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DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NOVEL 1,3-INDANEDIONE DERIVATIVES

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Absract:

In quest of elucidating the diverse pharmacological properties of 1,3-indanedione derivatives, we have synthesized a new series of 1,3-indanedione derivatives via Knovevanegal condensation, by condensing with the different aldehydes (Nitro benzalyhade) to form a styrylated indane dione leading to the formation of different Schiff base. The structures of compounds were characterized by ^{1}H and ^{13}C NMR, FT-IR and Mass spectral analysis. The newly synthesized compounds are evaluated for their antioxidant (NO and DPPH scavenging, and inhibition of lipid peroxidation), antimicrobial/antifungal, and anti-inflammatory activities. Compounds with phenolic group as the terminal substitution or meta- and para- di-substitutions are reported with superior antimicrobial, antifungal and anti-inflammatory activities. Compound 10 reported highest antimicrobial and antifungal activities and moderate antioxidant activity. Anti-inflammatory activity of compound 10 is statistically similar at 50 mg/kg dose with celecoxib (20 mg/kg). Molecular docking studies against COX2 enzyme were performed and reported similar observations and provided deeper understanding of the ligand conformations in the protein environment.

Keywords: *Indanedione, antibacterial agents, anti-oxidative, anti-inflammatory activity, molecular docking*

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1.INTRODUCTION:

During the years, indandione is established as an important starting material in various organic transformations because of its low cost, eco-friendliness and operational simplicity, easy to handle, and low toxicity properties and affording higher yields of corresponding products [1]. For the same reasons, indanedione has become a vital component in multicomponent chemical reactions in developing various drugs, bio conjugates, agrochemicals, etc. The β-di carbonyl moiety of the 1,3-indanedione structure serves as a key group for the synthesis of structurally complex compounds via condensation, decomposition, reduction, cyclization, rearrangements reactions [2]. Earlier research on 1,3-indanedione derivatives have reported various pharmacological potentials including anti-inflammatory [3], antioxidant [4,5] activities. Jayachendran et al. had recently reported antibacterial and anticoagulant activities of 2-(Arylsulfonyl) indane-1,3-diones [6]. Similarly, Chen et al has reported anticoagulant activity of fluorine containing indanedione containing rodenticides [7]. In 2017, Dhayabaran and colleagues reported the efficiency of the binding interaction of Co(II), Cu(II), Ni(II) and Zn(II) complexes with Schiff Base compounds derived from 1,3-Indandione complexes with calf thymus DNA (CT-DNA) [8]. Other biological activities include cholinesterase inhibition, anti-β-amyloid aggregation, and neuroprotection properties against Alzheimer's disease [9], hGlyT1 inhibition [10], embryotoxic and teratogenic activities [11], and anti-allergic activity [12]. In this study, we have designed and synthesized a novel series of 1,3-indanedione derivatives and evaluated for their pharmacological activities such as antioxidant, antimicrobial and antifungal, and anti-inflammatory activities along with molecular docking studies against COX2 enzyme.

2. MATERIALS AND METHODS:

2.1. Chemistry

All the chemicals used in the synthesis of the intermediates and final derivatives are of analytical grade and obtained from S.D fine chem. Limited (Mumbai). Purity of the synthesized compounds was analyzed by using TLC on silica gel-G plate as adsorbent and solvent system (or) mobile phase was used with various ratios of hexane, chloroform, ethanol, ethyl acetate appropriately. R_f values produced for each compound were correlating with the literature and assumed to be pure. Characterizations of synthesized compounds were interpreted by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and Mass Spectroscopy. Synthesis of the novel series is shown in **Scheme 1**.

General procedure for Synthesis of styrylated indanedione derivatives:

Synthesis of 2-(3-nitro benzylidene)-2H-indane-1,3-dione: Knowevanegal condensation reaction (I)

2-(3-nitro benzylidene)-2H-indane-1,3-dione was synthesized by condensation of 1,3-indanedione (0.1mol) with nitro benzaldehyde (0.1mol) (piperidine as base and benzyl alcohol as a solvent (5ml)) under reflux for 4 to 5 hours at 90 ^{0}C a solid pale yellow to yellow product was collected . **Yield:** 98 %, **m.p.:** 159 ^{0}C; **FT-IR** (KBr, cm-1): 1531, 1377 (NO2); 3068 (C=C); 3344, 3390 (C=0); 988 (Ar-H). **^{1}H NMR** (300 MHZ, $CDCl_3$) PPM: 8.57-7.1 (S, Ar-H), 8.54, 8.35, 8.33, and 7.86 (d, 4H); 7.9-8.05 (T, 3H). **m/z**: 279.

Synthesis of 2-(3-amino benzylidene)-2H-indene 1, 3-dione (II): Reduction

The nitro group of the compound I was reduced to amine in the presence of $SnCl_2.H_2O$ (10 moles) under ultra-sonication at 30 ^{0}C. After 2hours, solvent was removed under reduced pressure. Crude residue partitioned between ethyl acetate and KOH (2M). The aqueous layer was extracted with further partitioned of ethyl acetate and hexane whitish yellow product was collected. **Yield**: 90%, **m.p.:** 126 ^{0}C; **FT-IR** (KBr, cm^{-1}): 3300, 3400 (NH2); 3068 (C=C); 1367 (C-N), 3030-3070 (C=0); 988 (Ar-H). **^{1}H NMR** (300 MHZ, $CDCl_3$) PPM: 8.57, 8.54, 8.35, 8.33 (d, 4H); 7.9-8.05 (T, 3H); 4.0; 8.4 (S, 2H); 7.1 (S, Ar-1H). **m/z**: 249.

