, nitrendipine and felodipine). Thus, a) GPCR : all our compounds were found to be moderately bioactive, the bioactivity scores (-0.391 to -0.181 and -0.326 to -0.123 for 2-iodo- and 3-iodo- derivatives respectively) comparing with standards (-0.45 to -0.24). b) Ion channel : all our compounds were found to be good bioactive, the bioactivity scores (-0.127 to 0.07 and -0.137 to 0.048 for 2-iodo- and 3-iodo- derivatives respectively) comparing with references (-0.33 to -0.13).c) Protein kinase : the bioactivity scores (-0.944 to -0.599 and -0.907 to -0.571 for 2-iodo- and 30-iodo- derivatives respectively) comparing with standards (-1.07 to -0.98).d) Nuclear receptor : all our compounds were found to be good bioactive, thus the bioactivity scores were -0.196 to 0.003 and -0.151 t0 0.035 for 2-iodo- and 3-iodo- derivatives respectively, in comparison with standards (-0.42 to -0.25). e) Protease-activated receptors : all our compounds were found to be moderate bioactive, the bioactivity scores (-0.691 to -0.394 and -0.662 to -0.373 for 2-iodo- and 3-iodo- derivatives respectively), while references have bioactivity scores raged between -0.73 to -0.53.

Table 3: Bioactivity of 2-iodo derivatives comparing with standards (nifedipine, nitrendipine and felodipine)

Comp. No.	GPCRL	ICM	KI	NRL	PI
2a	-0.305	-0.064	-0.828	-0.096	-0.622
2b	-0.27	-0.029	-0.756	-0.093	-0.52
2c	-0.181	0.07	-0.679	0.003	-0.43
2d	-0.315	-0.101	-0.721	-0.172	-0.592
2e	-0.186	-0.001	-0.599	-0.102	-0.394
2f	-0.36	-0.093	-0.942	-0.12	-0.691
2g	-0.33	-0.055	-0.89	-0.12	-0.597
2h	-0.231	0.055	-0.804	-0.012	-0.496
2i	-0.362	-0.113	-0.836	-0.188	-0.662
2j	-0.25	-0.008	-0.765	-0.138	-0.49
2k	-0.391	-0.102	-0.944	-0.131	-0.69
2l	-0.333	-0.049	-0.869	-0.112	-0.588
2m	-0.265	0.041	-0.811	-0.027	-0.504

2n	-0.382	-0.127	-0.832	-0.196	-0.665
2o	-0.282	-0.019	-0.772	-0.147	-0.5
Nifedipine	-0.45	-0.13	-1.07	-0.25	-0.73
Nitrendipine	-0.39	-0.33	-0.98	-0.42	-0.61
Felodipine	-0.24	-0.26	-1.03	-0.34	-0.53

Notes: GPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor

Table 4: Bioactivity of 3-iodo derivatives comparing with standards (nifedipine, nitrendipine and felodipine)

Comp. No.	GPCRL	ICM	KI	NRL	PI
3a	-0.243	-0.087	-0.791	-0.05	-0.595
3b	-0.212	-0.05	-0.722	-0.051	-0.495
3c	-0.123	0.048	-0.646	0.046	-0.405
3d	-0.258	-0.122	-0.687	-0.129	-0.567
3e	-0.138	-0.019	-0.571	-0.067	-0.373
3f	-0.293	-0.118	-0.903	-0.071	-0.662
3g	-0.266	-0.079	-0.852	-0.072	-0.569
3h	-0.166	0.031	-0.767	0.035	-0.468
3i	-0.297	-0.137	-0.798	-0.141	-0.634
3j	-0.192	-0.029	-0.731	-0.095	-0.465
3k	-0.326	-0.126	-0.907	-0.084	-0.662
3l	-0.271	-0.072	-0.833	-0.067	-0.561
3m	-0.203	0.018	-0.775	0.019	-0.477
3n	-0.32	-0.15	-0.795	-0.151	-0.638
3o	-0.227	-0.04	-0.739	-0.106	-0.476
Nifedipine	-0.45	-0.13	-1.07	-0.25	-0.73
Nitrendipine	-0.39	-0.33	-0.98	-0.42	-0.61
Felodipine	-0.24	-0.26	-1.03	-0.34	-0.53

Notes: GPCRL: GPCR ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor

Taken altogether, the results herein and from **Table 3 and 4** show that the target compounds may be active toward both ion channel and nuclear receptor, especially compound 2c, 3h and 3m whereas 3c, 2h and 2m are only active against ion channel. So the designed compounds may be useful as a lead compound for ion channel modulator and nuclear receptor inhibitors. Therefore, we will synthesize these target compounds and will evaluate their biological properties *in vitro*.

