International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 7s, 2025
https://www.theaspd.com/ijes.php

Hydantoin Derivatives Bearing Morpholine Moiety: Design, Synthesis, Characterization, In-Silico ADMET And Molecular Docking Investigations

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Abstract: *Using the basic mannich reaction, a number of new hydantoin derivatives with morpholine and substituted phenyl appendages connected to the common methyl group were created as mannich bases. The produced compounds underwent mass spectral analysis, FT-IR, 1H-NMR, and physical characterization. The in-silico ADME/toxicity properties of the novel compounds were computed using the SwissADME web tool. The results demonstrated adequate values of absorption, distribution, and excretion–parameters pertinent to bioavailability. For certain compounds, low estimates of toxicity were also proposed. Molecular docking experiments were performed at the voltage-gated sodium channel protein target (PDB ID-3RVY) and the protein targets of cyclooxygenases (PDB IDs - 2OYE and 3LN1) to predict anti-inflammatory and anti-convulsant effects The compounds overall yields were good, and molecular docking indicated that few compounds had a strong binding affinity at 2OYE, 3LN1, and 3RVY in a favourable way.*

Keywords: *Glyoxal, N-methylurea, hydantoins bearing morpholine, mannich reaction, ADME/Toxicity properties, docking studies*

INTRODUCTION

A substantial portion of recent organic chemistry publications is in the discipline of heterocyclic chemistry, which is known as organic chemistry. Heterocyclic compounds are those that have ring structures with non-carbon atoms like oxygen, sulphur, or nitrogen. This class includes three- to four-membered and five- to seven-membered ring systems, whose properties are mostly determined by the presence of ring strain. But the aromatic cyclic counterparts have at least one heteroatom in the ring and, aside from adhering to Huckel's principles, are exactly like benzene in terms of their characteristics. Heterocycles find application in asymmetric catalytic inorganic synthesis as metal ligands, chiral auxiliaries, protective groups, synthetic intermediates, and organic catalysts. Heterocyclic compounds have important roles in biological structure and function in addition to being effective medications for treating illnesses. Approximately sixty percent of the most significant medications include one or more heterocyclic nuclei. Numerous medication classes contain heterocyclic moieties as essential structural elements.1,2 Heterocyclic compounds often have a rigid ring structure and are difficult to hydrolyze or depolymerize. Three atoms in the ring structure give heterocycles ring strain, which makes them more reactive. Generally speaking, single heteroatom systems are stable. For many years, the most beautiful targets have been N-containing heterocycles because of their biological significance and structural diversity for synthesis.3 For the treatment of epilepsy, hydantoin, also known as imdiazolidine-2,4-dione, is the most promising scaffold. Hydantoin (TH), or imidazilidine-2,4-dione, is a well-known five-membered heterocyclic molecule with four flexible areas of operation within its structure. Since the discovery of hydantoin, several synthetic techniques have been established through functionalization, and it has been discovered that the related derivatives have a wide range of scientific uses.Due to its ability to slow down the rate at which voltage-activated Na+ channels recover from inactivation and to reduce the recurrent firing of action potentials triggered by prolonged depolarization, phenytoin, the prototype, continues to be the most popular medicine worldwide.4 Hydantoin, sometimes referred to as glycolylurea, is a heterocyclic organic molecule with the formula CH2C(O)NHC(O)NH. It is a solid that is produced when urea and glycolic acid/glyoxal combine. In a larger sense, compounds that share the ring structure

of their parent compounds might be referred to as groupings or classes of compounds, or hydantoins. For example, the number 5 carbon in a hydantoin molecule of phenytoin has two phenyl groups substituted onto it.5,6

A great deal of work has gone into the synthesis and research of these five-membered heterocycles throughout the last ten years. Hydantoin can be synthesised using a number of different routes, the three most popular ones being the Bucherer-Bergs reaction, the Urech or Read synthesis, and the Biltz reaction. Racemic hydantoins, derived from carbonyl or dicarbonyl condensation of carbonyl compounds, potassium or sodium cyanide, and ammonium carbonate, are produced by the Bucherer-Bergs process. The synthesis of the antiepileptic medication phenytoin from benzil and urea is the historical significance of the Biltz reaction, while the reaction between amino acid derivatives and isocyanates is associated with the Urech or Read synthesis.[7] Several physiologically active substances have the crucial structural framework known as the hydantoin moiety. A wide range of anticonvulsant, antiulcer, antiarrhythmic, antimuscarinic, anti-inflammatory, antiviral, and antidiabetic properties have been found for hydantoin derivatives. Certain hydantoin compounds have also been employed as inhibitors of platelet aggregation and antidepressants.[8]

