The Pharma Innovation

Received: 11-04-2013
Accepted: 09-05-2013

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Vol. 2 No. 5 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Synthesis and Characterisation of 3-Acetylindole Derivatives and Evaluation of Their Anti-Inflammatory and Anti-Microbial Activity

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A series of 3-Acetylindole derivatives were synthesised by a three step process by reacting 3-acetylindole and aromatic aldehydes in the first step. The purity and structure confirmation of the synthesised compounds were done by TLC and 1H-NMR. The compounds were evaluated for anti-microbial and anti-inflammatory activity. The test compound LV-5 showed highest anti-inflammatory activity and the test compounds LV-5, LV-6 and LV-8 showed highest anti-microbial activity.

Keyword: 3-Acetylindole, Aromatic Aldehyde, Anti-Inflammatory, Anti-Microbial.

1. Introduction

The immune response also known as inflammation occurs when immunologically competent cells are activated in response to foreign organisms or when antigenic substances are liberated during the inflammatory response[1]. The four major symptoms of inflammation are rubor (redness), calor (heat), dolor (pain) and tumor (swelling). There is a fifth sign termed as functio laesa meaning loss of function. Inflammation is classified into acute and chronic patterns. The chronic use of Non-steroidal anti-inflammatory drugs (NSAIDs) to treat pain and inflammation is often accompanied by side effects such as gastric ulceration, bleeding, and renal function suppression[2-6].

Indoles when condensed with aromatic aldehydes in the presence of a base give rise to chalcones. Chalcones are one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices and soy-based foodstuffs. Chalcones are suitable intermediates for the synthesis of biologically active heterocyclic compounds, *viz*., pyrimidine, cyclohexanone, pyrazole and isoxazole derivatives. Indoles have been reported to possess a wide variety of biological activities like anti-inflammatory[7], anti-cancer[8] and anti-fungal[9], anti-viral[10], anti-malarial[11] etc. The 3-acetylindole derivatives have been the centre of the attention of researchers over many years due to high practical value of these compounds, in the first place, the unusually broad spectrum of biological activities. The compounds derived from the 3-acetylindoles are used in the treatment of gastrointestinal, cardiovascular and central nervous system (CNS) disorders, HIV-1 integrase inhibitors for antitumor activity, inhibitors of hepatitis, as anti-bacterials, as anti-malarial agents etc[12-15].

2. Materials and Methods:

2.1 Experimental:

A series of 3-acetylindole compounds were synthesised starting from 3-acetylindole and different aromatic aldehydes. The scheme of the synthesis is given by Fig.1. The list of aromatic aldehydes used is provided in Table 1. The melting point ranges of newly synthesized compounds were determined by open glass capillary tube using Lab India's visual melting point apparatus and were uncorrected. All the commercially available reagent grade chemicals were used as received. All the reactions were followed by Thin Layer Chromatography (TLC), with detection by Ultra-violet (UV) light and/or spots were visualised by exposure to iodine vapours. Infra-red (IR) spectra were recorded as thin films in Potassium bromide (KBr) pellets with a Nicolet spectrophotometer. Proton Nuclear Magnetic Resonance (1H-NMR) spectra were recorded on a Brucker in Dimethyl sulphoxide d6 (DMSO d6). The Chemical shift values are reported in parts per million (ppm) relative to $SiMe_4$ (Tetra methyl silane) as internal reference.

