DESIGN, MOLECULAR DOCKING, ADMET PREDICTION AND IN-VITRO SCREENING OF NOVEL INDANE-1, 3-DIONE DERIVATIVES AGAINST HELMINTHIC INFECTIONS

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Abstract: *The Indane 1.3 dione nucleus is a useful structural moiety for the development of molecules for various pharmacological activities. We herein report the design, docking, and Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) prediction studies of substituted of 2-(aryl methylene)-(1H)-indane-l,3-(2H)-diones derivatives as antheminitics. The synthesized molecules were subjected for the calculations of drug-likeness properties, Lipinski rule, Veber's rule, ADME analysis and molecular docking. From this initial screening through Lipinski rule, Veber's rule, ADME calculations, and drug-likeness properties, all the molecules successfully passed all the filters and displayed most drug-likeness nature. From molecular docking results, we have selected Compound I, VII, IX, XIII, XV for the wet lab synthesis and evaluation of anthelmintic activity. The structures of all the synthesized compounds were confirmed by spectral analysis and screened for antihelminthic activity against Pheretima posthuma using albendazole as reference compounds. Compounds selected I, VII, IX, XIII, XV showed good activity against Indian earthworms (Pheretima posthuma) in comparison to albendazole.*

Keywords*: Antihelminthic Activity ,Indane 1.3 dione, Synthesis,β-Tubulin ,Molecular Docking.*

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INTRODUCTION

Indane-1, 3-dione and its derivatives are important organic compounds showing wide range of their biological and pharmacological activities [1]. Researchers have paid a lot of attention to this compound with dyeing properties due to its easy self-condensation under both acid and basic conditions [2]. The last two decades have witnessed profound changes in indane-1, 3- dione chemistry both in quality and quantity. Indane-1, 3-dione constitutes a unique group of compounds due to its 1, 3-dicarbonyl nature. It has wide range of biological activity covering anticoagulant, bactericidal, neurotropic, antiphlogistic, radioprotective effects, zoocide, insecticide, and fungicide [3]. Specific physiochemical properties which offer wide scope for studies in the problems of theoretical organic chemistry, particularly on the basis of tautomerism, dual reactivity, electrochemical redox and corresponding quantum chemical calculations, unique properties of polycrystalline films etc [4]. In past decades, Indane diones and its derivatives have received much attention due to their chemotherapeutic value in the development of novel anthelmintic and antimicrobial agents. In this work, we turned our interest to study the incorporation of different aromatic aldehydes on parent Indane 1.3 dione ,there docking, Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) prediction studies to afford a variety of new derivatives of our lead compound .

The anthelmintic activity was evaluated on adult Indian earthworm, Pheretima posthuma due to its anatomical and physiological resemblance with the intestinal roundworm parasites of human beings and easy availability [5, 6]

2 METHODOLOGY

2.1 Computer System and Software

Computer system (Dell), with the following specifcation properties; CPU Dual@0.30 GHz, Intel® Core i3-6100U, 12 Gigabyte RAM was used throughout the present study. The software download and installed include PyRx virtual screening software, Discovery Studio Visualizer v16.1.0.15350, Chemdraw Ultra software V. 12.0.2, Swiss ADME online software.

2.2 In-Silico Docking And ADME/Pharmacokinetics Prediction

The in-silico studies helped to determine the activity of the compound when inside the body and served as an important tool for drug discovery and lead optimization. Molecular descriptors and druglikeliness properties of 2-(aryl methylene)-(1*H*)-indane-l,3-(2*H*)-diones derivatives were analyzed using the Molinspiration tool server (http://www.molinspiration. com), which is based on Lipinski's rules of five (RO5)[7]. The pharmacokinetic properties, such as absorption, distribution, metabolism, excretion, and toxicity, of the compounds were checked using the SwissADME online database[8]. The structures were drawn using Advanced Chemistry Department (ACD)/ChemSketch version 12.0, and Simplified molecular-input line-entry system (SMILES) notation data were generated and fed into these softwares to calculate the parameters.

The chemical structure of the molecules was accurately drawn with ChemDraw Ultra level software V12.0.2. **(Table 1)**

2.3 X-ray crystal structure

The X-ray crystal structure of PDB – alpha- and beta- tubulin in GMPCPP-microtubules (3j7i) was imported from Protein Data Bank (available at http:// www.rcsb.org/). The X-ray crystal structure of the 3j7i domain had a resolution of 8.9 Å.

2.4 Preparation of ligands & Target Proteins

The crude Protein Data Bank (PDB) structure of the receptor was refined by completing the incomplete residues. Chloride ions and Adenosine diphosphate (ADP) were deleted. Water molecules were also removed, and hydrogen atoms were added. The optimized receptor was saved as a .mol file and used for docking simulation.

The 2D structures of the designed molecules and the reference ligand, albendazole, were sketched using MarvinSketch 5.11.5.

In-silico docking operation was carried out with the downloaded receptor using AutoDock Vina of PyRx virtual screening software [9]. The vina wizard uses a stochastic gradient optimization algorithm for predicting the binding affinities between ligands and receptors. The docking output with the highest binding affinity was visualized to study the residual interactions using Discovery Studio Visualizer.

Energy of the 3j7i was minimized based on GROMAS6 43B1 algorithm using Swiss Model Viewer, water was removed and Polar hydrogens were added to the 3j7i protein of β-tubulin followed by calculation of gasteiger Charges using the AutoDock MG Tool and saved in PDBQT file format. The receptor grid was developed using AutoDock Grid tool with grid dimensions of $25A^0 \times 25A^0 \times 25A^0$ with 0.375 A^0 spacing and the grid box was set at -62.69,-56.30,-66.03 in X, Y and Z dimension.