Synthesis of Schiff bases (1-13):

Schiff bases (1-13) were prepared by the equimolar concentrations of the compound II condensed with various aromatic aldehydes under probe sonication for 2 hours at 37 ^{0}C or 5-6 hours at 40^{0}C under reflex and ethanol as solvent. Mobile phase used for collecting of pure compounds by using hexane and ethyl acetate with the various ratios.

Synthesis of 2-[3- (benzylidene amino) benzylidene]-2H-indene-1, 3-dione (1)

Yield: 94 %, **m. p.:** 160-162 ^{0}C; **FT-IR** (KBr, cm^{-1}); 3068 (C=C); 1350 (C-N), 3070 (C=0); 992 (Ar-H); 1679 (N=C). **^{1}H NMR** (300 MHZ, $CDCl_3$) PPM: 7.86-8.57 (d, 6H); 7.9- 8.05 (T, 6H); 8.4 (S, 1H); 8.3 (S, 1H); 7.1 (S, Ar-1H). **^{13}C NMR** ($CDCl_3$): 118.5, 124.9, 128.9, 129.2, 130.4, 131.1, 135.4,140, 153; **m/z:** 337.

Synthesis of 2-[3-(4-chlorobenzylideneamino) benzylidene]-2H-indene-1, 3-dione (2):

Yield: 95 %, **m.p.**:163-165 ^{0}C; **FT-IR** (KBr, cm^{-1}): 3068 (C=C); 1350 (C-N), 3070 (C=0); 992 (Ar-H);

1679 (N=C), 762 (Chlorine). **^{1}H NMR** (300 MHZ, $CDCl_3$) (PPM): 8.57, 8.54, 8.35, 8.33, 7.86 (d, 6H); 8.05-8.07, 7.89-7.9 (T, 2H); 8.4 (S, 1H). **^{13}C NMR** ($CDCl_3$): 118.5, 124.9,129, 130.4, 130.6, 136,140,153. **m/z**: 371.

Synthesis of 2-[3-(2-chlorobenzylideneamino) benzylidene]-2H-indene-1, 3-dione (3):
Yield: 95%; **m.p.:** 163^{0}C; **FT-IR** (KBr, cm^{-1}); 3068 (C=C); 1350 (C-N), 3070 (C=0); 992 (Ar-H); 1679 (N=C), 762 (Chlorine). **^{1}H NMR** (300 MHZ, $CDCl_3$) PPM: 8.57, 8.54, 8.35, 8.33, 7.86 (d, 6H); 8.05-8.07, 7.89-7.9 (T, 2H); 8.4(S, 1H**). ^{13}C NMR** ($CDCl_3$): 118.5, 124.9, 129, 130.4, 130.6, 136, 140, 153. **m/z:** 371.

Synthesis of 2-[3-(4-nitrobenzylideneamino) benzylidene]-2H-indene-1, 3-dione (4):
Yield: 95 %, **m.p.:** 161-165 ^{0}C; **FT-IR** (KBr, cm^{-1}): 1348, 1595 ($N0_2$); 3068 (C=C); 1350 (C-N), 3070 (C=0); 992 (Ar-H); 1679 (N=C). **^{1}H NMR** (300 MHZ $CDCl_3$) PPM: 8.57, 8.54, 8.35, 8.33-7.86 (d, 8H); 7.92-8.05 (T, 3H); 8.4, 8.3 (S, 2H) 7.1 (S, Ar-1H)**. ^{13}C NMR** ($CDCl_3$): 118.5, 121.2, 130.1, 130.4, 140, 150, 153.1. **m/z:** 396.

Synthesis of 2-[3-(3-nitrobenzylideneamino) benzylidene]-2H-indene-1, 3-dione (5):
Yield: 95 %, **m.p.:160-**165 ^{0}C; **FT-IR** (KBr, cm^{-1}): 1348, 1595 (N02); 3068 (C=C); 1350 (C-N), 3070 (C=0); 992 (Ar-H); 1679 (N=C). **^{1}H NMR** (300 MHZ, $CDCl_3$) PPM: 8.57, 8.54, 8.35, 8.33-7.86 (d, 8H); 7.92-8.05 (T, 3H); 8.4, 8.3 (S, 2H) 7.1 (S, Ar-1H)**. ^{13}C NMR** ($CDCl_3$): 118.5, 121.2, 130.1, 130.4, 140, 150,153.1. **m/z:** 396.

Synthesis of 2-[3-(2-nitrobenzylideneamino) benzylidene]-2H-indene-1, 3-dione (6):
Yield: 95 %, **m.p.:160-**165 ^{0}C; **FT-IR** (KBr, cm^{-1}): 1348, 1595 (N02); 3068 (C=C); 1350 (C-N), 3070 (C=0); 992 (Ar-H); 1679 (N=C). **^{1}H NMR** (300 MHZ $CDCl_3$) PPM: 8.57, 8.54, 8.35, 8.33-7.86 (d, 8H); 7.92-8.05 (T, 3H); 8.4, 8.3 (S, 2H) 7.1(S, Ar-1H)**. ^{13}C NMR** ($CDCl_3$): 118.5, 121.2, 130.1, 130.4, 140, 150,153.1. **m/z**: 396.

Synthesis of 2-[3-(4-methoxybenzylideneamino) benzylidene]-2H-indene-1, 3-dione (7):
Yield: 95 %, **m.p.:**171 ^{0}C; **FT-IR** (KBr, cm^{-1}): 1350 (C-N), 3070 (C=0); 992 (Ar-H); 1679 (N=C), 2808 (CH_3). **^{1}H NMR** (300 MHZ, $CDCl_3$) PPM: 8.57, 8.54, 8.35, 8.33-7.86 (d, 8H); 7.92-8.05 (T, 3H), 8.4, 8.3 (S, 2H); 7.1 (S, Ar-1H) 3.99 (S, 1H). **^{13}C NMR** ($CDCl_3$): 59, 118.5, 121.2, 130.1, 130.4, 140, 153.1,160. **m/z:** 367.