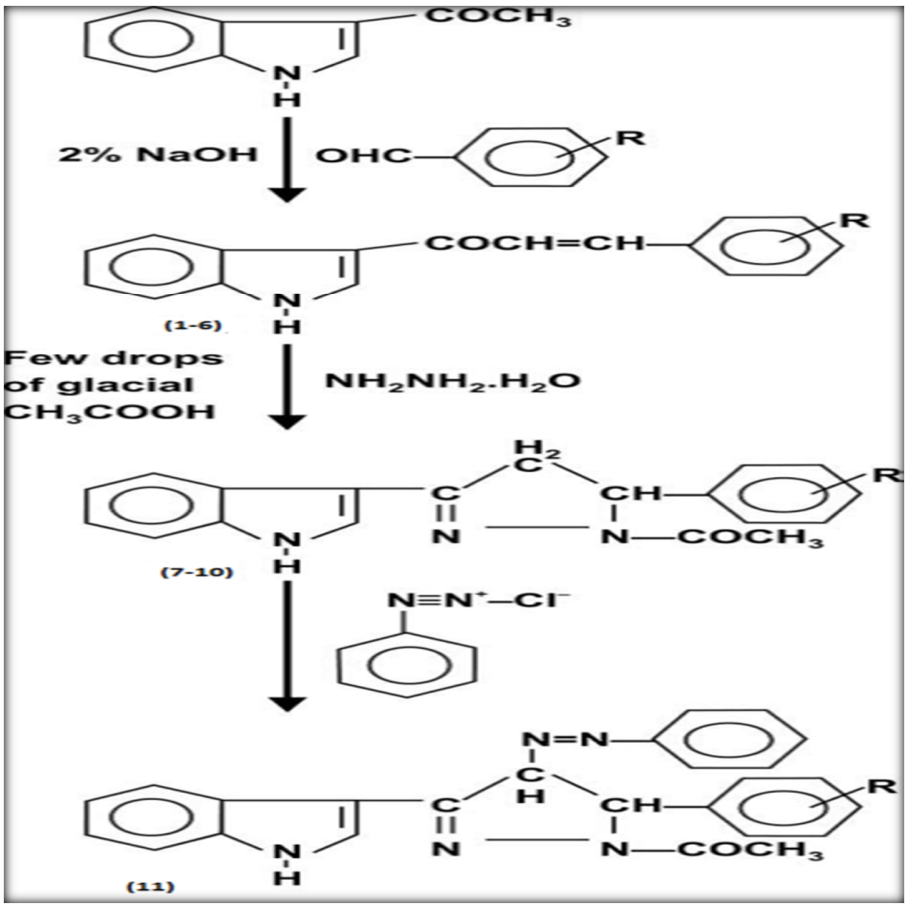
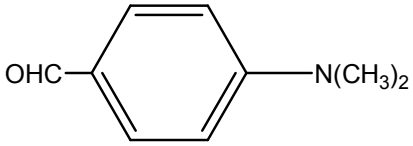
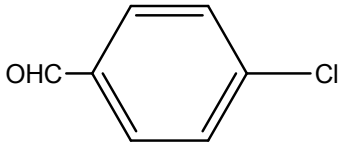
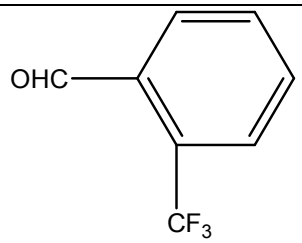
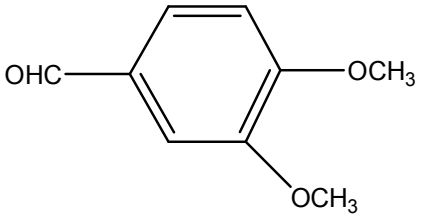
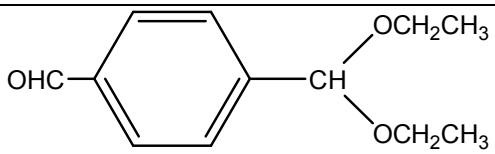
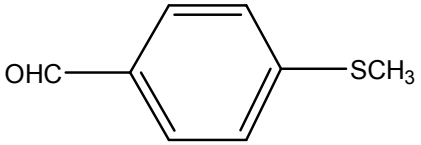


Fig 1: The Scheme for Synthesis

Table 1: The aromatic aldehydes used in the synthesis.

S. no.	Aromatic aldehyde	Name
1		4-(dimethylamino) benzaldehyde

2		p-chlorobenzaldehyde
3		2-(trifluromethyl)benzaldehyde
4		3,4-(dimethoxy) benzaldeyde
5		4-(diethoxymethyl)benzaldehyde
6		4-(methylthio) benzaldehye

3. Method of Synthesis:

LV-1: 3-(4-(dimethylamino)phenyl)-1-(1H-indol-3-yl)prop-2-en-1-one

To a solution of 3-acetylindole (0.01 mol) in methanol (dry, 50 ml), 4-dimethylamino benzaldehyde (0.01 mol) was added in the presence of 2% Sodium hydroxide (NaOH). The reaction mixture was stirred for 9-10 hours at room temperature. The solvent was distilled off and the crude product was poured into ice water. The compound obtained was filtered, washed with water and was recrystallized from methanol.

The compound was obtained as buff yellow solid with yield of 55% and melting point (m.p.) of 186-187°C.