3.3. Molecular docking studies

Molecular docking aids in studying drug/ligand and receptor/protein interactions by recognizing the suitable active sites in protein, obtaining the top geometry of ligand-receptor complex and calculating the energy of interactions for different ligands to design more effective ligands. In order to recognize the interactions at a molecular level for our derivatives with the biotargets, we have picked model of protein structures which are available in the Protein Data Bank (PDB) (www.rcsb.org/pdb). The structures of biotargets have been instrumental in orientation not only lead optimization and target identification but also lead discovery and screening [30]. The molecular docking study was performed to examine the binding affinities and interaction modes between our compounds and the target protein using the Molegro Virtual Docker (MVD). The thirty (30) designed compounds and references (nifedipine, nitrendipine and felodipine) were incorporated into the active site of the preferable protein only herein we selected two protein which have a higher bioactivity scores: ion channel (5KMH) and nuclear receptor (5EWM). The

docking scores were expressed in negative energy terms; the lower binding free energy is the better binding affinity. To further progress docking accuracy, a re-ranking scoring function is introduced. As we realize, binding free energies can serve as a powerful tool in drug design, where correct ranking of inhibitors is often conformed [30].

From the results, the docking study displayed that all of target compounds showed superior binding interactions with the amino acid residues of the proteins so these molecules may be able to inhibit biotargets by fitting inside the pocket of the active site better than standards (nifedipine, nitrendipine and felodipine) (**Figure 1-2**). As indicated from docking analysis, the lowest binding free energies were observed for 3-iodo derivatives than 2-iodo derivatives especially with NMDA receptors (5EWM). This is proofed by good binding affinity between the compounds 3e, 3n and 3o and NMDA receptors (5EWM) and thus ability to inhibit NMDA receptors comparing with other enzyme and standards). Revealing that, the position of iodo- group plays significant roles in the overall binding energy.