Synthesis of 2-[3-(4-hydroxy, 3-methoxybenzylideneamino) benzylidene]-2H-indene-1, 3-dione (8)
Yield: 94 %; **m.p.:**173 ^{0}C; **FT-IR** (KBr, cm^{-1}): 3068 (C=C); 1350 (C-N), 3070 (C=0); 992 (Ar-H); 1679 (N=C), 2800 (CH_3)**; ^{1}H NMR** (300 MHZ, $CDCl_3$, PPM): 8.57, 8.54, 8.35, 8.33-7.86 (d, 7H); 7.92-8.05 (T, 3H); 8.4, 8.3 (S, 2H); 3.99 (S, 1H); 1.9 (S, 1H); 7.1 (S, Ar-1H). **^{13}C NMR ($CDCl_3$)**: 118.5, 121.2,126, 130.1, 130.4, 140, 153.1,160. **m/z:** 387.

Synthesis of 2-[3-(3, 4-dimethoxybenzylideneamino) benzylidene]-2H-indene-1, 3-dione (9)
Yield: 95 %; **m.p.:** 174 ^{0}C; **FT-IR** (KBr, cm^{-1}): 3068 (C=C); 1350 (C-*N),* 3070 (C=0); 992 (Ar-H); 1679 (N=C), 2808 (CH_3). **^{1}H NMR** (300 MHZ, $CDCl_3$, PPM): 8.57, 8.54, 8.35, 8.33-7.86 (d, 7H); 7.92-8.05 (T, 3H); 8.4, 8.3 (S, 2H); 3.99 (S, 1H) 7.1 (S, Ar-1H). **^{13}C NMR** ($CDCl_3$): 118.5, 121.2, 130.1, 130.4, 140,149, 152.1; **m/z:** 397.

Synthesis of 2-[3-(2-hydroxybenzylideneamino) benzylidene]-2H-indene-1, 3-dione (10):
Yield: 90 %, **m.p.:**161 ^{0}C; **FT-IR** (KBr, cm^{-1}): 3068 (C=C); 1350 (C-*N),* 3070 (C=0); 992 (Ar-H); 1679 (N=C). **^{1}H NMR** (300 MHZ, $CDCl_3$, PPM): 8.57, 8.54, 8.35, 8.33-7.86 (d, 6H); 7.92-8.05 (T, 5H); 8.4, 8.3 (S, 2H) 7.1, 1.99 (S, 2H). **^{13}C NMR** ($CDCl_3$): 118.5, 121.2,126, 130.1, 130.4, 140, 153.1; **m/z:** 353.

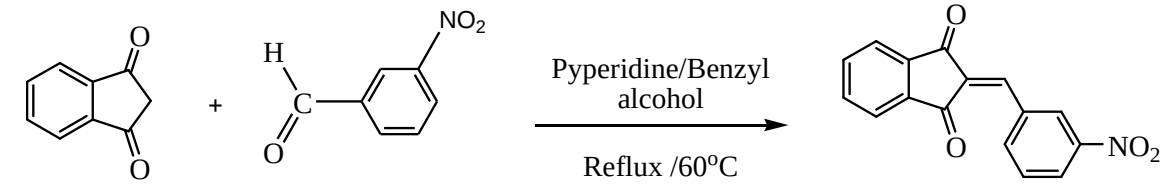
Synthesis of 2-[3-(4-dimethylaminobenzylideneamino)benzylidene]-2H-indene-1, 3-dione (11)
Yield: 90 %; **m.p.:** 135^{0}C; **FT-IR** (KBr, cm^{-1}): 3068 (C=C); 1350 (C-*N),* 3070 (C=0); 992 (Ar-H); 1679 (N=C), 2858 (CH_3). **^{1}H NMR** (300 MHZ, $CDCl_3$, PPM): 8.57, 8.54, 8.35, 8.33-7.86 (d, 6H); 7.92-8.05 (T, 5H); 8.4, 8.3 (S, 2H) 7.1, 3.8 (S, 2H) 4.99 (S, Ar-2H). **^{13}C NMR** ($CDCl_3$): 49,118.5, 121.2, 130.1, 130.4, 140, 153.1; **m/z:** 383.

Synthesis of 2-[3-(4-methyl benzylideneamino)benzylidene]-2H-indene-1, 3-dione (12)
Yield: 90 %, **m.p.:** 149^{0}C; **FT-IR** (KBr , cm^{-1}): 3068 (C=C); 1350 (C-*N),* 3070 (C=0); 992 (Ar-H); 1679 (N=C), 2858 (CH_3); **^{1}H NMR** (300 MHZ, $CDCl_3$, PPM): 8.57, 8.54, 8.35, 8.33-7.86 (d, 6H); 7.92-8.05 (T, 5H); 8.4, 8.3 (S, 2H) , 3.8 (S, 1H), 4.99 (S, Ar-2H); **^{13}C NMR** ($CDCl_3$): 24, 118.5, 121.2, 130.1, 130.4, 140, 153.1.**m/z:** 353.