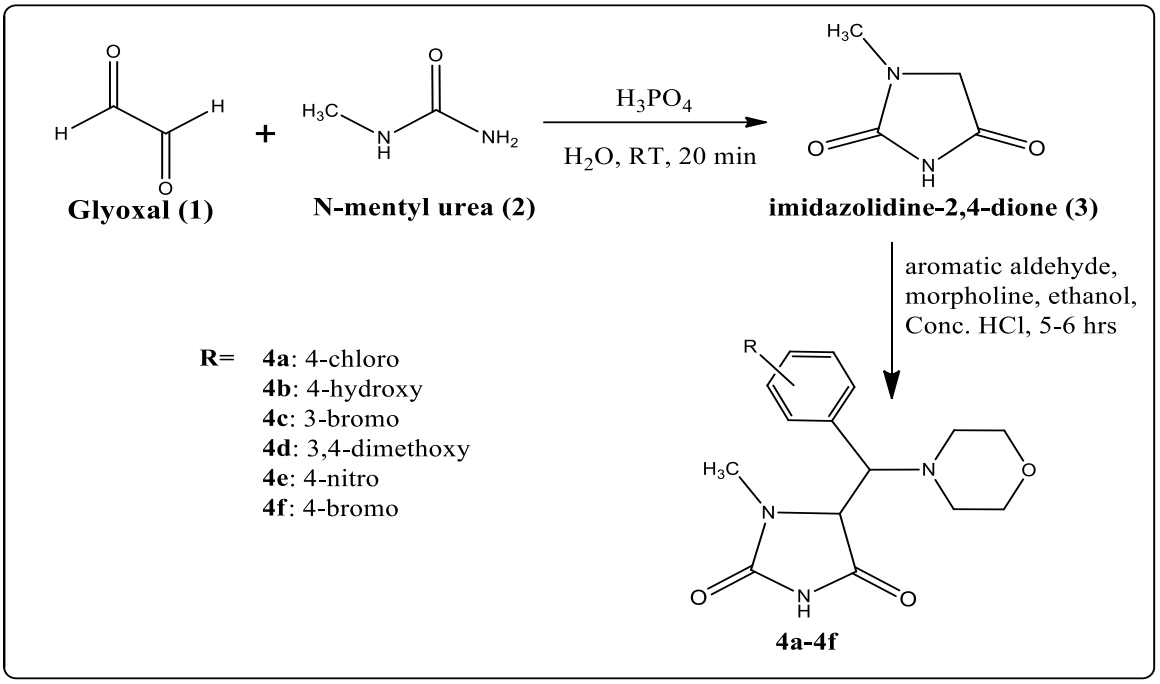
The creation of hydantoin scaffolds with morpholine moiety was the main goal of this investigation. A number of hydantoin derivatives were produced by the Mannich reaction, which involved combining 1-methyl-imidazolidine-2,4-dione with morpholine, substituted aromatic benzaldehyde, and a catalytic quantity of conc. HCl. The newly synthesised hydantoin derivatives were categorised using spectroscopic and physical properties. To evaluate the effects or dangers of these substances, in-silico ADME/toxicity characteristics were carried out. Using in-silico molecular docking experiments, the active site regions of voltage-gated sodium channel (PDB ID: 3RVY), cyclooxegenase-1 (PDB ID: 2OYE), and cyclooxegenase-2 (PDB ID: 3LN1) were examined in order to anticipate anti-inflammatory and anti-convulsant effects.

Materials and Methods

All the chemicals required for the synthesis of novel hydantoins such as reagents and solvents were obtained from commercial suppliers Merck grade and further those were used without purification. Reaction progress and completion was monitored by thin layer chromatography with the help of E.Merck grade silica gel 60GF-254 precoated TLC plates, spots were observed under UV-light and in iodine chamber.FT-IR spectra of the compounds were recorded in on Bruker FT-IR analyzer spectrophotometer by compression of compound with anhydrous KBr under vacuum using KBr pressed pellet technique. Chemical shifts in δ, ppm of ^{1}H-NMR spectra were recorded on Bruker AMX400 MHz spectrometer using deuterated DMSO solvent and tetramethylsilane (TMS) as internal standard. Mass spectra of the compounds were recorded on Agilent LC-MSD 1200 mass spectrometer. Melting points were determined by using electrical melting point apparatus and those were uncorrected. The SwissADME online programme was used to conduct in-silico ADME/Toxicity investigations. Using the software programmes AutoDock Vina, ChemDraw, and BIOVIA discovery studio, molecular docking investigations were performed at several target protein active sites.

Experimental Work

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 7s, 2025
https://www.theaspd.com/ijes.php



Scheme: synthesis of hydantoin derivatives (**4a-4f**)

Synthesis of 1-methyl-imidazolidine-2,4-dione (**3**)

As the scheme illustrates, using phosphoric acid as a catalyst, dissolve 0.01 mol of glyoxal (**1**) and 0.01 mol of N-methyl urea (**2**) in 15-20 mL of water, then transfer the mixture into a 100 mL round-bottomed flask. In order to obtain 1-methyl-imidazolidine-2,4-dione, the reaction was conducted for 10–20 minutes at room temperature in aqueous solutions, providing gentle and environmentally friendly conditions. Thin layer chromatography was used to track the reaction development (TLC). Once the reaction was finished, the reaction mixture was added to 25 ml of water. The product was recrystallized from ethanol following the standard workup.[9,10]

78.68% yield, pale yellow crystalline powder, melting point 156-158°C, R_f value 0.58 from using chloroform and methanol (7:3). IR [KBr ν cm^{-1}]: 3317 (-NH-), 1726, 1718 (C=O), 2962 (C-H), 1301(C-N). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 11.85 (s, 1H, NH), 4.11 (s, 2H, CH_2), 3.51 (s, 3H, CH_3).^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 174, 170, 45, 33. ESI-MS: (M^+) m/z 114.General Procedure for synthesis of compounds (**4a-4f**)

Dissolve 0.01 mol of 1-methyl-imidazolidine-2,4-dione (**3**) in 5 ml of ethanol, 0.01 mol of substituted aromatic benzaldehyde was added to it. At room temperature, the mixture was agitated for approximately half an hour. 0.01 mol of morpholine and three to five drops of catalytic conc. HCl were added to the reaction mixture, which was then refluxed for five to six hours. TLC was used to monitor the reaction's completion, and the mobile phase consisted of n-hexane and ethylacetate (9:1). The reaction mixture was allowed to cool before being placed into ice-cold water. After filtering the product, it was cleaned with cold water and then dried toluene. used pure ethanol to recrystallize it after drying it. [11,12]

5-[(4-chlorophenyl)-morpholin-4-yl-methyl]-imidazolidine-2,4-dione (**4a**)

IR [KBr ν cm^{-1}]: 3356 (-NH-), 1681 (C=O), 1285 (C-N), 2954 (C-H), 3052 (=C-H), 1104 (C-O-C), 765(C-Cl). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 12.05 (s, 1H, NH), 3.26 (s, 3H, CH_3), 4.28-4.30 (d, 1H, HYD CH), 3.97-4.06 (d, 1H, N-CH), 7.45-7.52 (d, 2H, 3'-H&5'-H), 7.02-7.17 (d, 2H, 2'-H&6'-H), 3.54-3.65 (t, 4H, CH_2-O-CH_2), 2.51-2.65 (t, 4H, CH_2-N-CH_2).^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 171, 163, 137, 134, 131, 125, 67, 58, 54, 51, 32. ESI-MS: (M^+) m/z 323.