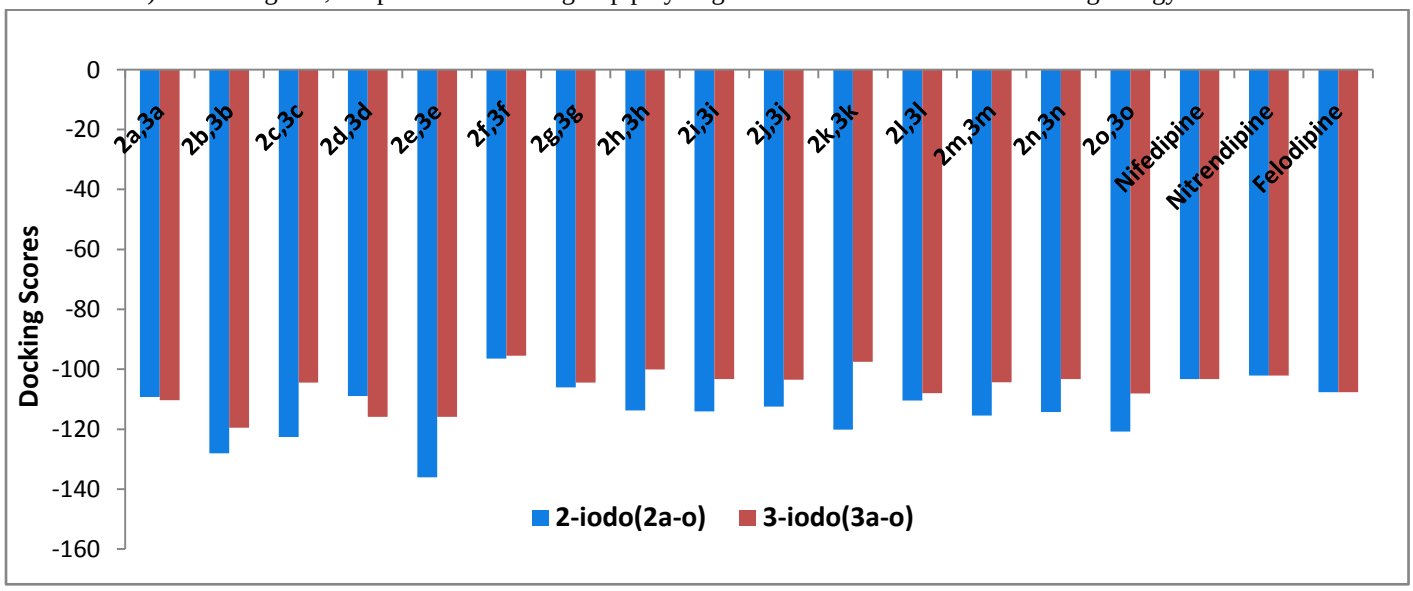


Figure 1: Docking Score of 1,4-dihydropyridine derivatives with nuclear receptor ligand (5EWM) comparing with references (nifedipine, nitrendipine and felodipine)

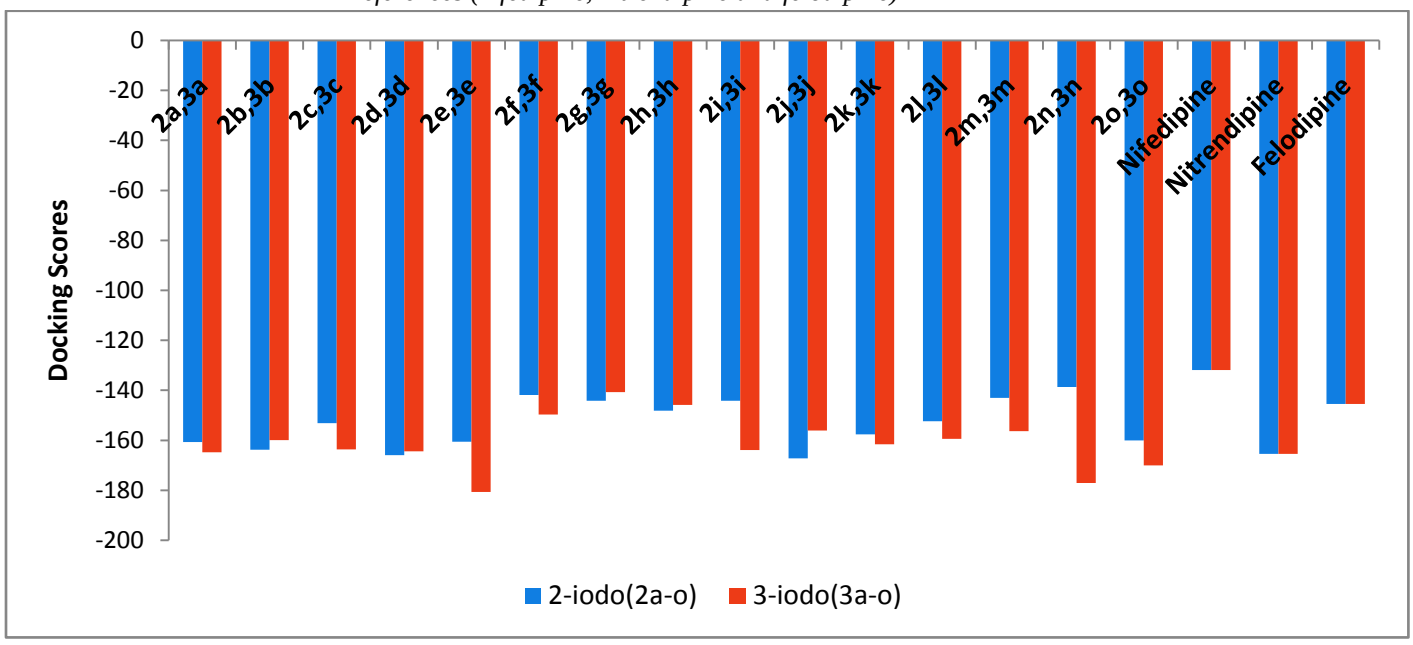


Figure 2: Docking Score of 1,4-dihydropyridine derivatives with ion channel modulator (5KMH) comparing with references (nifedipine, nitrendipine and felodipine)