Synthesis of 2-[3-(4-propylbenzylideneamino) benzylidene]-2H-indene-1, 3-dione (13)

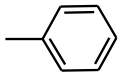
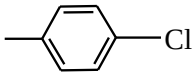
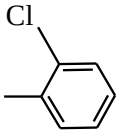
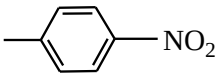
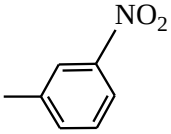
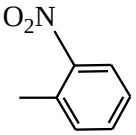
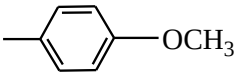
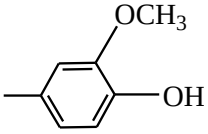
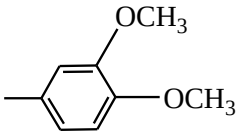
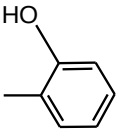
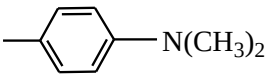
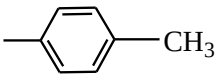
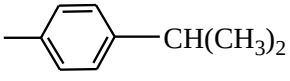
Yield: 90 %, **m.p.:** 152^{0}C; **FT-IR** (KBr , cm^{-1}): 3068 (C=C); 1350 (C-*N)*, 3070 (C=0); 992 (Ar-H); 1679 (N=C), 288 (CH_3): **^{1}H NMR** (300 MHZ, $CDCl_3$, PPM): 8.57, 8.54, 8.35, 8.33-7.86 (d, 6H); 7.92-8.05 (T, 5H); 8.4, 8.3 (S, 2H), 3.8 (S, C(CH3)), 4.99 (S, Ar-2H); **^{13}C NMR** ($CDCl_3$): 31,118.5, 121.2, 130.1, 130.4, 140, 153.1. **m/z**: 382.

Scheme 1: Synthesis of Novel 1,3-Indanedione Derivatives



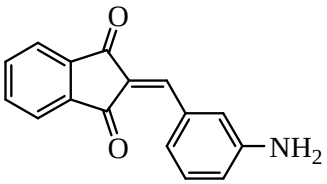
2*H*-indene-1,3-dione + 4-nitrobenzaldehyde → 2-(3-nitrobenzylidene) -2*H*-indene-1,3-dione

Ar:

1: 
2: 
3: 
4: 
5: 
6: 
7: 
8: 
9: 
10: 
11: 
12: 
13: 

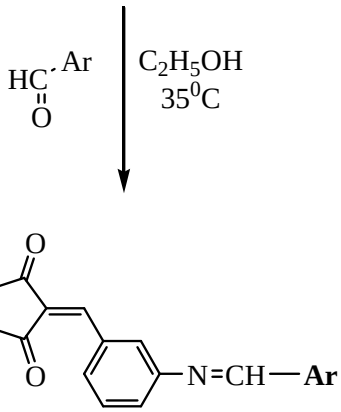
I

$SnCl_2$, H_2O/C_2H_5OH, Ultra sonication



2-(3-aminobenzylidene)-2*H*-indene-1,3-dione

II



SCHIFF BASE

1-13

***1.2* Pharmacological Evaluation**

1.2.1. In vitro Antioxidant Activity

Assay of Nitric oxide scavenging activity:

Sodium nitroprusside (10 mM) in phosphate buffer (pH 7.4) was incubated with the newly synthesized compounds (100 µM) dissolved in a suitable solvent (dioxin/methanol) at 25 ^{0}C for 2 hours. Control experiment was conducted similarly. 2 ml of incubation solution was diluted with 2ml Griess Reagent (1% sulfanilamide, 2% H_3PO_4 and 0.1% N-(1-naphthyl) ethylenediamine dihydrochloride)). The absorbance of the chromophore formed during diazotization of nitrite with sulphanilamide and subsequent N-naphthalene di amine was read at 546 nm [13].

Interaction with stable free radical DPPH:

Di phenyl picryl hydrazyl (DPPH) radical scavenging assay was carried out by adding 100µl of test compound to standard solution. 100µl of DPPH solution was added to earlier mixture. Control was performed with 100µl of DMSO and DPPH. Sample blank and control blank were also performed. The mixture was incubated at 37 ^{0}C for 30 minutes without exposing to light and the absorbance of each solution was measured at 540 nm [14].

Lipid peroxidation:

Formation of lipid peroxide was measured by a modified thiobarbituric acid-reactive species (TBARS) assay using egg yolk homogenate (lipid rich medium). 0.5ml of egg homogenate (10% v/v) and 0.1ml of the test compound were added to a test tube and made up to 1ml with distilled water. Lipid peroxidation was induced by adding FeSO4 (0.07M) to the mixture and incubated for 30 min. To this, 1.5ml of 20% acetic acid (pH adjusted to 3.5 with NaOH), 1.5 ml of 0.8% (w/v) TBA in 1.1%sodium dodecyl sulphate and 0.5ml 20% TCA were added and vortexed and heated for 60 min at 95 ^{0}C. Butanol (5 ml) were added to each tube after cooling and centrifuged at 3000 rpm for 10 min. The absorbance of the organic upper layer was measured at 532 nm [15].

1.2.2. Anti-microbial activity

The antibiotic potency of the newly synthesized compounds was determined by using Cup-Plate method and *Pseudomonas aureus* (Gram positive), and *Eeshricia coli* (Gram negative) as test organisms. Initially, the prepared nutrient agar medium was sterilized by autoclaving at 15 lbs pressure and 121 ^{0}C for 25 min. Agar media was cooled to room temperature and the organism was inoculated to the media. 15 ml of media was transferred to a petri plates aseptically. Synthesized Compounds were dissolved in water and diluted to get 10mg/ml of concentration, whereas, streptomycin is used as standard drug at a concentration of 10µg/ml. The cultured plates were incubated at 37 ^{0}C for 24 hrs. The zones of inhibition produced by test compounds and were recorded in mm [16].

1.2.3. Anti-fungal activity

Anti-fungal activity of the newly synthesized derivatives was evaluated by Disc diffusion method. Sabour and dextrose agar plates (5-6mm) were prepared aseptically and were dried at 37 ^{0}C before inoculation. *Candida albicans* were inoculated into sabour and dextrose agar plates by using sterile inoculation loop and were incubated at 37 ^{0}C for about 24hrs. Ketoconazole (10µg/disc) was used as standard. Sterile Whatman No.2 filter paper disc (5 mm diameter) was soaked in to synthesized compounds (20µg/disc) separately and evaporated to dryness and placed on the media. One more disc immersed in dimethyl sulphoxide and placed on the media as control .The petridishes were incubated at 37 ^{0}C for 24 hrs, cooled them for an hour in a refrigerator to facilitate uniform diffusion.