5-[(4-hydroxyphenyl)-morpholin-4-yl-methyl]-imidazolidine-2,4-dione (**4b**)

IR [KBr ν cm^{-1}]: 3395 (-NH-), 1696 (C=O), 1279 (C-N), 2962 (C-H), 3056 (=C-H), 1128 (C-O-C), 3545 (Ph-OH). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 12.05 (s, 1H, NH), 3.37 (s, 3H, CH_3), 4.05-4.18 (d, 1H, HYD CH), 9.75 (s, 1H, C_6H_4-OH), 4.35-4.48 (d, 1H, N-CH), 7.49-7.61 (d, 2H, 3'-H&5'-H), 7.19-7.30 (d, 2H, 2'-H&6'-H), 3.54-3.62 (t, 4H, CH_2-O-CH_2), 2.75-2.88 (t, 4H, CH_2-N-CH_2).^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 177, 165, 158, 137, 134, 116, 65, 60, 54, 51, 35. ESI-MS: (M^+) m/z 305.

5-[(3-bromophenyl)-morpholin-4-yl-methyl]-imidazolidine-2,4-dione **(4c)**
IR [KBr ν cm^{-1}]: 3326 (-NH-), 1683 (C=O), 1256 (C-N), 2952 (C-H), 3045 (=C-H), 1131 (C-O-C), 579 (C-Br). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 11.96 (s, 1H, NH), 3.21 (s, 3H, CH_3), 4.28-4.39 (d, 1H, TZD CH), 4.08-4.20 (d, 1H, N-CH), 7.97 (s, 1H, 2'-H), 7.57-7.68 (d, 1H, 4'-H), 7.20-7.31 (t, 1H, 5'-H), 6.90-7.11 (d, 1H, 6'-H), 3.54-3.71 (t, 4H, CH_2-O-CH_2), 2.43-2.65 (t, 4H, CH_2-N-CH_2). ^{13}C-NMR [400 MHz, δ, ppm, DMSO-d_6]: 178, 166, 138, 135, 133, 131, 126, 122, 66, 58.74, 56, 51, 36. ESI-MS: (M^+) m/z 368.
5-[(3,4-dimethoxyphenyl)-morpholin-4-yl-methyl]-imidazolidine-2,4-dione **(4d)**
IR [KBr ν cm^{-1}]: 3405 (-NH-), 1678 (C=O), 1276 (C-N), 2980 (C-H), 3079 (=C-H), 1125 (C-O-C). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 12.04 (s, 1H, NH), 3.34 (s, 3H, CH_3), 4.20-4.37 (d, 1H, TZD CH), 4.41-4.55 (d, 1H, N-CH), 6.56 (s, 1H, 2'-H), 6.79-6.93 (d, 2H, 5'-H&6'-H), 3.84 (s, 6H, 3'-OCH_3&4'-OCH_3), 3.55-3.78 (t, 4H, CH_2-O-CH_2), 2.67-2.84 (t, 4H, CH_2-N-CH_2).^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 178, 168, 154, 148, 133, 126, 117, 114, 68, 62, 58, 56, 52, 38. ESI-MS: (M^+) m/z 349.
5-[(4-nitrophenyl)-morpholin-4-yl-methyl]-imidazolidine-2,4-dione **(4e)**
IR [KBr ν cm^{-1}]: 3352 (-NH-), 1685 (C=O), 1267 (C-N), 2981 (C-H), 3074 (=C-H), 1148 (C-O-C), 1359, 1541 (NO_2). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 12.41 (s, 1H, NH), 3.19 (s, 3H, CH_3), 4.17-4.29 (d, 1H, HYD CH), 4.42-4.56 (d, 1H, N-CH), 7.50-7.62 (d, 2H, 3'-H&5'-H), 7.24-7.38 (d, 2H, 2'-H&6'-H), 3.76-3.89 (t, 4H, CH_2-O-CH_2), 2.81-2.95 (t, 4H, CH_2-N-CH_2).^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 179, 167, 152, 142, 130, 121, 67, 60, 56, 51, 36. ESI-MS: (M^+) m/z 334.
5-[(4-bromophenyl)-morpholin-4-yl-methyl]-imidazolidine-2,4-dione **(4f)**
IR [KBr ν cm^{-1}]: 3365 (-NH-), 1683 (C=O), 1284 (C-N), 2966 (C-H), 3041 (=C-H), 1141 (C-O-C), 566 (C-Br). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 11.85 (s, 1H, NH), 3.36 (s, 3H, CH_3), 4.41-4.57 (d, 1H, TZD CH), 4.03-4.17 (d, 1H, N-CH), 7.37-7.51 (d, 2H, 3'-H&5'-H), 6.82-7.0 (d, 2H, 2'-H&6'-H), 3.58-3.78 (t, 4H, CH_2-O-CH_2), 2.52-2.78 (t, 4H, CH_2-N-CH_2).^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 179, 167, 137, 134, 131, 121, 67, 58, 52, 50, 39. ESI-MS: (M^+) m/z 368.

ADME/Toxicity Studies [13-15]

For the purpose of determining the pharmacokinetic parameters and properties of drug-like substances based on their molecular structures, a computer programme known as ADMET Predictor was developed. Absorption, Distribution, Metabolism, Excretion/Elimination, and Toxicity are the acronyms for these processes. Merely possessing a low dangerous profile and strong bioactivity does not deem a molecule as a promising contender. A novel chemical should only be investigated in the process of finding new pharmaceuticals and drug-like compounds if it has a better pharmacokinetic profile. It is critical to evaluate the ADMET profile of novel drugs as soon as feasible to avoid losing time or money. Consequently, we predicted the ADMET properties of produced compounds **(4a–4f)** using the online swissADME software. The Lipinski "Rule of Five" was the "most widely utilised rule-based filter" of drug-likeness, which assessed a molecule's oral absorption capacity. The components that comprise the rule of five are as follows: molecular weight (MW) ≤ 500, octanol/water partition coefficient (iLOGP) ≤ 5, number of hydrogen bond donors (HBDs) ≤ 5, and number of hydrogen bond acceptors (HBAs) ≤ 10.6. The quantitative estimate of drug-likeness (QED) concept (ALERTs) produced the four rules of five (MW, iLOGP, HBAs, and HBDs) as well as four additional parameters: molecular topological polar surface area (TPSA), number of rotatable bonds (RB), number of aromatic heavy atoms (nAH), and number of alerts for undesirable substructures. When comparing QED to conventional drug-likeness principles, the latter is the more extensively applied and versatile notion. Some ADMET parameters and features are shown below, along with the allowed limitations for each. To evaluate the pharmacokinetic properties of the created compounds, the 2D structures of the compounds were drawn using Chemdraw Ultra 12.0. Every structure was imported, and the smiley structure had to be entered in order for the website's interface (http://swissadme.ch/) to function. The SwissADME drug design project provided the ADMET characteristics and properties.

