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RESEARCH ARTICLE

INSILICO DESIGN, SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL 1-HYDROXYNAPTHELENE-2-YL DERIVATIVES

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ABSTRACT

Chalcones belongs to natural and synthetic origin has various biological activities like anti-inflammatory, anti-oxidant, anti-parasite, and anti-tumor activities. The aim of this study is to perform insilico design, docking by Hex 8.0 and synthesis, characterization and to investigation of anti-inflammatory activity in vivo. Novel Chalcones are prepared from 2-acetyl-1-naphthol and substituted aromatic aldehydes. All the synthesized compounds were characterized and evaluated for anti inflammatory and anti microbial studies.

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INTRODUCTION

Molecular properties of the compounds were studied by using pkCSM (predicting small-molecule pharmacokinetic properties using graph-based signatures) A series of chalcone derivatives have been reported to have potent anti-inflammatory activity. In an effort to continually develop potent anti-inflammatory agents, novel series of napthyl chalcones were synthesized and their inhibitory effects on the bovine albumin and heat induced hemolytic were evaluated in-vitro. It was thought worthwhile to design few Synthesis of 1-(1-hydroxynaphthalen-2-yl) ethanone from α-napthol and to synthesize 1-hydroxynapthalen-2-yl derivatives by reacting 1-(1-hydroxynapthalen-2-yl) ethanone with substituted benzaldehydes (https://en.wikipedia.org/wiki/ Chalcone; Chetana, 2009). The Chalcones were prepared by Claisen-Schmidt condensation. The active chalcones exhibiting dual activities were submitted to docking in hex 8.0.

Experimental Work

Internet Based In-Silico Design: Molecular docking was performed in Hex.8. Targets which we have chosen for our study are based on the pharmacological activity like anti-inflammatory activity. Targets proteins are downloaded from PDB.

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Procedure for Docking Studies using HEX: The parameters used in HEX for the docking process were; Correlation type – Shape only

FFT Mode – 3D fast lite
Grid Dimension – 0.6
Receptor range – 180
Ligand Range – 180
Twist range – 360
Distance Range – 40

Ligands

The structures were drawn in ACD Labs and then converted to PDB format using Open Babel GUI 2.2.1 and further used for docking studies (http://openbabel.org/wiki/Main_Page).

Synthetic Study

Chemicals and Solvents

All the chemicals and reagents used in the project along with their source of purchased from SD Fine chemicals, Mumbai.

Instruments Used: NMR Spectrophotometer (BRUKER 400MHZ), Mass Spectrophotometer, UV Spectrophotometer (UV Pharma Spec. 1700 (SHIMADZU)), Hot air Oven (Vision Lab Equipments), Magnetic stirrer (Vision Lab Equipments), Vacuum pump(Vision Lab Equipments), Precision weighing

Balance (Contech (0.1 mg precison)), Precision Melting point Apparatus (Vision Lab Equipments), IR Spectrophotometer (BRUKER)UV Chambe (Vision Lab Equipments).