1.2.4. *In-vivo* Anti-Inflammatory activity

Anti-inflammatory activity of the newly synthesized compounds was evaluated by carrageenan induced paw edema assay in Albino Whistar rats [17]. Test compounds with dose level 20 mg/kg and 50 mg/kg were administered and compared with that of standard drug Celecoxib (20mg/kg). The paw volumes were measured using the mercury displacement technique with the help of plethysmograph immediately before and 1h after carrageenan injection. The percent inhibition of paw edema was calculated from percent inhibition formula,

$$\%\text{inhibition (I)} = 100[1-(a-x)/(b-y)]$$

Where,

x = mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group)

a = mean paw volume of rats after the administration of carrageenan in the test group (drug treated)

b = is the mean paw volume of rats after the administration of carrageenan in the control group

y = mean paw volume of rats before the administration of carrageenan in the control group.

1.3. Molecular Docking and Post-docking Calculations

The 3D structure of the COX2 protein was retrieved from the Protein databank website (PDB Id: 3LN1) and was optimized by deleting unbound water

molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences, adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using OPLS-2005 force field using Protein Preparation Wizard tool of Schrodinger Suite. Similarly, 2D structures of the test compounds were converted to 3D, geometrical optimization and energy minimization of molecules were performed by using the Ligprep tool of Schrodinger suite [18].

Thus structurally optimized protein structure was used to examine protein-ligand interactions of the dataset ligands using Glide XP docking protocol. Initially, a 3D grid was established to the binding pocket (active site) of the protein, into which all the dataset ligands were docked into. Binding interactions and efficiency of the binding were calculated in terms of Glide Score, which is a combination of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, freezing rotatable bonds and polar interactions with receptor [19].

GScore = 0.065 x Van der Waals energy + 0.130 x Coulomb energy + Lipophilic term (Hydrophobic interactions) + H bonding + Metal binding + BuryP (Penalty for buried polar groups) + RotB (Penalty for freezing rotatable bonds) + Site (Polar interactions in the active site)

Binding energies of the docked complexes was calculated using Prime MM/GBSA (molecular mechanics based generalized Born/surface area) module of Schrodinger suite. In this, docking results were rescored through an energy function with a well-defined description of binding contributions. The total free energy of binding is then expressed in the form below mentioned equation [20]:

$\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand})$ where ΔG_{bind} is ligand binding energy

3. RESULTS& DISCUSSION:

3.1. Chemistry

All the newly synthesized 1,3-indanedione derivatives were purified and separated using column chromatography or recrystallization method. Synthesized compounds were characterized by using ^{1}H NMR, ^{13}C NMR and Mass Spectrometric studies. The orientation of protons in the analyzed compounds is fully supported by the integration curves. Furthermore, all the compounds demonstrated the characteristic chemical shifts for the indane dione nucleus. Additionally, synthesized compounds were analyzed by mass spectra under ESI conditions and indicate no difference in the fragmentation pattern among the set of synthesized series.

3.1. Anti-oxidative activity

The antioxidant activity of the newly synthesized 1,3-indanedione derivatives in determined in terms of % scavenging of NO and DPPH, and % inhibition of lipid peroxidation (**Table 1** and **Figure 1).** All the tested compounds exhibited moderate to low scavenging activity of NO and DPPH, and substantial inhibition of lipid peroxidation. NO scavenging is ranged between 7.9% (compounds 12, 13) and 29.5% (compounds 7), whereas, DPPH scavenging is from 8.12% (compound 5) to 28.14% (compound 8). Highest antioxidant activity in terms of inhibition of lipid peroxidation is observed with compound 3 (54.75%), followed by compound 13 (51.09).

Table 1: Antioxidant Activity of Newly Synthesized 1,3-indanedione Derivatives

Compound	Percentage Scavenging Nitric Oxide activity	Percentage DPPH Scavenging	Percentage Inhibition of Lipid Peroxidation
I	11.9	16.6	39.9
II	10.59	12.5	38.44
1	7.52	10.5	42.74
2	18.4	16.68	46.99
3	14.5	17.8	54.75
4	18.13	12.82	48.33
5	24.7	8.12	47.63
6	12.82	19.32	41.06
7	29.5	13.14	43.13
8	9.7	28.14	36.24
9	13.5	20.16	50.8
10	22.4	18.8	42.5
11	18.2	12.9	34.79
12	7.9	13.6	32.89
13	7.87	17.81	51.09