Table-1: Permitted limits of ADMET parameters

ADMET Parameter	**Permitted limit**
Molecular weight (MW)	50 to100
octanol/water partition coefficient (iLOGP)	-2 to 10
Topological Polar Surface Area (TPSA)	20 to 130
Number of H-Bond acceptors (HBA)	0 to 10

Number of H-bond Donors (HBD)	0 to 5
Rotatable bonds (RB)	0 to 5
Number of aromatic heavy atoms (nAH)	15 to 50
Lipophilicity of the compound (LogP)	-0.7 to 5.0
Molar refractivity (MR)	40 to 130

Molecular Docking Studies

Molecular docking experiments were performed on voltage gated sodium channel target proteins, cyclooxygenase-1, and cyclooxygenase-2 in order to find potential anti-inflammatory and anti-convulsant medicines. A target protein is chosen for docking based on a number of criteria, including having a resolution of 2.0 to 3.0A°, having a co-crystallized ligand, having its structure established by X-ray diffraction, and not having any protein breaks in its 3D structure.[16] Download the PDB files from the RCBS Protein Data Bank (https://www.rcsb.org/) for the 3D crystal structures of cyclooxegenase-1 PDB ID: 2OYE,[17] and cyclooxegenase-2 PDB ID: 3LN1 [18] and voltage-gated sodium channel PDB ID: 3RVY. [19,20] Water molecules and heteroatoms were eliminated from the acquired proteins using BIOVIA Discovery studio visualizer 2021 to prepare them for docking. To facilitate further analysis, the protein structures were reduced to their lowest energy state by including Kollman charges, Gasteiger charges, and polar hydrogens.[21] The desired and produced ligand structures were created using ChemDraw Ultra 12.0, and the structures were reduced and stored in SDF file format using Chem 3D-Pro 12.0. The standard ligand structure SDF file formats for phenytoin (Pubchem Id: 1775) and methacin (Pubchem Id: 3715) were acquired from the PubChem database. Furthermore, all SDF format files are converted to PDB format using the Open Babel programme. The completed tasks included grid-based docking studies with default parameters, protein conversions from PDB to PDBQT file format, and docking by linking the protein-ligand using MGL Autodock Vina. It was feasible to view the docking locations of ligands that connected to the protein active site regions most effectively by using the command prompt. With BIOVIA Discovery Studio 2021, the ligands two dimensional bindings to the target proteins were observed.

RESULTS AND DISCUSSION

The Biltz synthesis reaction between glyoxal and N-methyl urea yields 1-methyl-imidazolidine-2,4-dione (**3**), in accordance with the procedures outlined in the literature. A series of hydantoin derivatives with morpholine moiety (**4a–4f**) are produced by a further Mannich process using substituted aromatic benzaldehyde, morpholine, and a catalytic quantity of concentrated HCl. Scheme showed how the synthesis of hydantoin derivatives was done. The data on physical characterization was shown in Table-2.

Table-2: Physical characterization data of developed hydantoin derivatives **4a-4f**

Compd.	**R**	**m.p. (°C)**	**Molecular formula**	**mol. wt.**	**% yield**	**R_f value**
4a	4-chloro	192-194	$C_{15}H_{18}ClN_3O_3$	323.77	72.43	0.56
4b	4-hydroxy	180-182	$C_{15}H_{19}N_3O_4$	305.33	70.36	0.52
4c	3-bromo	196-198	$C_{15}H_{18}BrN_3O_3$	368.23	67.27	0.55
4d	3,4-dimethoxy	184-186	$C_{17}H_{23}N_3O_5$	349.38	69.45	0.61
4e	4-nitro	208-210	$C_{15}H_{18}N_4O_5$	334.33	73.60	0.57
4f	4-bromo	202-204	$C_{15}H_{18}BrN_3O_3$	368.23	68.92	0.53

The molecular weight (MW), number of rotatable bonds (RB), number of hydrogen donors (HBD), number of hydrogen acceptors (HBA), topological polar surface area (TPSA), octanol/water partition coefficient (iLOGP), number of aromatic heavy atoms (nAH), molar refractivity (MR), and lipophilicity (LogP) of the designed compounds were revealed by the ADMET results, which were listed in Table-3. In Table-4, it was reported that there were Lipinski violations, GI absorption, and blood brain barrier (BBB) violations. By committing only one infraction, each molecule that was produced consented to the rules. Put differently, all of the MW, RB, HBD, HBA, TPSA, iLOGP, nAH, and MR are within the permitted ranges. Furthermore, there is no caution for GI absorption, BBB penetration, or Lipinski violations, demonstrating the compounds great specificity. Therefore, it is now feasible to declare that the pharmacokinetic profile of discovered compounds is favourable.