IR (KBr) ***υ***: 3270cm^{-1} (N-H str), 3012cm^{-1} (Ar-C-H str), 1620 cm^{-1} (C=N str), 1457 cm^{-1} (C=C str), 1310cm^{-1} (C-N str).

NMR (DMSO d6) **δ:** 3.34 (s, 2H, CH_2), 7.14 (s, 1H, OH), 7.20-7.23 (m, 2H, Ar-H), 7.50-8.17 (m, 2H, Ar-H), 8.31 (s, 1H, NH).

LV-2: 2-(4-chlorocyclohexa-2,4-dien-1-ylidene)-1-(1H-indol-3-yl)ethanone

To a solution of 3-acetylindole (0.01 mol) in methanol (dry, 50ml), p-chlorobenzaldehyde (0.01mol) was added in the presence of 2% NaOH. The reaction mixture was stirred for 8-10 hours at room temperature. The solvent was distilled off and the crude product was poured into ice water. The compound obtained was filtered, washed with water and was recrystallized from methanol.

The compound was obtained as light yellow coloured solid with yield of 60% and m.p. of 194-196°C.

IR (KBr) υ: 3345cm^{-1} (N-H str), 3045cm^{-1} (Ar-C-H str), 1682 cm^{-1} (C-N str), 1448 cm^{-1} (C=C str), 1292 cm^{-1} (C-N str), 764-672cm^{-1} (C-Cl).

NMR (DMSO d6) **δ:** 3.34 (s, 2H, CH_2), 7.20-7.23 (m, 2H, Ar-H), 7.12-7.47 (m, 2H, Ar-H), 8.34 (s, 1H, NH).

LV-3: 1-(1H-indol-3-yl)-3(2-(trifluromethyl)phenyl) prop-2-en-1-one

To a solution of 3-acetylindole (0.01 mol) in methanol (dry, 50ml), 2-(trifluoromethyl) benzaldehyde (0.01mol) was added in the presence of 2% NaOH. The reaction mixture was stirred for 9-10 hours at room temperature. The solvent was distilled off and the crude product was poured into ice water. The compound obtained was filtered, washed with water and recrystallized from ethanol.

The compound was obtained as buff coloured solid with yield of 65% and m.p. of 183-185°C.

IR (KBr) υ: 3078cm^{-1} (Ar-C-H str), 2971 cm^{-1}(aliphatic- C-H str), 1570(C=N str) 1468 cm^{-1} (C=C str), 1315cm^{-1} (C-N str).

NMR (DMSO d6) **δ:** 2.50 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 7.14-7.23 (m, 2H, Ar-H), 8.16-8.30 (m, 2H, Ar-H).

LV-4: 3-(3,4-dimethoxyphenyl)-1-(1H-indol-3-yl)prop-2-en-1-one

To a solution of 3-acetylindole (0.01 mol) in methanol (dry, 50ml) 3,4-dimethoxybenzaldehyde (0.01mol) was added in the presence of 2% NaOH. The reaction mixture was stirred for 9-10 hours at room temperature. The solvent was distilled off and the crude product was poured into ice water. The compound obtained was filtered, washed with water and recrystallized from methanol.

The compound was obtained as yellow coloured solid with yield of 70% and m.p. of 190-193°C.

IR (KBr) υ: 3050cm^{-1} (Ar-C-H str), 2945 cm^{-1}(aliphatic- C-H str), 1662 cm^{-1} (C=O str),1598 cm^{-1}(C=N str), 1467 cm^{-1} (C=C str), 1292 cm^{-1} (C-N str).

NMR (DMSO d6) **δ:** 1.16 (s, 2H, CH_2), 2.51 (s, 2H, CH_2), 7.16-7.23 (m, 7H, Ar-H), 7.47-7.63 (m, 2H, Ar-H).

LV-5: 3-(4-(diethoxymethyl)phenyl)-1-(1H-indol-3-yl)prop-2-en-1-one

To a solution of 3-acetylindole (0.01 mol) in methanol (dry, 50ml), 4-diethoxy benzaldehyde (0.01mol) was added in the presence of 2% NaOH. The reaction mixture was stirred for 10-11 hours at room temperature. The solvent was distilled off and the crude product was poured into ice water. The compound obtained was filtered, washed with water and recrystallized from ethanol.

The compound was obtained as dark yellow solid with yield of 67% and m.p. of 145-147°C.