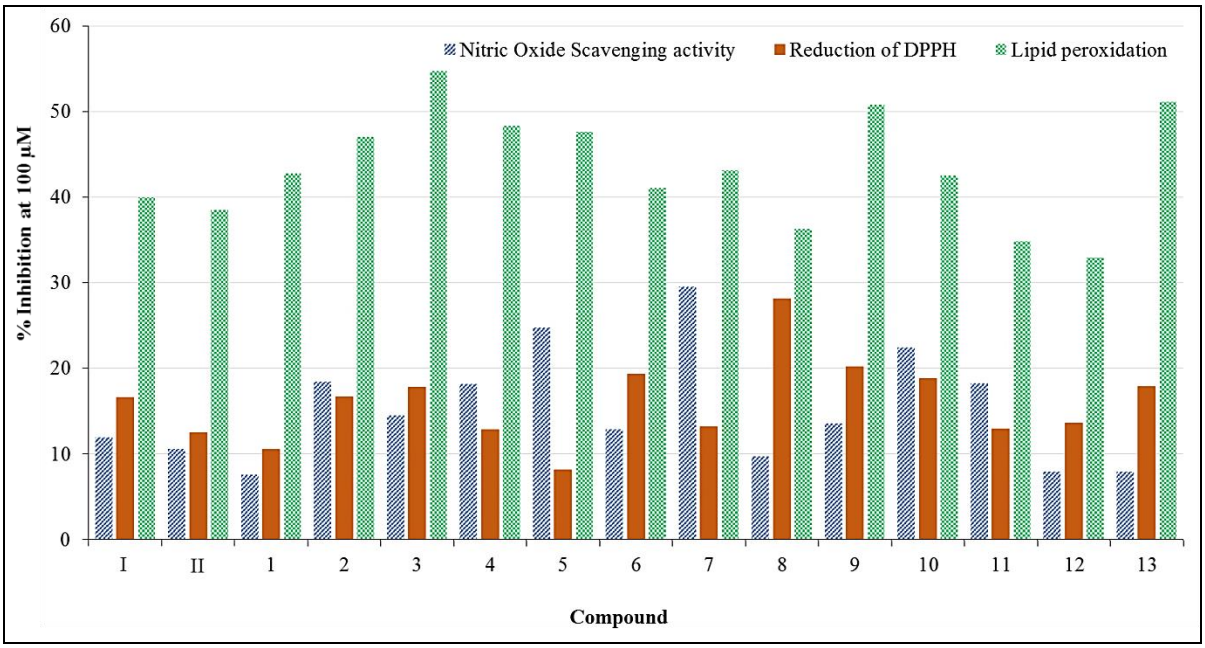


Fig. 1: Antioxidant Activity of Newly Synthesized 1,3-indanedione Derivatives

1.4. Antimicrobial and Antifungal Activities

The antimicrobial and antifungal activities of the newly synthesized 1,3-indanedione derivatives against bacterial/fungal strains are shown in the **Table 2.** All the tested compounds exhibited moderate to low activities when compared to that of the standard. Zone of inhibition in *P. aureus* is ranged from 5 mm (compounds I, 5, 12) to 9 mm (compounds 6, 10, 13), whereas, in *E. coli* screening is from 4 mm (compound 4, 12) to 8 mm (compounds 7, 10). Zone of inhibition of with standard is 15 mm and 21 mm against *P. aureus* and *E. coli*, respectively, and no inhibition was observed in control screening (**Figure 2**). Compound 8 has exhibited highest antifungal activity (8 mm inhibition) among the tested series against *C. albicans*, followed by compounds 2, 6, and 10 (7 mm) (**Figure 3**). Compounds with para-/hydrophilic group substituted compounds were reported with higher antimicrobial and antifungal activities. Additionally, compounds with meta- and para- di-substitutions were found to be more active compared to other substitutions.

Table 2: Antimicrobial and Antifungal Activities of Novel 1,3-Indanediones

Compound	Zone of inhibition(mm)		
	P. aureus	***E. coli***	***C. albicans***
I	5	6	5
II	8	7	4
1	7	6	6
2	8	7	7
3	7	5	6
4	6	4	6
5	5	3	5
6	9	7	7
7	8	8	6
8	7	6	8
9	6	6	5
10	9	8	7
11	6	5	5
12	5	4	4
13	9	5	6
Standard	15	21	14