Table-3: Predicted ADME parameters of developed hydantoin derivatives **4a-4f**

Comp.	MW	iLOGP	HBA	HBD	TPSA	RB	nAH	MR	LogP
4a	323.77	2.38	4	1	61.88	3	6	92.86	1.14
4b	305.33	1.72	5	2	82.11	3	6	89.87	0.19
4c	368.23	2.45	4	1	61.88	3	6	95.55	1.22
4d	349.38	2.71	6	1	80.34	5	6	100.83	0.62
4e	334.33	1.78	6	1	107.7	4	6	96.67	0.04
4f	368.23	2.57	4	1	61.88	3	6	95.55	1.25

Table-4: Predicted Lipinski violations, BBB permeation and GI absorption of developed hydantoin derivatives **4a-4f**

Comp.	Lipinski violations	BBB permeation	GI absorption
4a	0	No	High
4b	0	No	High
4c	0	No	High
4d	0	No	High
4e	0	No	High
4f	0	No	High

Docking at cyclooxegenase-1 (PDB ID: 2OYE)

The hydantoin derivatives hydrogen bonding interactions, both in terms of frequency and strength, provide insight into molecular compatibility, which is likely related to how well the ligands work at the cyclooxegenase-1 target. An analysis of the hydrophobic interactions between ligands and certain nonpolar amino acid residues with COX-1 using hydantoin derivatives showed a pattern of close contact. For example, interactions spanning many derivatives are often reported with VAL P:349, LEU P:352, and TRP P:387. The hydrophobic pocket formed by these residues seems to stabilise the ligands inside the binding site. Significantly, ligand **4E** exhibits a variety of hydrophobic interactions beyond those usually found with GLY P:526, VAL P:349, LEU P:352, and ALA P:525. These contacts have lengths ranging from 3.65 to 6.78 Å, indicating van der Waals stabilisation and efficient packing, both of which are correlated with moderate binding affinities. At the active site area, the standard ligand Indomethacin has been demonstrated to exhibit a docking energy ΔG of -9.1 kcal/mol. Ligand **4E** exhibits optimum alignment within the hydrophobic pocket due to its significant binding affinity (ΔG of -9.0 kcal/mol) and dense cluster of hydrophobic contacts. Upon closer inspection of the comprehensive information provided in Table-5, it is evident that hydrogen-bond interactions, while less common than hydrophobic interactions, are nevertheless important in determining the binding affinity of several hydantoin derivatives to COX-I. Significant binding affinity is exhibited by ligands **4E**, **4A**, and **4F**, with ΔG values of -9.0 kcal/mol, -8.9 kcal/mol, and -8.6 kcal/mol. These interactions help the ligands' specificity and docking stability, which may improve their pharmacological effects even though they are weaker than hydrogen bonds and van der Waals forces.

Table-5: Binding energies and interaction of designed ligands **4a-4f** with COX-1 (PDB: 2OYE)

Ligands	Binding Energy ΔG (Kcal/mol)	Amino acids involved and distance (Å)	
		Hydrogen-Bond Interactions	Hydrophobic Interactions
4a	-8.9	TYR P:355 (6.05)	TYR P:385 (4.80), LEU P:352 (5.53), VAL P:349 (5.20), TRP P:387 (6.78)
4b	-7.8	TYR P: 355 (6.06), SER P: 530 (3.81)	ALA P:527 (4.34), VAL P:349 (5.07), LEU P:352 (5.54), SER P:353 (3.72), VAL P: 349 (5.33), SER

			P:353 (3.68)
4c	-8.2	TYR P: 355 (6.03)	VAL P:349 (5.41), LEU P:352 (4.43), ALA P:257 (3.84), TRP P:387 (4.52)
4d	-8.0	TYR P:355 (5.95)	VAL P:349 (4.50), TYR P:348 (5.17), LEU P:352 (5.57, 5.69), LEU P:384 (4.67), MET P:522 (5.14), ALA P:257 (4.30), TRP P: 387 (6.39)
4e	-9.0	TYR P:355 (6.05), TYR P:385 (4.64)	GLY P:526 (3.65), VAL P:349 (5.33), LEU P:352 (3.61), ALA P:525 (4.26)
4f	-8.6	TYR P: 355 (6.07)	ALA P:257 (4.27), LEU P:352 (5.58), VAL P:349 (3.62)
Indomethacin	-9.1	MET P:522 (5.51)	VAL P:116 (3.91), LEU P:93 (5.58), TYR P: 355 (5.45), LEU P:359 (6.49), ALA P: 527 (3.88, 5.31, 5.01), VAL P: 349 (5.02), HIS P90 (6.07), LEU P: 352 (4.95, 6.06), SER P:353 (4.35, 4.58), ILE P:523 (4.80)