Figure 3-4 illustrate molecular docking of compound **3e** and nifedipine with NMDA receptor **(A and B respectively)** . The docking results suggest that the compound **3e** has good orientation shape with active site. Thus, compound **3e** has a good interaction with the receptor by forming two H-bonding interactions between the top pose of compound **3e** and receptor (**A**) ; H- bonds involving oxygen atoms of the ester group with $–NH_2$ group of Gln^{331} and oxygen atoms of second ester moiety with $–NH_2$ of Glu^{316}.

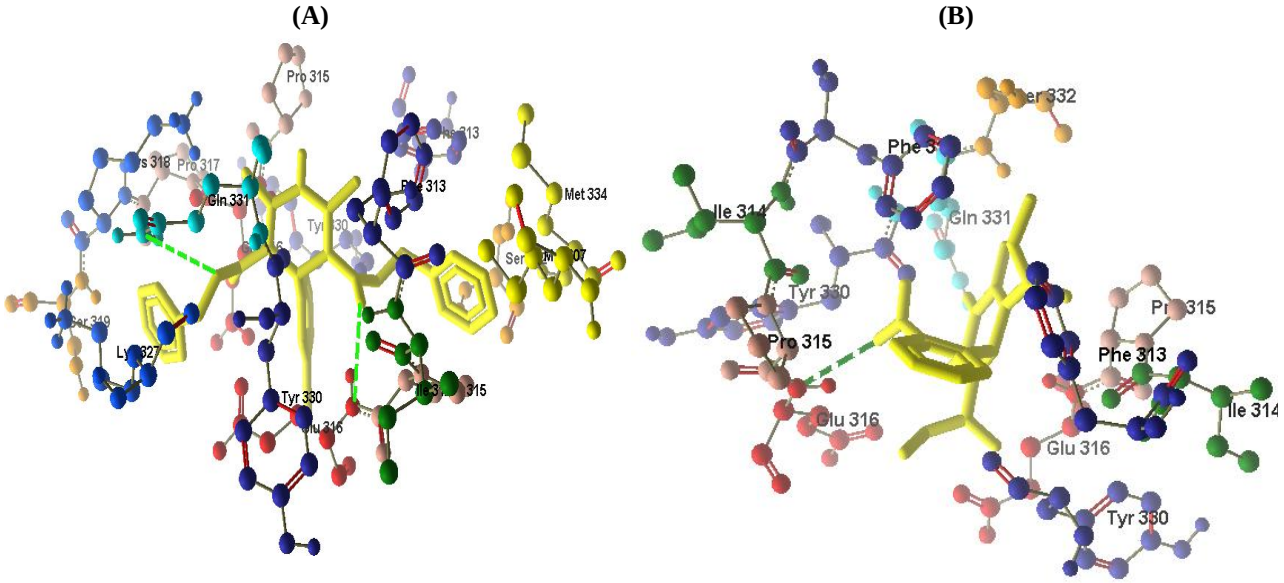


Figure 3: A) Shows two H-bond interactions between compound 3e and NMDA receptor (Gln^{331} and Glu^{316}). B) Illustrate hydrogen bonding between nifedipine and NMDA receptor. Ligands are shown in thick stick, receptor residues in ball and stick.