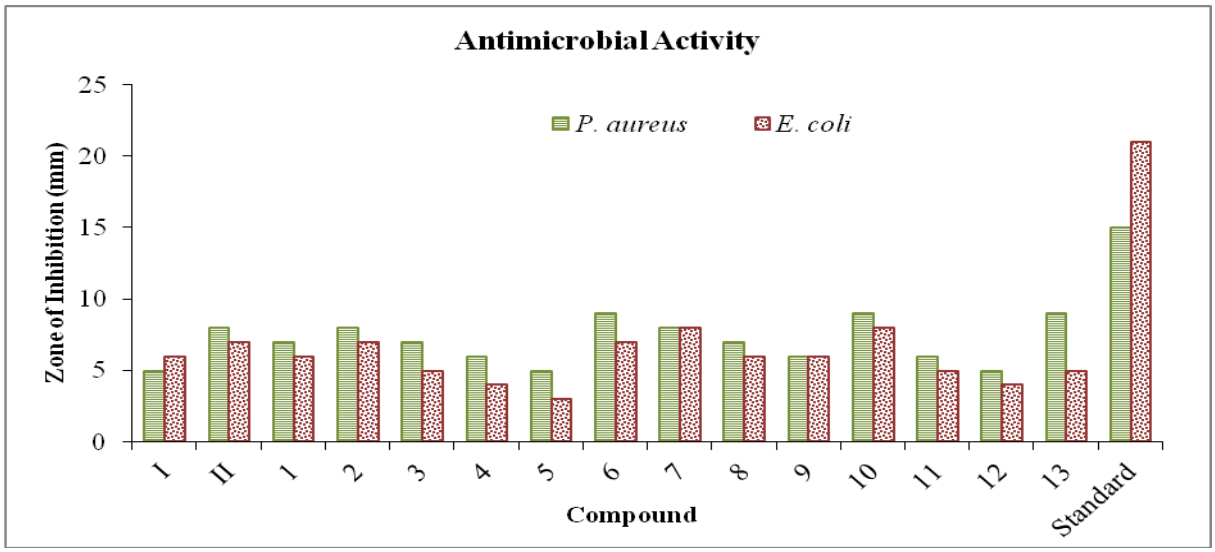


Fig. 2: Antimicrobial Activity of Novel 1,3-Indanediones

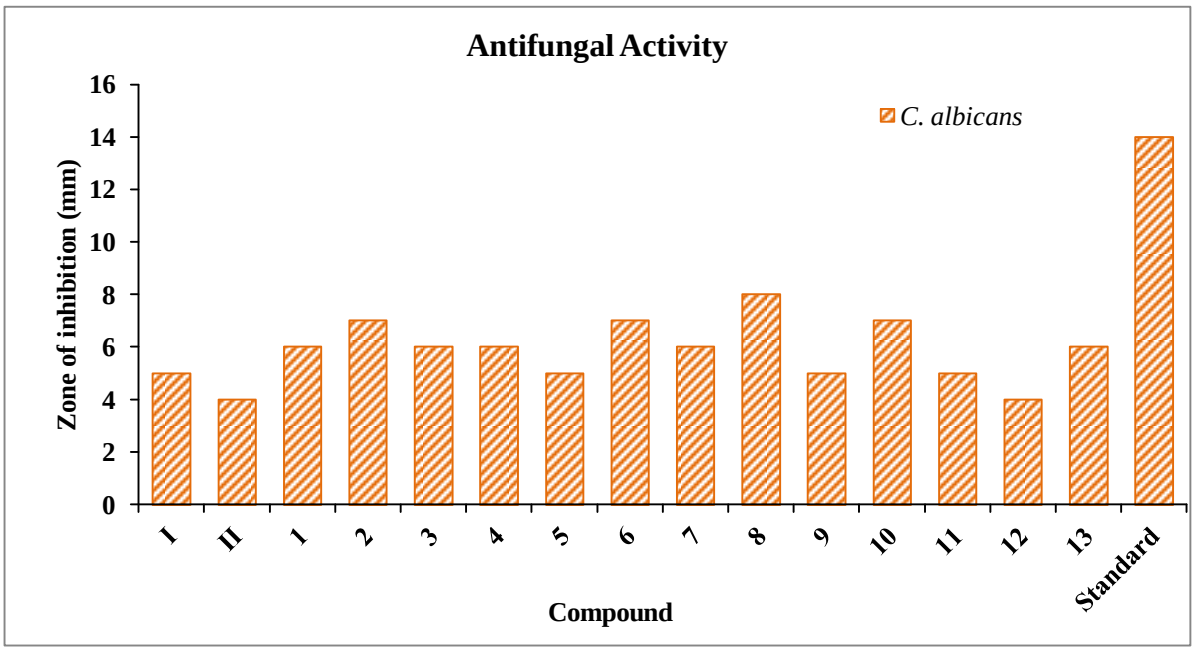


Fig. 3: Antifungal Activity of Novel 1,3-Indanediones

1.5. Anti-inflammatory Activity

Anti-inflammatory activity of synthesized 1,3-indanedione derivatives were evaluated by carrageenan induced paw edema bioassay in rats with Celecoxib (20 mg/kg) as standard. With dose of 20 mg/kg, %inhibition of paw edema is ranged between 17.5 (compound 9) and 39.8 (compound 10), whereas, with 50 mg/kg dose, it is between 57.5% (compound 1) and 84.6% (compound 10)**.** The results indicated that anti-inflammatory activity of all the compounds is significantly higher (two-tailed, paired *t* test; P<.0001) at dose of 50 mg/kg when compared to that of 20 mg/kg dose (**Figure 3**). However, the anti-inflammatory effect of compound 10 (50 mg/kg) and celecoxib (20 mg/kg) was found to be similar (84.6% vs. 86.2%; P = 0.113). The higher anti-inflammatory activity of compound 10 could be due to its substantial antioxidant activity and presence of the phenolic group as the terminal substitution. Overall, compounds with meta- and para di-substitutions were found to more active among the series.

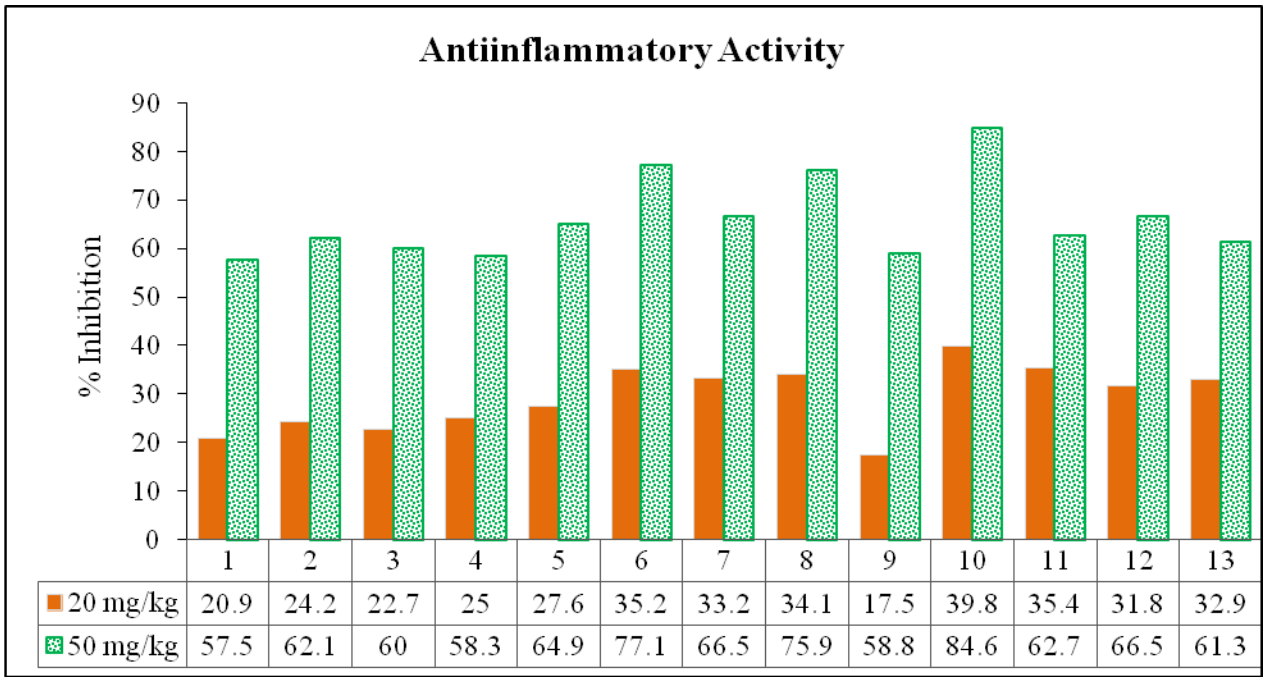


Fig. 4: Anti-inflammatory Activity of Newly Synthesized compounds (% inhibition of Paw Edema)