IR (KBr) υ: 3088 cm^{-1} (Ar-C-H str), 2955 cm^{-1}(aliphatic-C-H str) , 1725 cm^{-1} (C=O str), 1585 cm^{-1}(C=N str), 1478 cm^{-1} (C=C str), 1245 cm^{-1} (C-N str).

NMR (DMSO d6) **δ:** 2.56 (s, 2H, CH_2), 7.15-7.49 (m, 2H, Ar-H), 7.79-7.82 (m, 2H, Ar-H), 8.18-8.30 (m, 2H, Ar-H).

LV-6: 1-(1H-indol-3-yl)-3-(4-(methylthio)phenyl) prop-2-en-1-one

To a solution of 3-acetylindole (0.01 mol) in methanol (dry, 50ml) 4-(methylthio) benzaldehyde (0.01mol) was added in the presence of 2% NaOH. The reaction mixture was stirred for 10-11 hours at room temperature. The solvent was distilled off and the crude product was poured into ice water. The compound obtained was filtered, washed with water and recrystallized from ethanol.

The compound was obtained as light yellow solid with yield of 45% and m.p. of 150-152°C.

IR (KBr) υ: 3057 cm^{-1} (Ar-C-H str), 2925 cm^{-1}(aliphatic-C-H str) , 1725 cm^{-1} (C=O str), 1492 cm^{-1} (C=C str), 1197 cm^{-1} (C-N str), 1111 cm^{-1} (C-O str).

NMR (DMSO d6) **δ:** 7.14 (s, 3H, CH_3), 7.17 (s, 2H, CH_2), 7.45-7.58 (m, 2H, Ar-H), 7.72-7.84 (m, 2H, Ar-H), 8.16-8.36 (m, 3H, Ar-H).

LV-7: 1-(5-(4-(dimethylamino)phenyl)-3-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazo-1-yl)ethanone

To a solution of **LV-1** (0.01 mol) in absolute ethanol, hydrazine hydrate (99%, 0.02 mol) and a few drops of glacial acetic acid were added. The reaction mixture was refluxed for 6-8 hours. The excess of solvent was distilled off and the crude

product was poured into ice water. The separated solids were filtered and recrystallized from ethanol.

The compound was obtained as yellow coloured solid with yield of 25% and m.p. of 198-200°C.

IR (KBr) υ: 3098 cm^{-1} (Ar-C-H str), 2967 cm^{-1} (aliphatic-C-H str), 1644 cm^{-1} (C=O str), 1505 cm^{-1}(C=N str), 1450 cm^{-1} (C=C str), 1276 cm^{-1} (C-N str).

NMR (DMSO d6) **δ:** 4.62 (s, 2H, CH_2), 7.21-7.22 (m, 2H, Ar-H), 7.39-7.41 (m, 2H, Ar-H), 7.58-7.60 (m, 2H, Ar-H), 7.70-7.72 (m, 2H, Ar-H).

LV-8: **1-(-5-(4-chlorophenyl)-3-(1H-indol-3-yl)-4,5-dihyro-1H-pyrazol-1-yl)ethanone**

To a solution of **LV-2** (0.01 mol) in absolute ethanol, hydrazine hydrate (99%, 0.02 mol) and a few drops of glacial acetic acid were added. The reaction mixture was refluxed for 6-8 hours. The excess of solvent was distilled off and the crude product was poured into ice water. The separated solids were filtered and recyrstallised from ethanol.

The compound was obtained as light yellow solid with yield of 30% and m.p. of 205-207°C.

IR (KBr) υ: 3075 cm^{-1} (Ar-C-H str), 2923 cm^{-1} (aliphatic-C-H str), 1485 cm^{-1} (C=C str), 1276 cm^{-1} (C-N str), 764-672cm^{-1} (C-Cl).

NMR (DMSO d6) **δ:** 3.39 (s, 2H, CH_2), 7.12-7.25 (m, 4H, Ar-H), 7.43-7.46 (m, 1H, Ar-H), 7.13-7.57 (m, 2H, Ar-H),8.40-8.53(m, 2H, Ar-H).

LV-9: 1-(3-(1H-indol-3-yl)-5-(2-(trifluromethyl) phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone

To a solution of **LV-3** (0.01 mol) in absolute ethanol, hydrazine hydrate (99%, 0.02 mol) and a few drops of glacial acetic acid were added. The reaction mixture was refluxed for 6-8 hours. The excess of solvent was distilled off and the crude product was poured into ice water. The separated solids were filtered and recyrstallised from ethanol.