Figure 1 shows the 3D prepared Crystal structure of PDB – 3j7i (Structure of α and β-tubulin in GMPCPP-microtubules) adapted from protein data bank. Furthermore, the Simplified Molecular Input Line Entry System (SMILES) format of the molecules was pasted on the swiss ADME webserver (Swiss Institute of Bioinformatics, Switzerland) to generate their ADME/pharmacokinetic profile and drug-likeness parameters

2.5 Molecular docking studies

In order to further optimization, the derivatives were subjected for binding affinity studies with 3j7i enzyme. The Autodock vina 1.1.2 with PyRx Virtual Screening Tool 0.8 software of the Chimera version 1.10.2[10] and the Biovia Discovery studio was used to perform molecular docking[11].The structures of 2-(aryl methylene)-(1*H*)-indane-l,3-(2*H*)-diones derivatives and native ligand were drawn using ChemDraw Ultra 8.0 version and saved in mol file format. The energy minimization was executed by Universal Force Field (UFF) in PyRx software[12].The crystal structure of Cystal structure of PDB –3j7i (Structure of alpha- and beta- tubulin in GMPCPP-microtubules) was obtained from the RCSB Protein Data Bank (https://www.rcsb.org/)shown in Fig 1. The 3D ribbon view of 3j7i in complex with native ligand is described in Fig. 2. The binding affinity and binding mode of native ligand was used to validate

the results of synthesized derivatives. The total molecular docking approach was carried out using the methods explained by S. L. Khan *et al* [13]

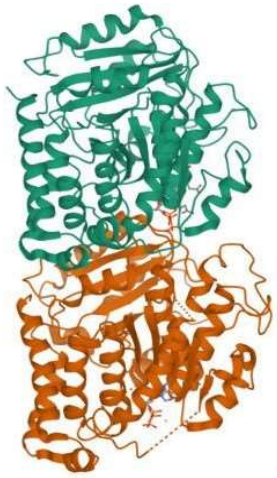


Figure 1: Cystal structure of PDB – 3j7i (Structure of β- tubulin in GMPCPP-microtubules) adapted from protein data bank

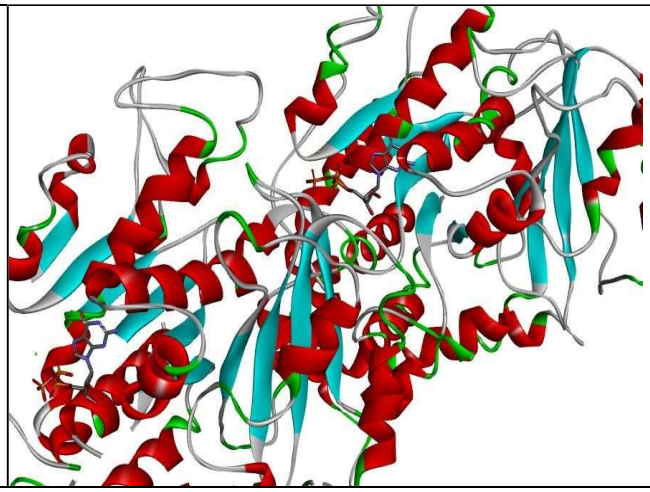


Figure 2: The 3D ribbon view of 3j7i complex withα- and β-tubulin in GMPCPP-microtubules (native ligand)

Reaction scheme and derivatives

Wet lab synthesis of selected derivatives

All research chemicals were purchased from Merck or Cosmo Chem Pvt. Ltd. and used as such for the reactions. Solvents except LR grade were dried and purified according to the literature whereas necessary. The glasswares used in the reactions are made of borosil. All the glasswares were cleaned by using chromic acid and acetone before use.

The derivatives were designed by taking ethanolic solution of indane-l,3-dione as starting material which have to be treated with different aromatic aldehydes in presence of piperidine to produce 2-(aryl methylene)-(1*H*)-indane-l,3-(2*H*)-diones.

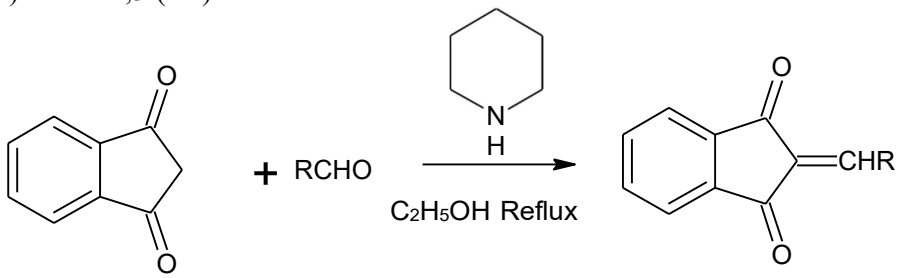


Fig 3. The proposed reaction scheme to design 2-(aryl methylene)-(1*H*)-indane-l,3-(2*H*)-diones derivatives

General procedure for the preparation of 2-(aryl methylene)-(1*H*)-indane-l,3-(2*H*)-diones [5] (I-XIII)

1. To an ethanolic solution of indane-l,3-dione (14.6gm~0.1 mole) were added different distilled aromatic aldehydes (12.6gm~0.1 mole) followed by a drop of piperidine.
2. The mixture was refluxed for 3 hr.
3. The resultant reaction mixture was concentrated to half of its volume and poured onto crushed ice.
4. The solid that separated was filtered using vacuum pump and washed repeatedly with ice- cold aqueous ethanol.
5. Then it was recrystallized from ethanol. (Meena et al.,2006).