1.6. Molecular Docking

Molecular docking was performed to identify the possible interactions of the newly synthesized 1,3-indanedione derivatives with COX2 enzyme, and the conformational changes of the ligand in the protein environment. Glide XP dock sores of the dataset ligands were shown in **Table 3** along with the interaction amino acids and number of H-bond distance. Among the docked compounds, compound 3 reported highest dock score of -8.667 with binding energy of -68.179 Kcal/mol. Compound 3 possessed zero hydrogen bonds, and the interaction profile is dominated by the hydrophobic or electrostatic interactions, particularly with Arginine 106 (**Figure 5**). Dock scores of all the compounds ranged from -8.667 (compound 3) to -3.211 (compound 13). Most commonly interacted amino acids include Glutamine 336, and followed by Phenyl alanine 566. Other amino acids include Glutamine 510 (compound 10) and Lysine 82 (compound 11).

Table 3: Docking Results and Protein-ligand Binding Interactions

Compound	Glide XP Dock Score	#H-bonds	Interacting Amino Acids	H-bond Distance	Binding Energy
3	-8.667	0	-	-	-68.179
7	-7.735	1	GLN 336	1.96	-40.761
6	-7.155	2	GLN 336 PHE 566	1.93 1.87	-94.295
8	-6.402	0	-	-	-42.036
9	-6.254	0	-	-	-45.838
4	-5.831	0	-	-	-50.965
1	-5.502	2	GLN 336 PHE 566	2.01 2.19	-55.841
2	-4.752	0	-	-	-46.755
10	-4.63	1	GLU 510	1.59	-57.417
5	-4.151	0	-	-	-42.386
12	-3.827	1	PHE 566	1.97	-47.159
11	-3.753	1	LYS 82	2.32	-36.804
13	-3.211	1	GLN 336	2.41	-39.753

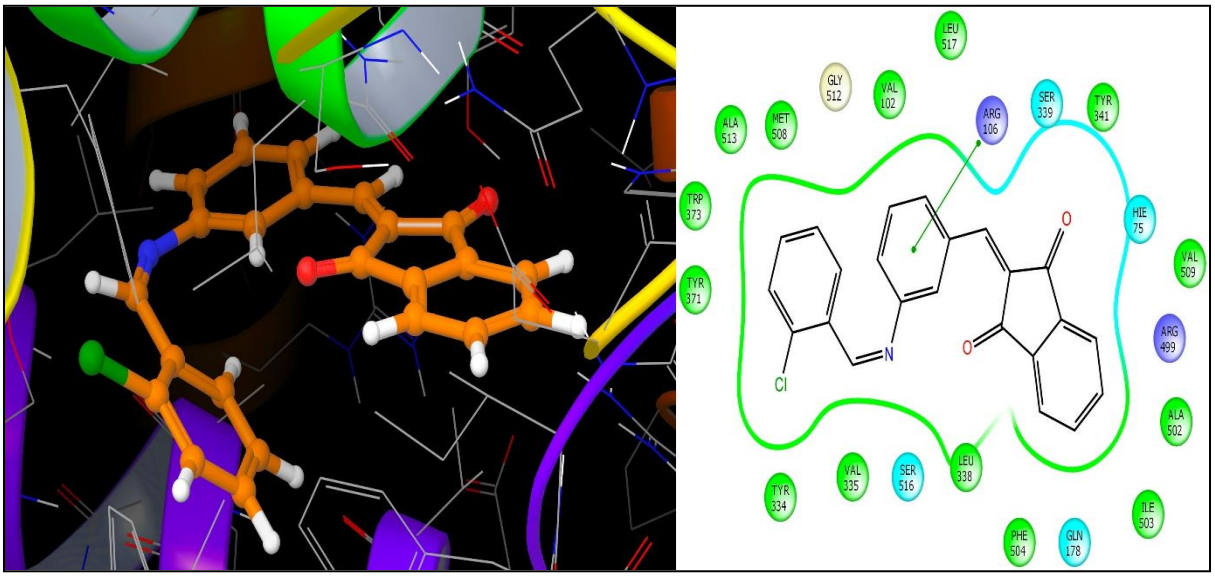


Fig. 5: Binding Interactions of Compound 3 with COX2 Enzyme

CONCLUSION:

Novel series of 1,3-indanedione derivatives were synthesized and evaluated for their pharmacological potentials in terms of antioxidant, antimicrobial and antifungal, and anti-inflammatory activities. Compounds with phenolic group as the terminal substitution or meta- and para- di-substitutions were observed to have higher antimicrobial/antifungal and anti-inflammatory activities. Compound 10 reported with superior anti-inflammatory activity and moderate antioxidant activity among tested compounds and statistically similar anti-inflammatory activity at 50 mg/kg dose with celecoxib (20 mg/kg). Molecular docking studies against COX2 enzyme provided deeper understanding of the ligand conformations in the protein environment.

Conflicts of Interests

Authors declare no conflicts.

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