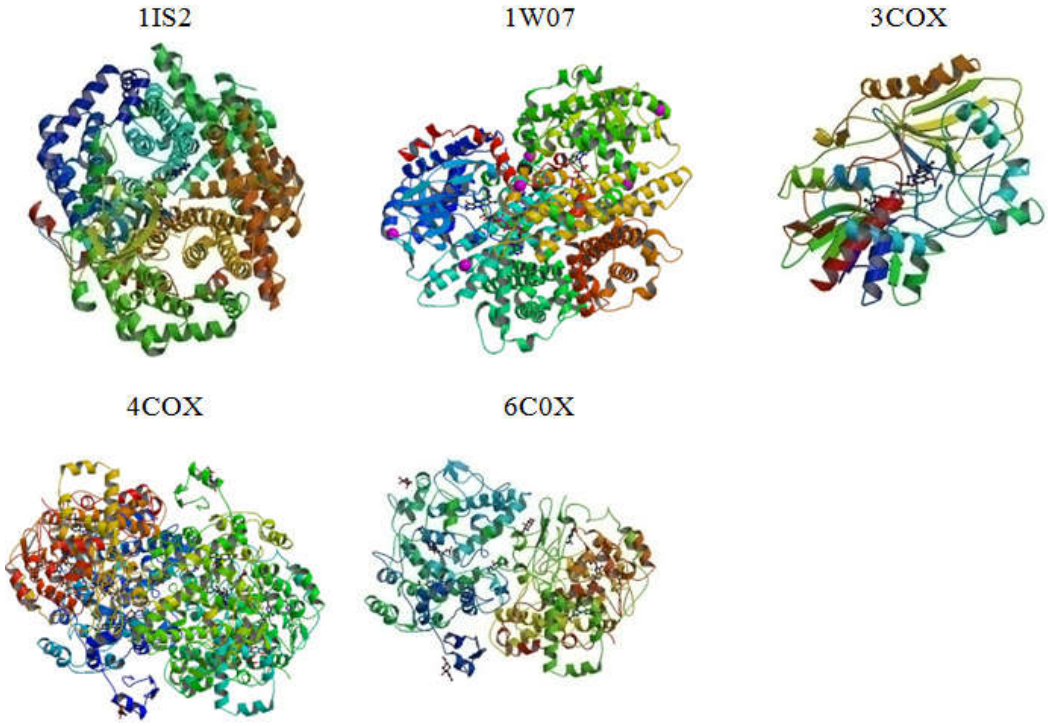
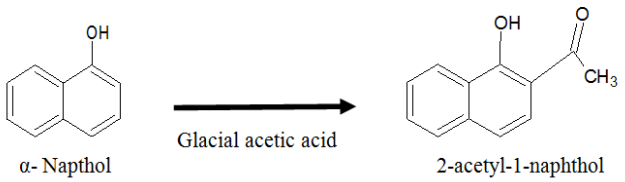


Fig. 1. Crystallography images of Targets

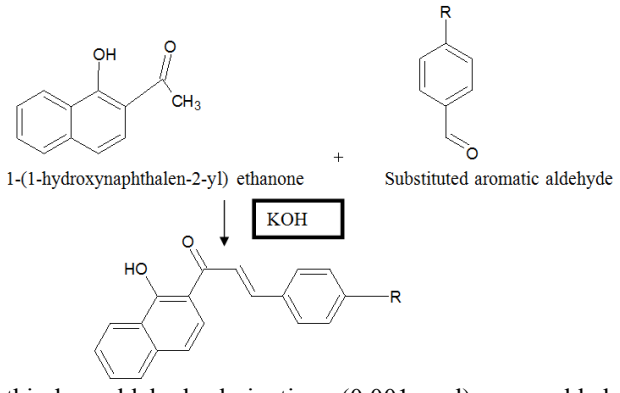
Experimental Procedure

Step I: Synthesis of 1-(1-hydroxynaphthalen-2-yl)ethanone from α-napthol: In hot glacial acetic acid (80ml), fused $ZnCl_2$(50 gm) was added and refluxed till dissolved, then powdered 1-naphthol (30gm)was added and the mixture was refluxed for about 8 hours then cooled & poured in acidulated water. The solid obtained was filtered, washed, dried and recrystallized from rectified spirit to obtain compound 2.



α- Napthol 2-acetyl-1-naphthol

Step II: Synthesis of Chalcones: To a 20 ml solution of 20% Potassium hydroxide in distilled water, 2-acetyl-1-naphthol (0.001 mol) was added and dissolved.



To this benzaldehyde derivatives (0.001 mol) were added in small amounts with continuous stirring with the help of a mechanical stirrer or about 2 h. The mixture was left in refrigerator for 24 h. Then the yellowish product thus formed is filtered, dried and recrystallized from ethanol.

The synthesized compounds were monitored by TLC. Physical data of the compound is given in Table 5.

Physico-Chemical Characterization of the Synthesized Compounds

Physical properties of the Chalcone derivatives like color and melting point range and R_f are presented in Table No. 4.