Compound I: 2-[(2-bromo-5-fluorophenyl)methylidene]-1*H*-indene-1,3(2*H*)-dione
Pale yellow solid, yield: 84%, molecular formula: $C_{16}H_8BrFO_2$, melting point: 172-176^{0}C. Elemental analysis (*cal.*): C(58.03%) H(2.44%) Br(24.13%) F(5.74%) O(9.66%). FT-IR (neat, cm^{-1}) ν_{max}: 2905(CH), 834(C-F),1605 (C=O),680(C-Br), 988(Ar-H),1555(C=C). ^{1}H NMR (300MHz, DMSO-d_6, chemical shift (ppm));δ: 8.10 (m, 4H, Ar-H), 7.53 (m, 3H, Ar-H), 3.85 (s, 1H, CH_3) MS m/z: 331.20

Compound VII : 2-{[2-nitro-4-(trifluoromethyl)phenyl]methylidene}-1*H*-indene-1,3(2*H*)-dione
Pale yellow solid, yield: 79%, molecular formula: $C_{17}H_8F_3NO_4$, melting point: 235-240^{0}C. Elemental analysis (*cal.*): C(58.80%) H(2.32%) F(16.41%) N(4.03%) O(18.43%). FT-IR (neat, cm^{-1}) ν_{max}: 3005(CH), 1605 (C=O), 1568, 1348 (Ar-NO_2), 840(C-F), 1350(C-N). ^{1}H NMR (300 MHz, DMSO-d_6, chemical shift (ppm)); δ: 8.09-8.25(m, 4H, Ar-H), 8.55 (d, 3H, Ar-H), 3.35(s, 1H, CH_3). MS m/z: 346.45

Compound IX: 2-[(3,4-dichlorophenyl)methylidene]-1*H*-indene-1,3(2*H*)-dione
Pale yellow solid, yield: 69%, molecular formula: $C_{16}H_8Cl_2O_2$, melting point: 170-175^{0}C. Elemental analysis (*cal.*): C(63.39%) H(2.66%) Cl(23.39%) O(10.56%).FT-IR (neat, cm^{-1}) ν_{max}: 3050 (CH), 754(C-Cl),750(Di-substituted benzene)1705 (C=O), ^{1}H NMR (300 MHz, DMSO-d_6, chemical shift (ppm)); δ:8.02-8.4 (m, 4H, Ar-H), 7.8(m, 3H, Ar-H), 3.26 (s, 1H, CH_3). MS m/z: 303.29

Compound XIII: 3-[(1,3-dioxo-1,3-dihydro-2H-inden-2-ylidene)methyl]benzonitrile
Pale yellow solid, yield: 91%, molecular formula: $C_{17}H_9NO_2$, melting point: 127-129^{0}C. Elemental analysis (*cal.*): C(78.76%) H(3.50%) N(5.40%) O(12.34%). FT-IR (neat, cm^{-1}) ν_{max}:2998(CH), 1620(C=O), 730(Mono-substituted benzene) 2240(C=N) 1568, 1090 (C-N), 1428 (C=N) 1090 (C-N). ^{1}H NMR(300 MHz, DMSO-d_6, chemical shift (ppm)); δ: 7.7-7.9 (m,3H, Ar-H),8-8.9(m, 4H, Ar-H), 3.3 (s, 1H, CH_3). MS m/z: 258.35

Compound XV: 2-[(4-chloro-2-fluorophenyl)methylidene]-1*H*-indene-1,3(2*H*)-dione
Pale yellow solid, yield: 76%, molecular formula: $C_{16}H_8ClFO_2$, melting point: 174-180^{0}C. Elemental analysis (*cal.*):C(67.03%) H(2.81%) Cl(12.37%) F(6.63%) O(11.16%). FT-IR (neat, cm^{-1}) ν_{max}: 3015 (CH), 1615 (C=O), 740(C-Cl), 836(C-F),775(Di-substituted benzene). ^{1}H NMR (300 MHz, DMSO-d_6, chemical shift (ppm)); δ: 7.5-8 (m, 3H, Ar-H), 8.03-8.8(m, 4H, Ar-H), 3.12 (s, 1H, CH_3) MS m/z: 287.49

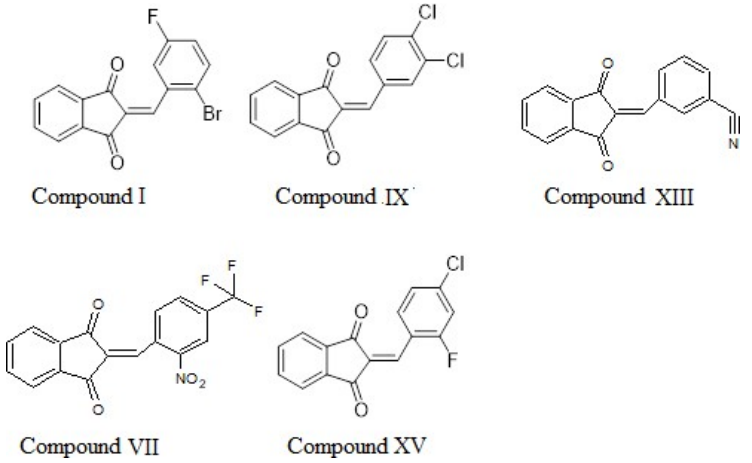


Figure 4. The structures of synthesized compounds

In-vitro Activity[14]
Anthelmintic activity:
The efficacy of the synthesized derivatives as anthelmintic was carried as per the procedures described by Ajaiyeoba et al [15] with slight modification by Satish et.al [16]Indian adult earthworms (*pheretima posthuma*) were used to study anthelmintic activity. The earthworms (collected from the water logged areas of soils, Pune.) were washed with normal saline to remove all fecal materials. The earthworms in 4-5 cm. in length and 0.1 - 0.2 cm in width were used for all experimental protocol. The earthworm resembles both anatomically and physiologically to the intestinal roundworm parasites of human beings,