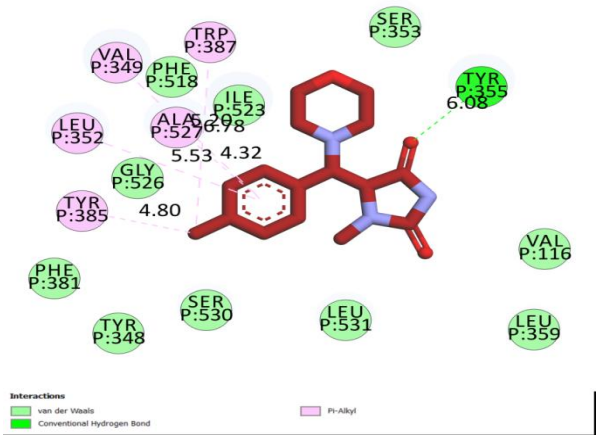


Fig-1: 2D view interaction of 4a with 2OYE

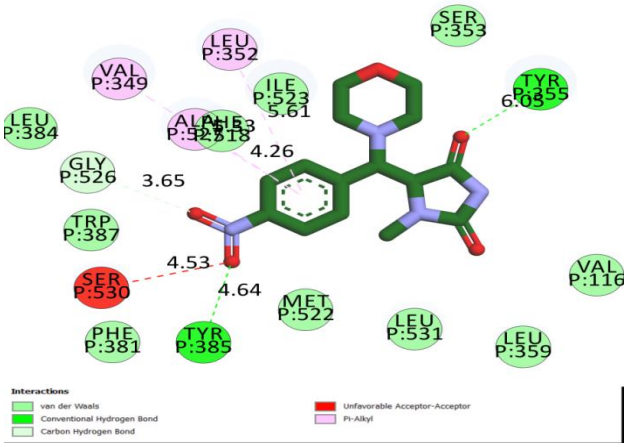


Fig-2: 2D view interaction of 4E with 2OYE

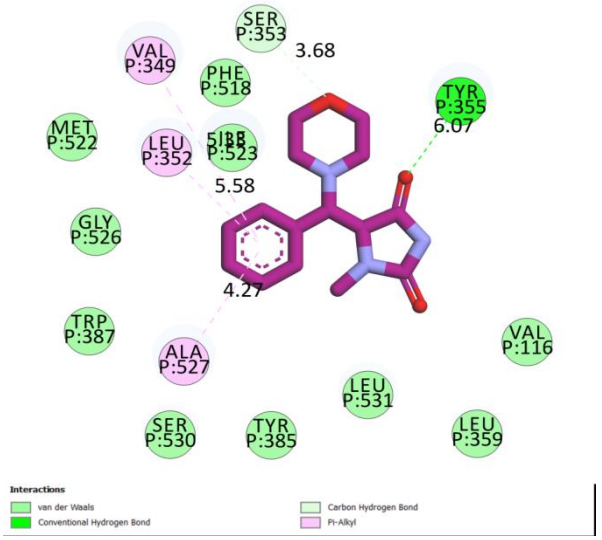


Fig-3: 2D view interaction of 4f with 2OYE

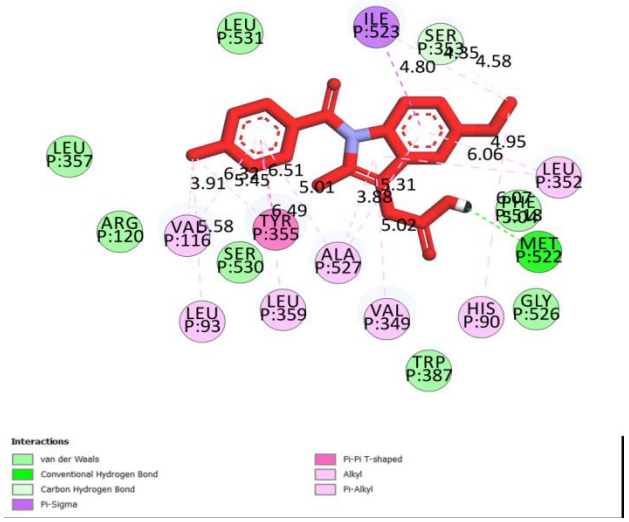


Fig-4: 2D view interaction of indomethacin with 2OYE

Docking at cyclooxegenase-2 (PDB ID: 3LN1)

The degree of molecular compatibility shown by the frequency and strength of hydrogen bonding contacts within the hydantoin derivatives is probably indicative of how well the ligands work at the cyclooxegenase-2 target. Analysis of the hydrophobic interactions between hydantoin derivatives and COX-2 showed that the ligands and specific nonpolar amino acid residues formed close contact. For example, interactions between GLY A:512, VAL A:509, ALA A:513 and VAL A:335 are often seen throughout several derivatives. The hydrophobic pocket formed by these residues seems to stabilise the ligands inside the binding site. The hydrophobic interactions that ligand **4A** exhibits with GLY A:512, TYR A:371, ALA A:513, VAL A:509, and VAL A:335 are noteworthy since they go beyond those that are frequently found.Modest binding affinities are correlated with these interactions' distances, which range from 3.75 to 5.63Å and indicate efficient packing and van der Waals stabilisation. A docking energy ΔG of -9.5 kcal/mol was found for the standard ligand Indomethacin in the active site area. The hydrophobic pocket of ligand **4A** is optimally aligned due to its dense cluster of contacts and significant binding affinity (ΔG of -9.3 kcal/mol). Analysing the specific information in Table-6, it is evident that hydrogen-bond interactions are more important in the binding affinity of some hydantoin derivatives to COX-2 than hydrophobic interactions, while being less common at first. Significant binding affinity is exhibited by ligands **4A**, **4F**, and **4E**, with ΔG values of -9.3 kcal/mol, -9.1 kcal/mol, and -8.7 kcal/mol accordingly. These interactions help the ligands specificity and docking stability, which may improve their pharmacological effectseven though they are weaker than hydrogen bonds and van der Waals forces.

Table-6: Binding energies and interaction of designed ligands **4a-4f** with COX-2 (PDB: 3LN1)

Ligands	**Binding Energy ΔG (Kcal/mol)**	**Amino acids involved and distance (Å)**	
		Hydrogen-Bond Interactions	**Hydrophobic Interactions**
4a	-9.3	-	GLY A:512 (5.62), TYR A:371 (5.55), ALA A:513 (3.75), VAL A:509 (4.85), VAL A:335 (5.63)
4b	-8.0	LEU A:338 (4.75), SER A:516 (4.02)	LEU A:338 (5.24), VAL A:509 (4.83), SER A:516 (4.80), TYR A:341 (5.89)
4c	-8.4	-	VAL A:509 (5.46), TYR A:371 (4.82), ALA A:513 (4.73), LEU A:338 (5.54)
4d	-7.9	-	VAL A:335 (4.09), TYR A:341 (6.34), TRP A: 373 (7.41), ALA A:513 (3.70), TYR A:371 (5.30), GLY A:512 (3.43, 5.62), VAL A:509 (4.22)
4e	-8.7	TYR A:371 (5.44)	VAL A:335 (4.04, 5.67), VAL A:509 (4.79), ALA A:513 (3.77), GLY A: 512 (5.58)
4f	-9.1	-	VAL A:335 (5.61), ALA A:513 (3.75), GLY A:512 (5.61), VAL A:509 (4.87)
Indomethacin	-9.5	-	LEU A:370 (4.37), TRP A:373 (5.49), MET A:508 (3.91), PHE A:504 (5.70), GLY A:512 (4.10), VAL A:335 (4.74), ALA A:513 (4.18), VAL A:509 (4.35), LEU A:338 (4.54), SER A:339 (4.04), ARG A:499 (5.43), ALA A:502 (6.41)

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 7s, 2025
https://www.theaspd.com/ijes.php