Assessment of Invitro Anti-Inflammatory Activity & Anti Microbial Activity (Siva sanker reddy, 2015; Siva sanker reddy, 2015 and Siva sanker reddy, 2016)

Inhibition of albumin denaturation: Various concentrations of the test samples ranging from 100-500 µg/ml prepared. 1% aqueous solution of bovine albumin fraction prepared and pH of the reaction mixture was adjusted using small amount of 1N HCl. The samples were incubated at 37 ºC for 20 min and then heated to 51º C for 20 min, cooled, turbidity was measured at 660nm. The experiment was performed in triplicate. The Percentage inhibition of protein denaturation was calculated as follows:

Percentage inhibition = (Abs Control –Abs Sample) X 100/ Abs control

Preparation of Red Blood cells (RBCs) suspension: The Blood was collected from healthy human volunteer who has not prescribed with any NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) for 2 weeks prior to the experiment and transferred to the centrifuge tubes. The tubes were centrifuged at 3000 rpm for 10min and were washed three times with equal volume of normal saline. The volume of blood was measured and re constituted as 10% v/v suspension with normal saline.

Table 1. List of Synthesized molecules

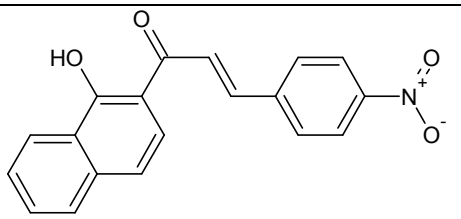
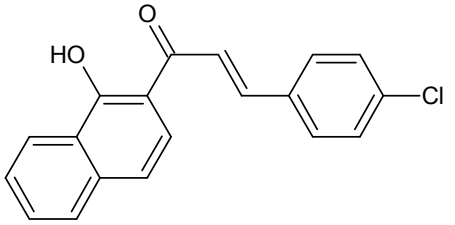
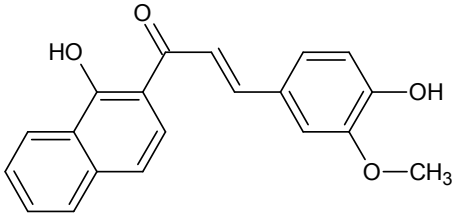
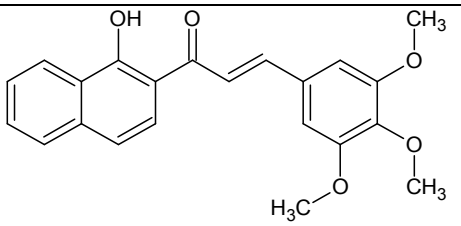
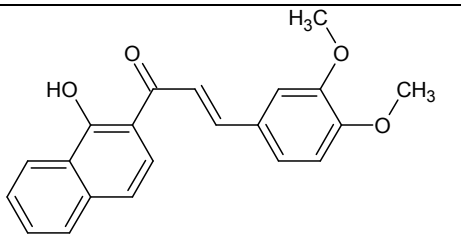
Code	Structure	IUPAC Name
A		(2*E*)-1-(1-hydroxynaphthalen-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one
B		(2*E*)-3-(4-chlorophenyl)-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one
C		(2*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one
D		(2*E*)-1-(1-hydroxynaphthalen-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one
E		(2*E*)-3-(3,4-dimethoxyphenyl)-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one

Table 2. Type of Chalcones Substitutions

Product	R_1	R_2
A	4-NO_2	-
B	4-Cl	-
C	2-OCH_3	3-OH
D	3-OCH_3	4-OCH_3
E	3-OCH_3	4-OCH_3 , 5-OCH_3

Table 3. List of Synthesized molecules

S.No	SMILE Notation
A	[O-][N+](=O)c1ccc(cc1)/C=C/C(=O)c3ccc2ccccc2c3O
B	Clc3ccc(/C=C/C(=O)c2ccc1ccccc1c2O)cc3
C	Oc1ccc(cc1OC)/C=C/C(=O)c3ccc2ccccc2c3O
D	COc1c(cc(cc1OC)/C=C/C(=O)c3ccc2ccccc2c3O)OC
E	COc1cc(ccc1OC)/C=C/C(=O)c3ccc2ccccc2c3O