hence can be used to study anthelmintic activity. The newly synthesized compounds (scheme I) were tested for anthelmintic activity. *Pheretima posthuma* of nearly equal size were selected randomly for present study. The worms were acclimatized to the laboratory condition before experimentation. The earthworms were divided into four groups of six earthworms in each. Albendazole diluted with normal saline solution to obtain 0.2% w/v and 0.5% w/v served as standard and poured into petri dishes. The synthesized compounds (scheme I) were prepared in minimal quantity of DMSO and diluted to prepare two concentrations i.e. 0.2% w/v, 0.5% w/v for each compound. Normal saline served as negative control. Six earthworms nearly equal size are taken for each concentration and placed in Petri dishes at room temperature. The time taken for complete paralysis and death are recorded. The mean paralysis time and mean lethal time for each sample was calculated. The time taken for worms to become motionless was noted as paralysis time and to ascertain death, each worm was frequently applied with external stimuli which stimulates and induce movement in the earthworms, if alive[17-20]. The synthesized compounds shows good anthelmintic activities indicated (Table 4) compared to standard drug.

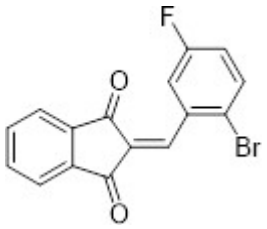
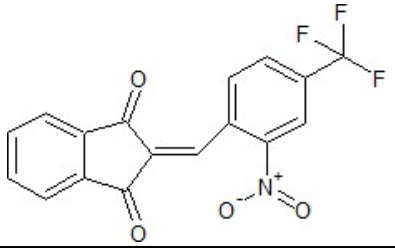
RESULTS AND DISCUSSIONS

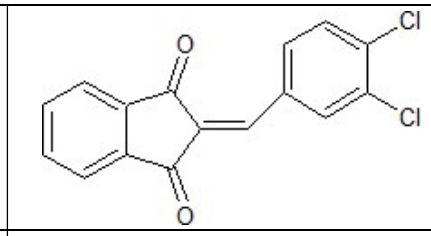
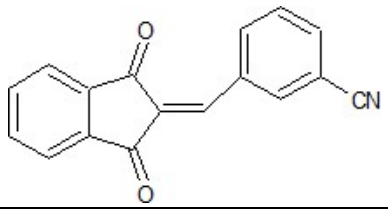
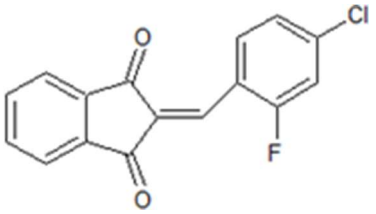
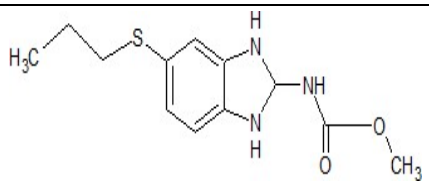
1. Molecular Docking and Virtual Screening

Molecular docking is powerful in silico approach in computational drug design by which one can predict the predominant binding mode(s) of a ligand with a target protein [21]. This technique involves the selection of 3D- coordinate space of the binding site in the target and calculating the binding affinity of the resultant orientation of the molecule within the binding site which forms the complex. In addition, the molecular docking simulation was performed to validate the anthelmintic efficacy of synthesized 2-(aryl methylene)-(1H)-indane-l,3-(*2H*)-diones derivatives by investigating binding modes as well as orientation of ligands in the receptor pocket of β-tubulin target. Microtubules are dynamic polymers that stochastically switch between growing and shrinking phases. Microtubule dynamics are regulated by guanosine triphosphate (GTP) hydrolysis by β-tubulin.

The docking poses were ranked according to their score values, and Table 2 showed binding affinities of the best pose of the selected I, VII, IX,XIII and XV synthesized molecules with the β-tubulin target.It was observed that the binding affinity of complexes ranged from−9.8to– 11.4 kcal/mol which confirmed their excellent potency.

Table 1. Physical Characterization of synthesized compound (I-XV)

Compound Code	Chemical Structure	Mole. Wt (gm)	Percentage Yield(%)	R_f Value	Docking score (kcal/mol)
I		331.14	84	0.76	-10.4
VII		347.24	79	0.80	-11.4

IX		303.14	69	0.69	-10.4
XIII		259.26	91	0.79	-10.7
XV		286.69	76	0.59	-10.6
STD		265.33	--	Albendazole	-6.8

In-silico ADME/Pharmacokinetic Predictions

The in silico pharmacokinetic parameters of the synthesized drivatives were predicted by the online tool, admetSAR and the drug likeness and bioactive scores were predicted by the online tool, Molinspiration cheminformatics . The 2D structural models of the designed molecules were drawn on ACD/ChemSketch software and SMILES were generated for the molecules along with standard drugs, these smiles notations were used for predicting the individual ADMET, bioactive and drug likeness scores. Admet SAR gives data for the evaluation of active molecules and also for the removal of biologically defective major molecules with unwanted functional groups.