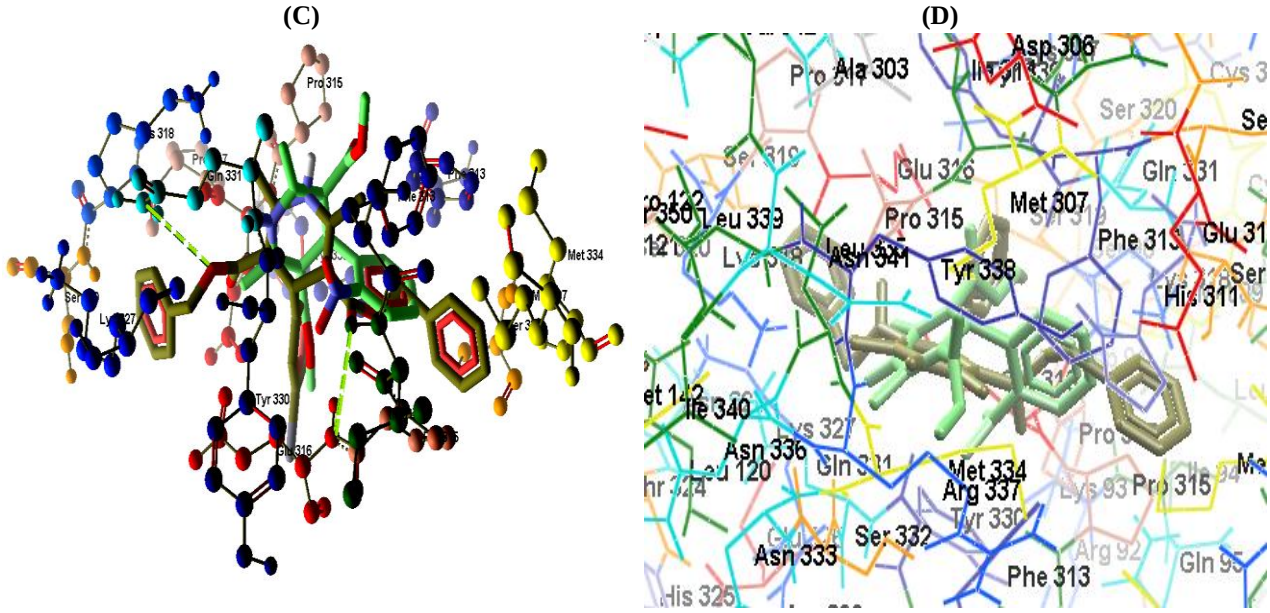


Figure 4: C) Comparison between compound 3e (green) and nifedipine (olive color) with the active site of NMDA amino acids. D) Comparing binding position of both compound 3e and nifedipine to show the optimal occupation of the NMDA active site by compound 3e.

In comparison with reference (nifedipine), the docking analysis for nifedipine (**B**) reveals that, it performs one hydrogen bond with amino acids Glu^{316}. Also, both compound **3e** and nifedipine have good orientation in active site of NMDA receptor (**C and D respectively)**.

From docking analysis of the putative interactions of the compound **3e** with binding site of human NMDA receptor indicated that these hits candidates may be useful as guide for further optimization. So, we well synthesized these derivatives to evaluate their calcium channel modulators *in vivo*.

4. Conclusions

Some of the selected compounds (2f, 2i, 2n, 3i and 3n) met Lipinski's rule and its extension and proved drug likeness (MiLog P value < 5, TPSA < 140 Å2, n violation = 0, molecular mass < 500, N rotb < 5, n HBD <5 and n HBA<8. This indicated that these compounds may be have good permeability across cell membrane and can readily bind to receptor. In addition, the bioactivity for all compounds towards G protein–coupled receptors (GPCR), ion channel, protein kinase, nuclear receptor and other enzyme targets was predicted based on Molinspiration software. The compounds were found to exhibit good to moderately bioactivities comparing with standards (nifedipine, nitrendipine and felodipine). Furthermore, *in silico* modelling revealed that the target compounds have good binding to the pocket of active domain of the fetched protein. The ester groups within the compounds played a key contributor for developing polar interactions such as hydrogen bonding. The compounds 3e, 3n and 3o are potentially motivating hit compound due to their affinity into the active sites of all protein especially NMDA receptors (5EWM). Based on these overall results and *in silico* modeling studies, iodo 1,4 DHP derivatives could be considered as possible hit for further studies.

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