Heat induced haemolysis: The reaction mixture (2ml) was prepared by mixing 1 ml test sample of different concentrations (100 - 500 µg/ml) and 1 ml of 10% RBCs suspension. Control contains only saline Instead of test sample. Ibuprofen was used as a standard drug. All the centrifuge tubes containing reaction mixture were incubated in water bath at 56 ºC for 30min, cooled under running tap water. The reaction mixtures were centrifuged at 2500 rpm for 5 min and the absorbance of the supernatants was measured at 560 nm. The experiment was performed in triplicates for all the test samples. The Percentage inhibition of haemolysis was calculated as follows:

Percentage inhibition = (Abs control –Abs sample) X 100/ Abs control

Antibacterial Studies

All the compounds were evaluated for antimicrobial activity using 2-fold serial broth dilution method in duplicates. This method depends upon the inhibition of growth of a microbial culture in a uniform solution of antibiotic in a liquid medium that is favourable to its rapid growth in the absence of the antibiotic. Minimum Inhibitory Concentration (MIC) of the all extracts was determined. The MIC is the lowest concentration of tested compounds that completely inhibited the growth of the test organisms after 24 and 48 h of incubation at 37 °C and 27 °C for bacteria and fungi, respectively. All the compounds were screened for their antimicrobial activities against *Bacillus subtilis*, *E.coli*, *Candida albicans* and *Aspergillus niger* by cup plate method.

Fluconazole was used as the standard drug for antifungal activity and ciprofloxacin for antibacterial studies. The Compounds were studied at concentrations 1000, 500, 250, 125, 62.5 and 31.25 µ g /ml. The zone of inhibition of the compounds were compared with that of standards (Siva sankerreddy, 2015).

RESULTS AND DISCUSSION

(2*E*)-1-(1-hydroxynaphthalen-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one:

IR (KBr cm-1): 1605 (C=C (Stetching)), 1706(C-O Group stretching), 2851 (CH-Aromatic stretching) 1197 (CO-CH_2 stretching), 1344- 1360–1290 ((m) N–O symmetric stretch

Table 4. Physicochemical characterization data for synthesized Chalcones compounds

Compound	Mol. Formula	Mol. weight	Yield (%)	M.P	TLC
A	$C_{19}H_{15}NO_4$	321.32	80	60-80˚c	0.7
B	$C_{19}H_{15}ClO_2$	310.77	72	90˚c	0.64
C	$C_{21}H_{20}O_4$	336.38	66	110˚c	0.74
D	$C_{22}H_{22}O_5$	366.40	60	119˚c	0.72
E	$C_{21}H_{20}O_4$	336.38	64	110˚c	0.74

Table 5. Molecule properties of Compounds

Molecule properties of Compound A

Descriptor	Value
Molecular Weight	321.332
LogP	3.5537
#Rotatable Bonds	4
#Acceptors	4
#Donors	1
Surface Area	138.267

Molecule properties of Compound B

Descriptor	Value
Molecular Weight	310.78
LogP	4.2989
#Rotatable Bonds	3
#Acceptors	2
#Donors	1
Surface Area	133.917

Molecule properties of Compound C

Descriptor	Value
Molecular Weight	320.344
LogP	4.1557
#Rotatable Bonds	4
#Acceptors	4
#Donors	2
Surface Area	138.804

Molecular Prediction of Compound D

Descriptor	Value
Molecular Weight	366.413
LogP	3.6713
#Rotatable Bonds	6
#Acceptors	5
#Donors	1
Surface Area	158.049

Molecule properties Compound E

Descriptor	Value
Molecular Weight	336.387
LogP	3.6627
#Rotatable Bonds	5
#Acceptors	4
#Donors	1
Surface Area	146.571

Hex Docking Scores of Compounds

Table 6. E-Minimum Scores

COMPOUNDS	1IS2	1W07	3COX	4COX	6COX
C-1 ($C_{19}H_{15}ClO_2$)	-366.4	-320.55	-313.04	-87.95	-148.99
C-2 ($C_{19}H_{15}NO_4$)	-343.41	-328.1	-324.77	-98.09	-128.87
C-3 ($C_{21}H_{20}O_4$)	-340.44	-362.55	-329.09	-56.14	-147.58
C-4 ($C_{21}H_{20}O_4$)	-327.9	-313.38	-325.02	-90.59	-151.85
C-5 ($C_{22}H_{22}O_5$)	-374.18	-320.76	-337.09	-45.04	-165.93