All the molecules (I-XIII) showed no violation from Lipinski's RO5. All compounds followed Veber'srule as they have rotatable bonds ≤10 and TPSA ≤140° indicates that most compounds may have good oral absorption (Veber et al., 2002).

Table 2: Calculations of Lipinski's rule of five and Veber's rule for the designed derivatives

Comp Codes	Lipinski's rule of five					Veber's rule	
	Log P (≤5)	Mol. Wt. (≤500)	HBA (≤10)	HBD (≤5)	Violations	Total polar surface area (Å²) (≤140)	No. of rotatable bonds (≤10)
Albendazole	2.39	265.33	3	02	00	92.31	06
I.	3.85	286.68	3	00	00	34.14	1
II.	3.93	331.14	3	00	00	34.14	1
III.	2.40	279.25	4	00	00	79.96	2
IV.	3.55	268.69	2	00	00	34.14	1

V.	2.98	294.30	4	00	00	52.60	3
VI.	4.21	290.36	2	00	00	34.14	2
VII.	3.00	234.25	2	0	00	34.14	1
VIII.	3.32	282.27	4	0	00	43.37	2
IX.	2.61	280.27	4	1	00	63.60	2
X.	2.58	250.25	3	1	00	54.37	1
XI.	4.05	302.25	5	0	00	34.14	2
XII.	3.31	278.30	3	0	00	43.37	3
XIII.	4.06	303.14	2	0	00	34.14	1
XIV.	4.08	303.14	2	0	00	34.14	1
XV.	2.95	292.29	4	0	00	60.44	3

Where: Mol. Wt., molecular weight; HBA, hydrogen bond acceptors; HBD,hydrogen bond donors

Table 3: The pharmacokinetics and drug-likeness properties of developed compounds

Compound codes	Pharmacokinetics									Drug-likeness			
	GI abs.	BBB pen.	P-gp sub.	CYP 1A2 Inhibitors	CYP 2C19 Inhibitors	CYP P2C9 Inhibitors	CYP 2D6 Inhibitors	CYP 3A4 Inhibitors	Log *Kp* (skin permeation, cm/s)	Ghose	Egan	Muegge	Bioavailability Score
ALb	High	No	No	Yes	No	No	No	No	-5.92	Yes	Yes	Yes	0.55
I	High	Yes	No	Yes	Yes	Yes	No	No	-5.05	Yes	Yes	Yes	0.55
II	High	Yes	Yes	No	No	No	No	No	-5.27	Yes	No	No	0.55
III	High	No	No	Yes	Yes	No	No	No	-5.64	Yes	No	No	0.55
IV	High	Yes	No	Yes	Yes	No	No	No	-5.01	Yes	No	No	0.55
V	High	Yes	Yes	Yes	Yes	No	No	No	-5.65	Yes	No	No	0.55
VI	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.24	Yes	Yes	Yes	0.55
VII	High	Yes	No	Yes	Yes	Yes	No	No	-5.49	Yes	Yes	Yes	0.55
VIII	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.79	Yes	Yes	Yes	0.55
IX	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.59	Yes	Yes	Yes	0.55
X	High	Yes	No	Yes	Yes	Yes	No	No	-5.03	Yes	Yes	Yes	0.55
XI	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.27	Yes	Yes	Yes	0.55
XII	High	Yes	No	Yes	Yes	Yes	No	Yes	-4.77	No	Yes	No	0.55
XIII	High	Yes	No	Yes	Yes	Yes	No	Yes	-4.77	Yes	Yes	Yes	0.55
XIV	High	Yes	No	Yes	Yes	Yes	No	No	-5.70	Yes	Yes	Yes	0.55
XV	High	Yes	No	Yes	Yes	Yes	No	Yes	-5.24	Yes	Yes	Yes	0.55

Where: ALB-Albendazole standard , GI abs., gastrointestinal absorption; BBB pen., blood brain barrier penetration; P-gp sub., p-glycoprotein substrate ,

From the initial screening through Lipinski rule, Veber's rule, ADME calculations, and drug-likeness properties, molecules I,VII,IX,XIII,XV successfully passed all the steps and showed maximum drug-likeness properties. Therefore only these molecules were taken for molecular docking studies. Many of the molecules selected for docking had exhibited potent interactions and binding energy than standard drug with the target. The active amino acid residues, bond length (A^0), bond type,bond category, binding affinities (kcal/mol)of the docked molecules are shown in Table 5. The molecules' 2D and 3D docking postures (most potent) are represented in Fig. 4. The Antihelminthic activity was performed on all of the synthesized compounds and the results are tabulated in Table 4.

Antihelminthic activity of 2-(aryl methylene)-(1*H*)-indane-l,3-(2*H*)-diones derivatives were evaluated for their activity against Pheretima posthuma. The antihelminthic activity showed that compounds I, VII, IX,XIII and XV good activity against Indian earthworms (Pheretima posthuma) in comparison to albendazole. The docking studies yielded fitness score ranging from -9.8 to -11.4. The docking study indicate that compounds bind with *β*-tubulin by forming hydrophobic interaction with amino acid residues ALA187,VAL172, ILE391, PHE388, THR168, LEU194, PRO173 ,LEU194, ILE391,VAL191,ALA187, LEU137, HIS139,ILE154,SER147, van-der waal interaction with amino acid residues SER190,MET425,LEU425,LEU137 and Hydrogen Bond interaction with amino acid residues ILE391,THR168, SER190, SER190,THR168, SER190,LEU194,SER147 . From the docking simulation it is found that title analogues have good interaction with *β*-tubulin.