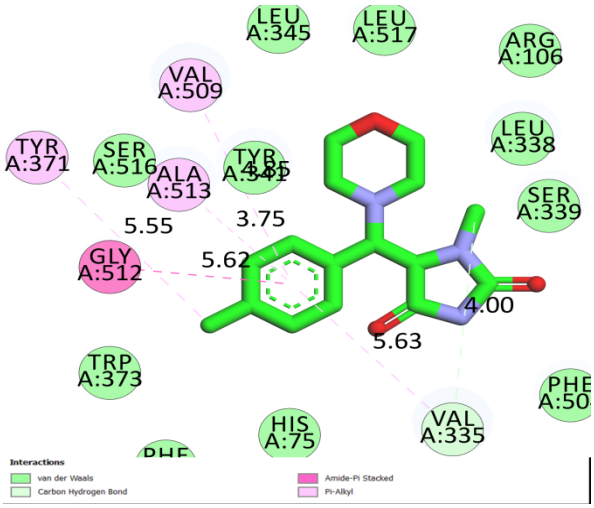


Fig-5: 2D view interaction of 4a with 3LN1

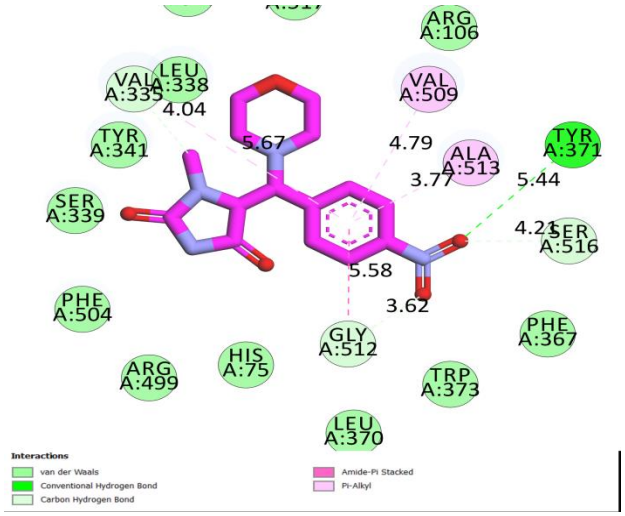


Fig-6: 2D view interaction of 4E with 3LN1

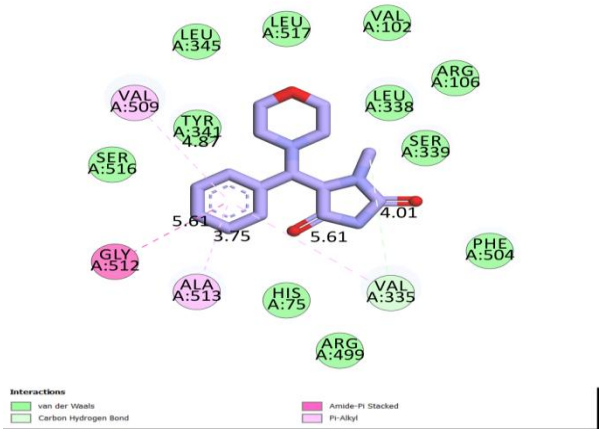


Fig-7: 2D view interaction of 4f with 3LN1

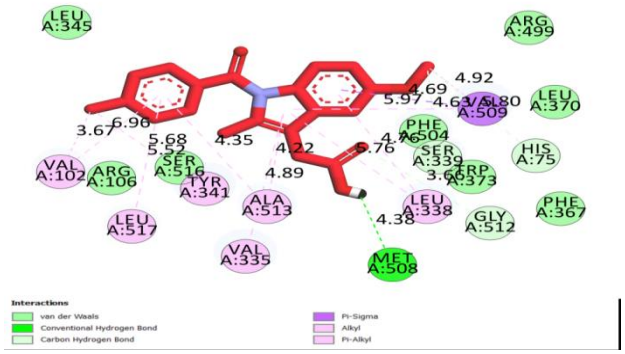


Fig-8: 2D view interaction of indomethacin with 3LN1

Docking at voltage gated sodium ion channels (PDB: 3RVY)

The hydantoin derivatives' hydrogen bonding interactions, both in terms of frequency and strength, provide insight into molecular compatibility, which is probably related to how well the ligands work at voltage-gated sodium ion channels. For example, interactions between ILE B:2199 and TRP B:2195 are often seen across several derivatives. The hydrophobic pocket formed by these residues seems to stabilise the ligands inside the binding site. Remarkably, ligand **4A** exhibits a variety of hydrophobic interactions beyond those usually observed with TRP B:2195, ILE B:2199, and TYR A:1168. These contacts had lengths ranging from 4.61 to 5.18Å, indicating van der Waals stabilisation and efficient packing, both of which are correlated with moderate binding affinities. At the active site area, the standard ligand phenytoin was shown to have a docking energy ΔG of -8.0 kcal/mol. Ligand **4A** exhibits an excellent alignment within the hydrophobic pocket, as evidenced by its dense cluster of hydrophobic interactions and considerable binding affinity (ΔG of -8.1 kcal/mol). A closer look at the specific information in Table-7 shows that hydrogen-bond interactions are nevertheless important for some hydantoin derivatives' binding affinity to voltage-gated sodium ion channels, even if they are less common than hydrophobic interactions. Significant binding affinity was observed for ligands **4A**, **4E**, and **4C** (ΔG values of -8.1 kcal/mol, -7.8 kcal/mol, and -7.5 kcal/mol, respectively).These interactions help the ligands specificity and docking stability, which may improve their pharmacological effects even though they are weaker than hydrogen bonds and van der Waals forces.