Table 7. E-Maximum Scores

COMPOUNDS	1IS2	1W07	3COX	4COX	6COX
C-1 ($C_{19}H_{15}ClO_2$)	564.79	585.33	485.10	315.50	147.99
C-2 ($C_{19}H_{15}NO_4$)	546.19	446.54	504.41	263.87	228.04
C-3 ($C_{21}H_{20}O_4$)	628.34	530.60	471.59	243.56	250.08
C-4 ($C_{21}H_{20}O_4$)	588.19	484.21	516.65	412.50	320.16
C-5 ($C_{22}H_{22}O_5$)	562.48	659.37	556.27	242.45	256.07

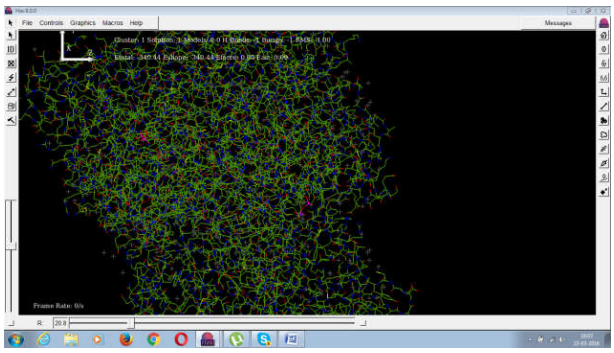


Fig. 2. E-Minimum Value of C5 at 1IS2

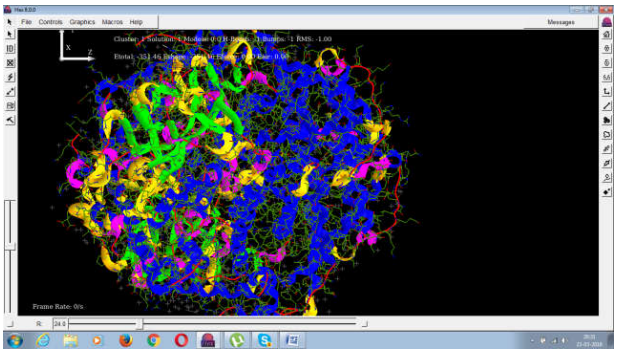


Fig.3. E-Minimum Value of C3 at 1W07

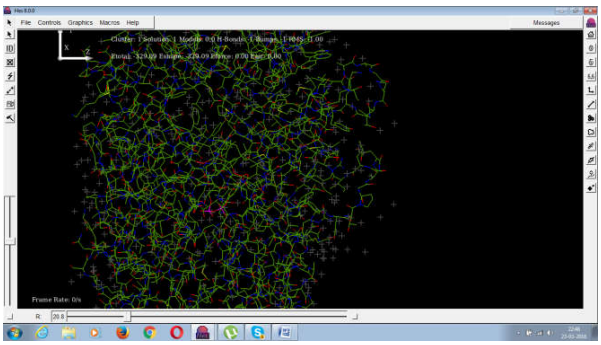


Fig. 4. E-Minimum Value of C5 at 3COX

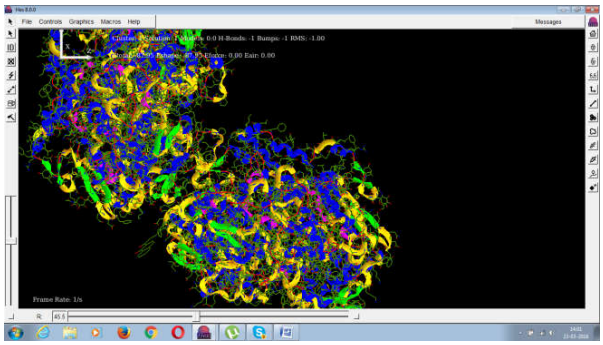


Fig. 5. E-Minimum Value of C2 at 4COX

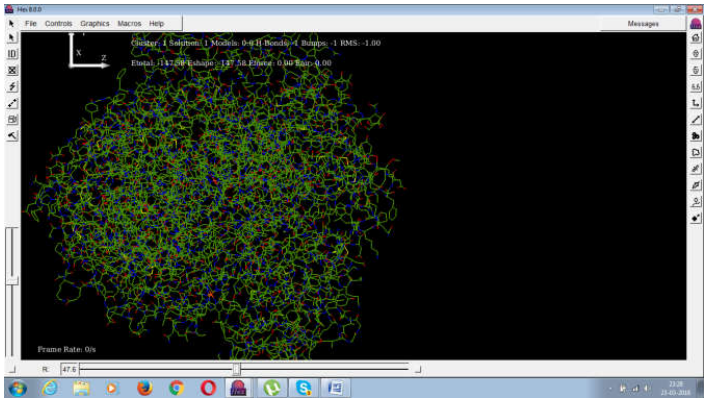


Fig.6. E-Minimum Value of C5 at 6COX

Table 8. Zone of inhibition (ZOI) of compounds against *Escherichia coli*

Compound Code	1000 (µg/ml)	500 (µg/ml)	250 (µg/ml)	125 (µg/ml)	62.5 (µg/ml)	31.25 (µg/ml)
A	16	12	9	7	4	2
B	15	11	8	3	3	0
C	13	10	9	4	3	0
D	14	11	8	6	4	2
E	11	8	9	4	2	0
Trimethoprim	28	-	-	-	-	-

nitro compounds), 3422 (O–H stretch, H–bonded), $_1$H –NMR(DMSO) 7.602-7.952(1H;d;CH-Ar); 6.920-6.922 (1H;d;CO-H=); 6.532-8.219(8H;m,Ar-H); 8.026 (OH)