The results of anthelmintic activity of the title compounds were shown in table-4

Table 4: Anthelmintic activity of synthesized Compounds

Comp	**Time of paralysis (min)**		**Time for death (min)**	
	% of Concentration		**% of Concentration**	
	0.2%	**0.5%**	**0.2%**	**0.5%**
I	12.15±0.54	13.27±0.52	14.42±0.18	19.41±0.53
II	7.11±0.90	9.52±0.30	11.25±0.24	13.36±0.81
III	7.23±0.15	9.33±0.38	11.41±0.60	13.57±0.51
IV	8.22±0.30	10.41±0.28	11.23±0.37	13.01±0.87
V	8.01±0.70	10.22±0.13	11.03±1.60	13.24±0.59
VI	9.12±0.49	11.36±0.45	12.36±0.21	14.51± 0.48
VII	8.41±0.21	10.03±0.83	12.41±0.58	14.09±0.74
VIII	9.14±0.38	11.52±0.42	14.21±0.33	13.52±0.59
IX	7.25±0.30	9.41±0.21	13.41±1.21	15.22±0.55
X	9.58±0.45	11.21±0.76	16.33±0.44	18.11±0.63
XI	12.08±0.61	13.25±0.47	17.63±0.38	19.21±0.29
XII	11.23±0.29	13.41±0.58	15.36±0.62	17.36±0.62
XIII	10.56±1.12	12.47±0.24	16.42±0.65	18.42±0.43
XIV	7.25±0.14	9.51±0.19	17.52±0.55	19.22±0.57
XV	09.56±0.26	11.22±0.26	18.26±0.79	19.51±1.18
Negative control	---	---	---	---
Standard (Albendazole)	13.22±0.31	15.45±0.43	21.65±0.76	29.45±0.46

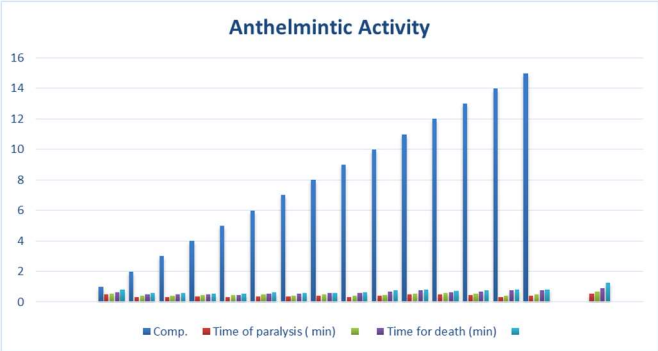
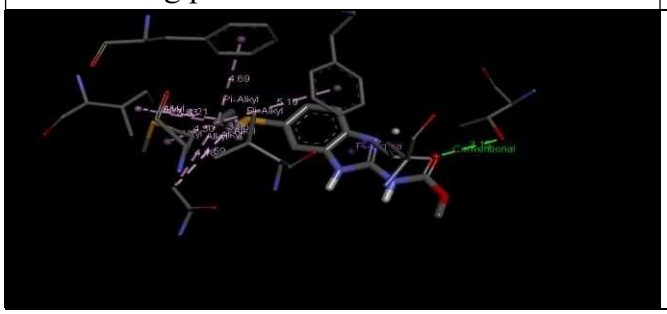
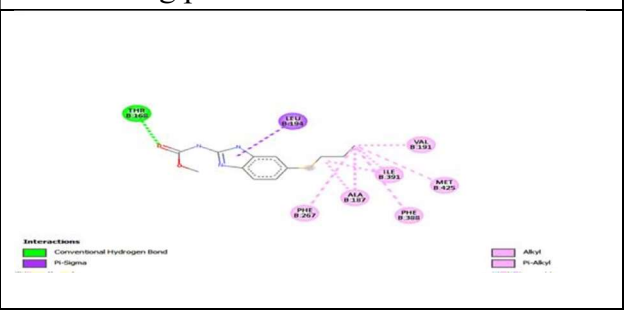


Fig. 5 Graph showing difference in time of paralysis & time of death in anthelmintic activity

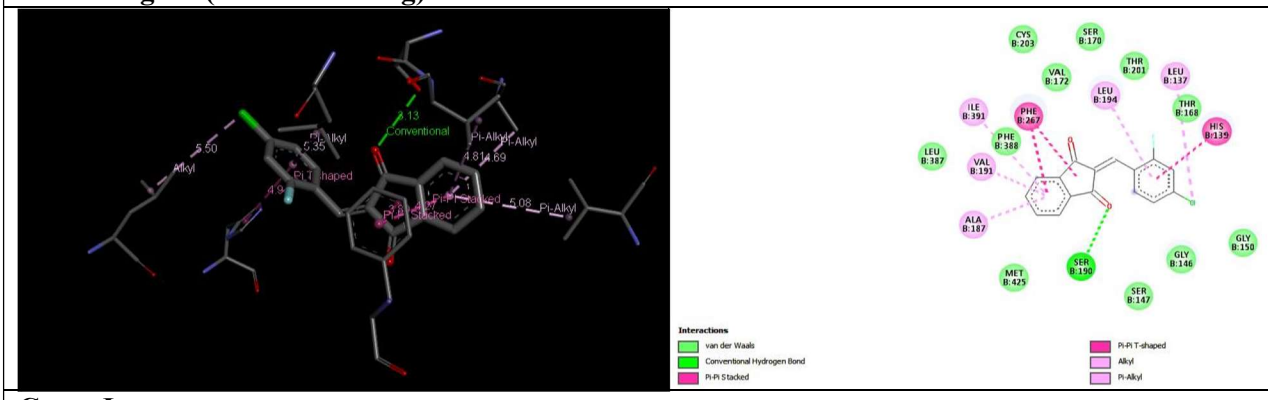
Table 5: The active amino acid residues, bond length (A0), bond type, bond category, binding affinities (kcal/mol), and the ligand energies (kcal/mol)