Table-7: Binding energies and interaction of designed ligands **4a-4f** with voltage gated sodium ion Channels (PDB: 3RVY)

Ligands	Binding Energy	Amino acids involved and distance (Å)

International Journal of Environmental Sciences
ISSN: 2229-7359
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	ΔG (Kcal/mol)	Hydrogen-Bond Interactions	Hydrophobic Interactions
4a	-8.1	-	TRP B:2195 (5.18, 4.61), ILE B:2199 (5.31), TYR A:1168 (4.61)
4b	-6.7	GLY A:1164 (3.48)	ILE A:2199 (5.43), TRP B:2195 (5.29)
4c	-7.5	-	PHE A:1167 (4.26), TRP B: 2195, ILE B:2199 (5.31)
4d	-6.8	-	ILE B:2199 (5.35), TRP B: 2195 (4.22, 5.15), TYR A:1168 (4.55), PHE A:1167 (4.24)
4e	-7.8	-	TRP B:2199 (5.15), PHE A:1167 (4.26)
4f	-7.3	-	ILE B:2199 (5.31), TRP B:2195 (5.48)
Phenytoin	-8.0	-	TRP B: 2195(5.27), ILE B: 2199 (5.57)

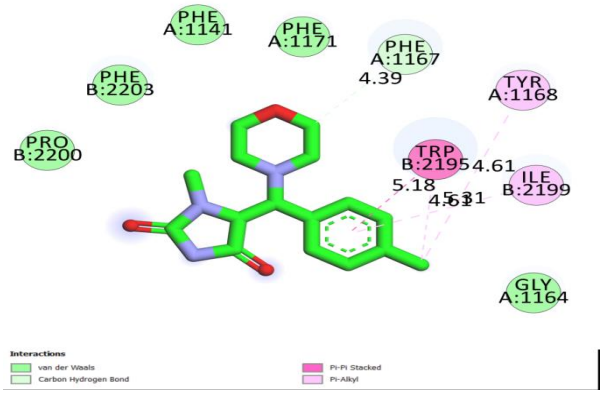

Fig-9: 2D view interaction of 4a with 3LN1

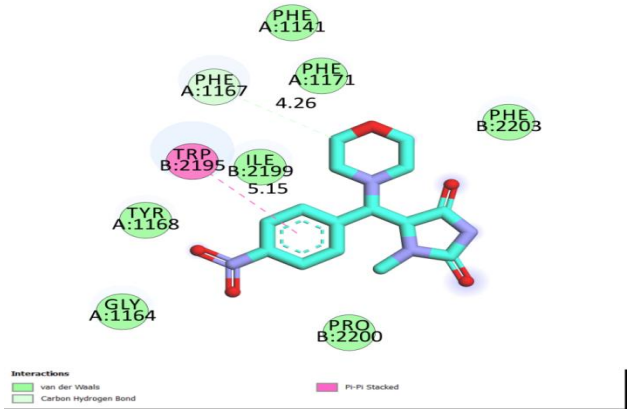

Fig-10: 2D view interaction of 4E with 3LN1

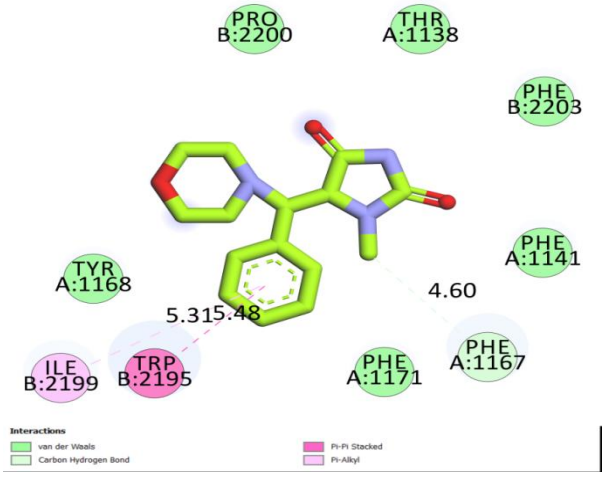

Fig-11: 2D view interaction of 4f with 3LN1

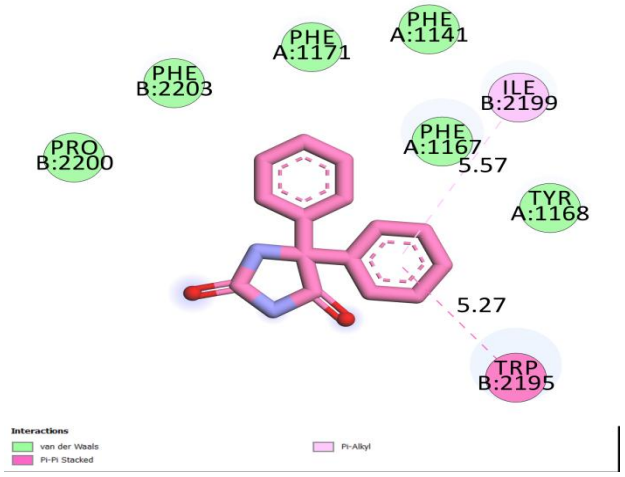

Fig-12: 2D view interaction of phenytoin with 3LN1

CONCLUSION

This study used the Biltz and Mannich reaction to create a variety of hydantoin derivatives with morpholine and substituted phenyl appendages connected to the common methyl group. Physical and spectroscopic characterization of the synthesised substances were performed. All of the substances satisfied the Lipinski rule since their computationally calculated lipophilicity parameters were less than five. As such, when used as medications, they might have oral activity. High levels of bioavailability are anticipated for hydanotin derivatives containing morpholine moiety as ADME analysis demonstrated sufficient absorption, distribution, and elimination parameters. The examined compounds may make good future therapeutic candidates, according to research on lipophilicity criteria and the ADME study. Compounds **4A**, **4E**, and **4F** showed strong binding

affinities at the COX-1 and COX-2 protein targets in molecular docking investigations. Based on molecular docking studies conducted at voltage-gated sodium channel targets, compounds **4A**, **4E**, and **4C** demonstrated noteworthy binding affinities. According to the structure-activity relationship (SAR), compounds containing electron-withdrawing groups on the phenyl ring may be able to have anti-inflammatory and anti-convulsant properties, according to in-silico molecular docking studies.

Acknowledgments

The authors are thankful to Acharya Nagarjuna University, Guntur; Krishna University College of Pharmaceutical Sciences & Research, Machilipatnam and Hindu College of Pharmacy, Guntur, Andhra Pradesh for providing necessary facilities to carry out the research work.

Conflict of Interest

Authors have no conflict of interest to declare.

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