(2*E*)-3-(4-chlorophenyl)-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one:

IR (KBr cm-1): 1600 (C=C (Stetching)), 1658 (C-O Group stretching), 2836 (CH-Aromatic stretching), 1182 (CO-CH_2 stretching), 756.68 (Aromatic bending Cl), $_1$H –NMR 3.69 (OCH_3); 6.912-6.916 (1H;d;CO-H=); 8.00-9.45 (1H;d;CH-Ar)

(2*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one:

IR (KBr cm-1): 1228 (OH Bending), 1636 (C-O stretching), 3447 (CH-Aromatic stretching) 1581 (CH-CH streching), 3447 (O–H stretch, H–bonded), **$_1$H –NMR** 7.604-9.553(1H;d;CH-Ar); 7.219-7.432 (1H;d;CO-H=); 7.145-8.577(8H;m,Ar-H); 3.69(9H;s;OCH_3)

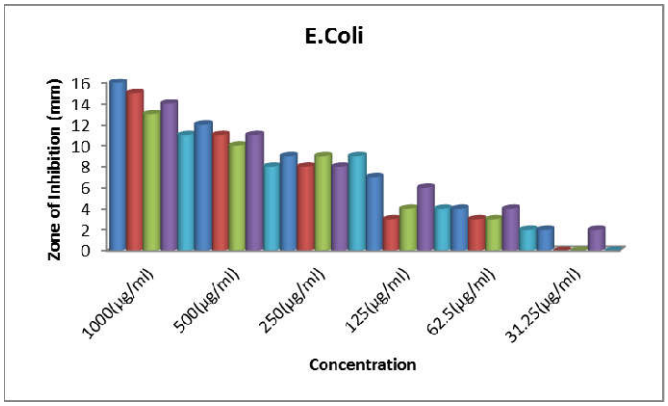


Fig.7. Comparison of Zone of inhibition (Diameter in mm) of all synthesized compounds against *Escherichia coli*

Table 9. Zone of inhibition (ZOI) of compounds against *Bacillus substilis*

Compound Code	1000 (µg/ml)	500 (µg/ml)	250 (µg/ml)	125 (µg/ml)	62.5 (µg/ml)	31.25 (µg/ml)
A	15	11	7	4	3	0
B	14	12	9	4	2	0
C	12	11	6	2	2	0
D	16	14	9	6	4	2
E	10	7	5	4	2	0
Trimethoprim	30	-	-	-	-	-