Active aminoresidues	Bond length(A^0)	Bond type	Bond category	Binding affinity (kcal/mol)
Native ligand(Standard drug)-Albendazole				
THR168	3.10	HydrogenBond	Conventional Hydrogen Bond	-6.8
LEU194	3.87	Hydrophobic	Pi-Sigma	
MET425	4.18	Electrostatic	Alkyl	
VAL191	4.21			
PHE267	5.19			
ALA187	4.69	Hydrophobic	Pi-Alkyl	
PHE388				
Comp I				
SER190	3.13	HydrogenBond	Conventional Hydrogen Bond	-10.4
PHE267	5.50	Electrostatic	Pi-Cation	
ALA187				
HTS139				
PHE388	4.69	Hydrophobic	Pi-Alkyl	
THR168	5.35			
Comp VII				
VAL172	3.67	Hydrophobic	Pi-Sigma	-11.4
ILE391				
PHE267	4.28	Electrostatic	Pi-Pi Stacked	
	5.34			
PRO173	3.69	Hydrophobic	Pi-Alkyl	
LEU194	4.70			
Comp IX				
SER190	2.83	HydrogenBond	Conventional Hydrogen Bond	-10.4
THR168				

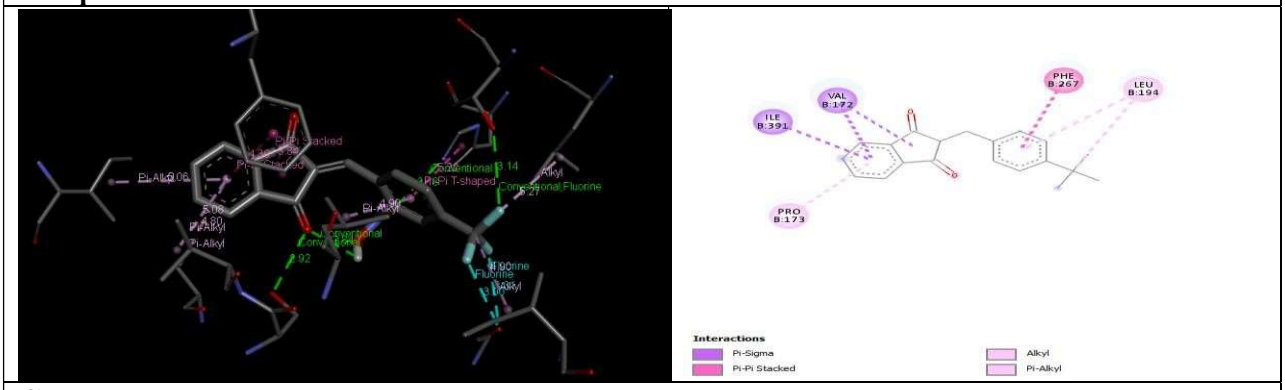
PHE267	4.91	Vander wall	Pi-Pi T-shaped	
LEU137				
ILE154	4.94	HydrogenBond	Pi-Alkyl	
LEU137	4.41			
HTS139	4.35	Electrostatic	Pi-Pi Stacked	
ILE391	5.11	Hydrophobic	Pi-Alkyl	
VAL191	4.74			
ALA187	5.38			
Comp XIII				
LEU137	3.91	Hydrophobic	Pi-Sigma	-10.7
LEU194	4.68	Other	Pi-Alkyl	
PHE267	4.07			
HIS139	4.44	Hydrophobic	Pi-Pi T-Shaped	
ALA89	5.46	HydrogenBond	Alkyl	
LEU153	5.42			
LEU194	2.69	HydrogenBond	Conventional Hydrogen Bond	-10.4
ILE154	5.34	Hydrophobic	Pi-Sigma	
SER147	3.51			
PHE388	4.21	Other	Pi-Alkyl	
LEU387	5.33			
PHE267	5.03			
VAL172	5.33			
Comp XV				
HIS139	4.90	Hydrophobic	Pi-Pi T-Shaped	-10.6
LEU137	5.08	HydrogenBond	Alkyl	
PHE267	3.80	Electrostatic	Pi-Pi Stacked	
	4.28			
SER190	2.89	HydrogenBond	Conventional Hydrogen Bond	
LEU194	5.37	Hydrophobic	Pi-Alkyl	
VAL191	4.78	HydrogenBond	Pi-Alkyl	
ALA187	5.04	Hydrophobic	Pi-Alkyl	
ILE391	4.98	HydrogenBond	Pi-Alkyl	

3D-docking poses	2D-docking poses
	

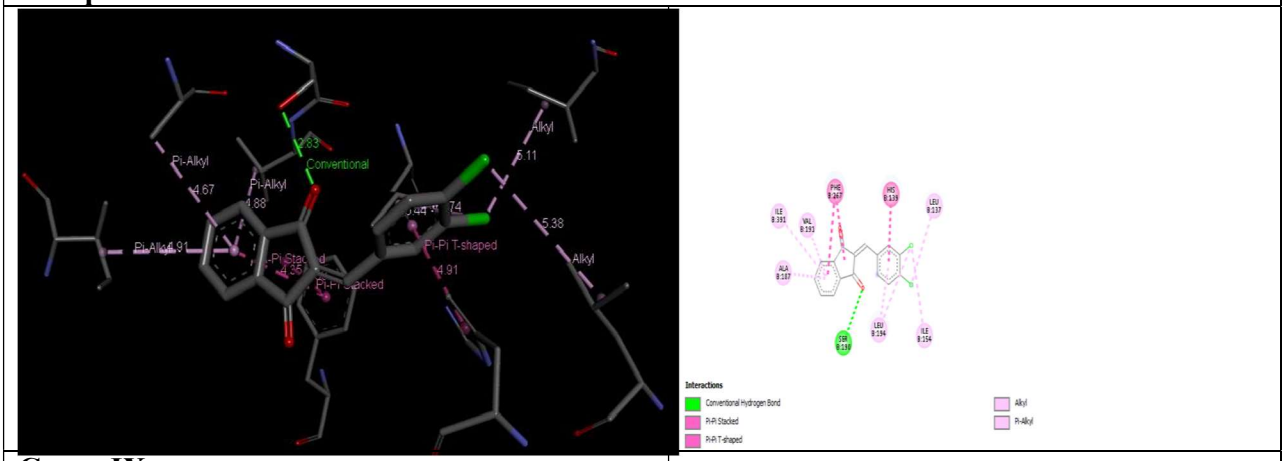
Native ligand(Standard drug)-Albendazole



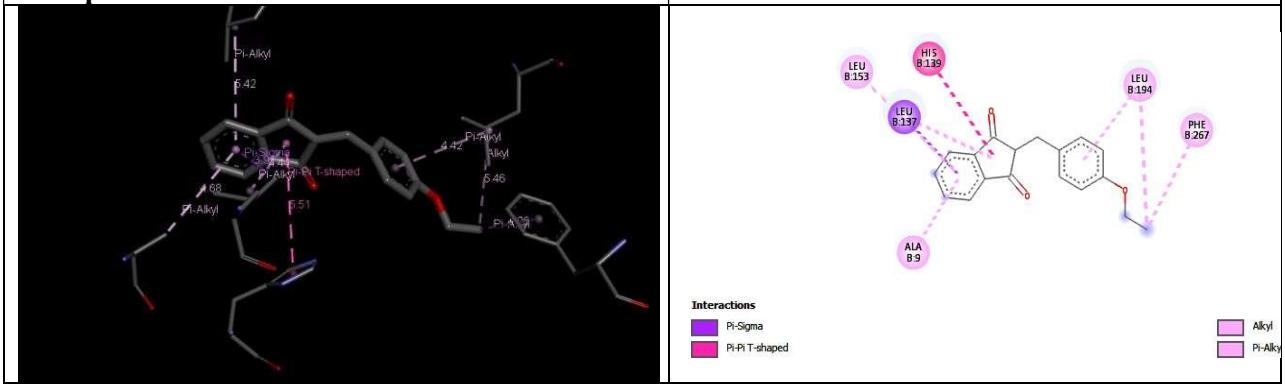
Comp I



Comp VII



Comp IX



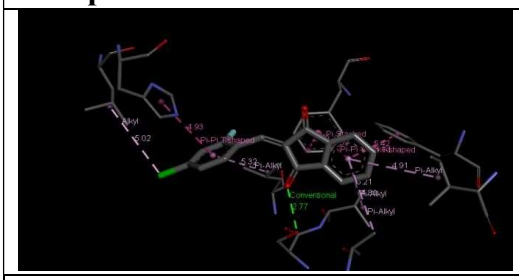
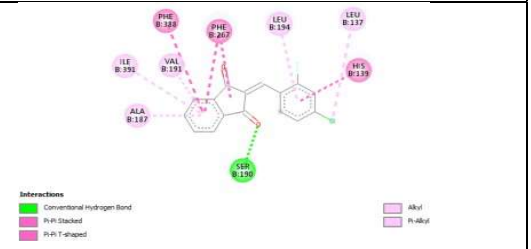
Comp XIII	
	
Comp XV	

Figure 6. The binding poses and 2D interactions of native ligand, and most potent derivatives

CONCLUSION

The novel Indane-1,3-Dione derivatives (Ia-XV)were synthesized and characterized by Physical characterization and spectral techniques. All this substituted 2-(aryl methylene)-(1*H*)-indane-l,3-(2*H*)-diones derivatives revealed significant anthelmintic activity against adult earth worms (P. posthuma) due to their anatomical and physiological resemblance with the intestinal roundworm parasites of human being. The compounds VII, IX, and XV show significant anthelmintic activity when compared to albendazole All the molecules (I-XV) showed no violation from Lipinski's RO5. All compounds followed Veber'srule as they have rotatable bonds ≤10 and TPSA ≤140º indicates that most compounds may have good oral absorption. The antihelminthic activity showed that compounds I, VII, IX,XIII and XV have good activity against Indian earthworms (Pheretima posthuma) in comparison to albendazole. The docking studies yielded fitness score ranging from -9.8 to -11.4.

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