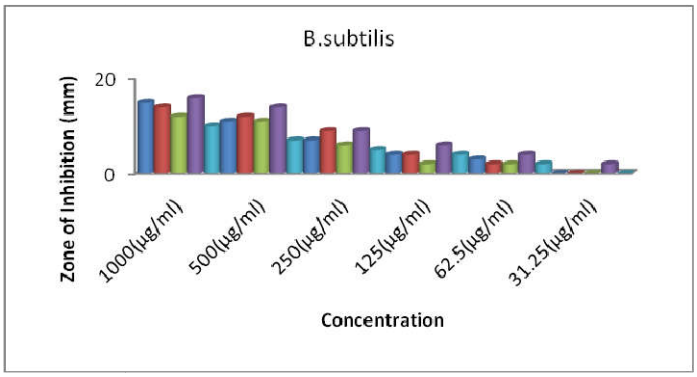


Fig. 8. Comparison of Zone of inhibition (Diameter in mm) of all synthesized compounds against *Bacillus substills.*

Table 10. Zone of inhibition (ZOI) of compounds against against *Aspergillus niger*

Compound Code	1000 (µg/ml)	500 (µg/ml)	250 (µg/ml)	125 (µg/ml)	62.5 (µg/ml)	31.25 (µg/ml)
A	16	12	9	7	3	0
B	14	10	8	6	4	0
C	12	9	7	4	2	0
D	13	11	9	4	2	0
E	10	10	9	6	3	0
Ciprofloxacin	26	-	-	-	-	-

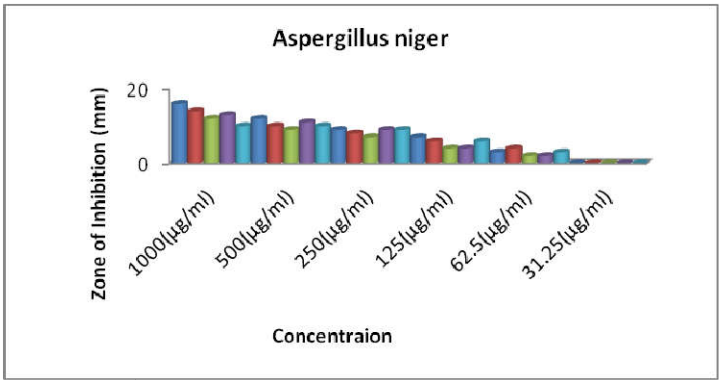


Fig. 9. Comparison of Zone of inhibition (Diameter in mm) of all synthesized compounds against *Aspergillus niger*

Table 11. Zone of inhibition (ZOI) of compounds against against *Candida albicans*

Compoud Code	1000 (µg/ml)	500 (µg/ml)	250 (µg/ml)	125 (µg/ml)	62.5 (µg/ml)	31.25 (µg/ml)
A	14	10	8	4	2	0
B	13	11	9	3	2	0
C	12	10	7	4	2	0
D	11	11	8	4	2	0
E	13	10	9	4		0
Ciprofloxacin	26	-	-	-	-	-

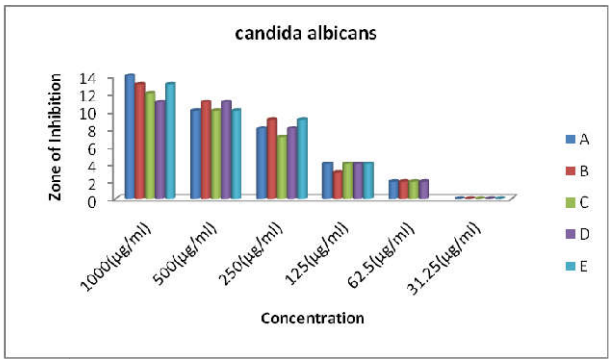


Fig. 10. Comparison of Zone of inhibition (Diameter in mm) of all synthesized compounds against Candida albicans

Anti inflammatory studies

Table 12. Percentage Inhibition of Albumin Denaturation Studies

Concentration µg/ml	Sample-A	Sample-B	Sample-C	Sample-D	Sample-E	STD
100	60.52	59.68	47.749	60.67	83.70	32.72
200	69.51	69.65	72.04	69.51	87.915	85.94
300	97.88	93.95	63.90	91.005	68.4	80.61
400	98.58	98.64	91.84	98.44	83.98	74.99
500	99.15	99.06	29.632	98.78	60.9	75.27

Table 13. Percentage Inhibition of Heat induced hemolysis

Concentration µg/ml	Sample-A	Sample-B	Sample-C	Sample-D	Sample-E	STD
100	75.118	80.72	68.58	79.36	88.190	77.24
200	82.758	59.246	65.35	74.94	79.87	86.322
300	73.08	90.82	56.02	73.166	66.036	79.95
400	75.11	89.20	59.50	73.251	61.962	78.514
500	72.57	73.08	74.43	69.26	57.71	75.88

(2*E*)-1-(1-hydroxynaphthalen-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one:

IR (KBr cm-1): 3252 (OH stretching), 1684 (C=O stretching), 1587 (CH-CH streching) 1504, 1459 (ring C=C), 3442 (O–H stretch, H–bonded), **$_1$H –NMR** 8.62 (OH); 7.96-7.98(1H;d;CH-Ar); 7.96-8.62 (8H;m,Ar-H), 3.664(9H;s;OCH_3)

(2*E*)-3-(3,4-dimethoxyphenyl)-1-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one:

IR (KBr cm-1): 1580.86 (C=C (Stetching)), 3372.01 (CH-Aromatic stretching), 1656.63 (C-O Group stretching), 1062 (CO-CH_2 stretching), 3372 (O–H stretch, H–bonded), **$_1$H –NMR** 7.604-7.659(1H;d;CH-Ar); 7.219-7.432 (1H;d;CO-H=); 7.145-8.577(8H;m,Ar-H); 8.855 (OH); 3.73(9H;s;OCH_3)

DISCUSSION

The synthesized compounds were characterized by TLC, melting point, IR spectroscopy, ^{1}HNMR Spectroscopy and mass spectroscopy.

The results obtained from this study confirmed that the product has formed. Henceforth viewing these characteristic properties more compounds can be synthesized and subjected to pharmacological evaluation. These Chalcone derivatives have biological activities like anti-bacterial and anti-inflammatory may be a pave for synthesis and characterization of some new chalcone derivatives. All the synthesized compounds were tested for *in vitro* antibacterial activity by agar dilution method. The MIC of the compounds against 16 gram-positive bacterial strains is presented in [Table 25-32]. All the Compounds showed good activity against all bacterial strains than ciprofloxacin taken as reference standard. The compounds showed moderate to efficient activity against all bacterial strains taken for the screening. The *in vitro* anti-inflammatory activity was performed by inhibition of bovine albumin denaturation method and heat induced hemolytic method. The inhibitory activity of the compounds was compared with the control and the significance factor "p" was less than 0.001 for all the compounds. The inhibitory activity of the compounds was compared with the control and the significance factor "p" was less than 0.001 for all the compounds. The result of the anti-inflammatory activity was given in table 33&34.

In an Albumin Denaturation Studies, Sample-A Shown 82.758% inhibition at 200 µg/ml, Sample-B 90.82 % at 300 µg/ml, Sample-C 74.43 % at 500 µg/ml, Sample-D 79.36 % at 100 µg/ml & Sample-E 88.190 % at 100 µg/ml. In Heat induced hemolysis, Sample-A Shown 99.15 % inhibition at 500 µg/ml, Sample-B 99.06 % at 500 µg/ml, Sample-C 91.84 % at 300 µg/ml, Sample-D 98.78 % at 500 µg/ml & Sample-E 85.94 % at 200 µg/ml. The existing designed analogs (Compound A-E) can be further modified so as to include substituted pyrazolines, pyrimidines, Oxazoles, hydrazones, benzodiazepines etc which can produce further substituted derivatives. Such analogs can be synthesized, and evaluated for their Anthelmentic and anti-tubercular activities and other activities.

Future Scope

It would be interesting to deduce the structure of potent compounds for the activity claimed, they may be our lead molecules and there is a possibility to extend the lead molecule towards drug design using various drug design software's like maestro, glide, scigress, autodock etc.

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