The compound was obtained as light yellow solid with yield of 35% and m.p. of 190-193°C.

IR (KBr) υ: 3063 cm^{-1} (Ar-C-H str), 2923 cm^{-1} (aliphatic-C-H str), 1559 cm^{-1}(C=N str), 1244 cm^{-1} (C-N str), 1242-1376 cm^{-1}(C-F str), 1013-1136 cm^{-1} (C=O str).
NMR (DMSO d6) **δ:** 2.65 (s, 3H, CH_3), 3.36 (s, 2H, CH_2), 7.12-7.21 (m, 2H, Ar-H), 7.75-7.83 (m, 2H, Ar-H).

LV-10: 1-(5-(3,4-dimethoxyphenyl)-3-(1H-indol-3-yl)-4,5-dihydro-1H-pyrazol-1-l)ethanone

To a solution of **LV-4** (0.01 mol) in absolute ethanol, hydrazine hydrate (99%, 0.02 mol) and a few drops of glacial acetic acid were added. The reaction mixture was refluxed for 6-8 hours. The excess of solvent was distilled off and the crude product was poured into ice water. The separated solids were filtered and recyrstallised from ethanol.

The compound was obtained as dark yellow solid with yield of 20% and m.p. of 190-191°C.

IR (KBr) υ: 3030 cm^{-1} (Ar-C-H str), 2940 cm^{-1} (aliphatic-C-H str), 1587 cm^{-1}(C=N str), 1455 cm^{-1} (C=C str), 1230 cm^{-1} (C-N str).

NMR (DMSO d6) **δ:** 2.56 (s, 2H, CH_2), 7.16-7.22 (m, 7H, Ar-H), 7.43-7.47 (m, 2H, Ar-H), 8.16-8.30(m, 2H, Ar-H).

LV-11: 1-(5-(4-chlorophenyl)-3-(1H-indol-3-yl)-4-(phenyldiazenyl)-4,5-dihyro-1H-pyrazol-1-yl)ethanone

To a solution of aniline (0.01mol) in glacial acetic acid, conc. hydrochloric acid (3 ml) was added at 0-5°C. A solution of sodium nitrite (1g in 5 ml of water) was then added drop wise to the above solution. The diazonium salt thus prepared was added to a solution of **LV-8** (0.01 mol) in methanol drop wise stirring below 0°C. The reaction mixture was kept at room temperature for 2-3 days and then poured into cold water (200 ml). The separated solids were then washed with water and recrystallized from methanol.

The compound was obtained as light brown solid with yield of 21% and m.p. of 234-236°C.

IR (KBr) υ: 3450cm^{-1} (O-H str), 3025cm^{-1} (Ar-C-H str), 2905 cm^{-1} (aliphatic- C-H str) , 1595 cm^{-1} (C=N str), 1457 cm^{-1} (C=C str), 1283cm^{-1} (C-N str), 635-751 cm^{-1} (C-Cl str).

NMR (DMSO d6) **δ:** 3.46 (s, 2H, CH_2), 7.14-7.24 (m, 2H, Ar-H), 7.47-7.51 (m, 2H, Ar-H).

3.1 Anti-Inflammatory Activity:

The anti-inflammatory activity was studied as per the method described by *Winter et al*[16]. The albino rats (150 - 200 g) were divided into 13 groups each consisting of six animals. The first group received solvent control (1 ml, 2% Carboxymethyl cellulose (CMC)) orally, second group received Diclofenac (10 mg/kg by weight(b.w.)) and the next eleven groups received test compounds (LV-1 to LV-11) (50mg/kg b.w., p.o) suspended in 2% CMC. Then, inflammation was induced after 60 minutes of drug administration by injecting carrageenan (0.1 ml of 1% solution) into the sub-planter tissue of the left hind paw in each rat. Then the volume of hind paw was measured by plethysmometer at 0, 1, 3, 6 hours.

The percentage inhibition of oedema was calculated as follows:

% inhibition = 100 (1 – Vt/Vc)

Where, Vt and Vc are increase in volume of paw oedema of treated animal and control animal respectively.

Table 2 and Fig. 2 show the percentage inhibition of oedema of test compounds and standard drug Diclofenac at 3 hours (180 min).

The study was approved by local institutional ethics committee of Delhi Institute of Pharmaceutical Sciences and Research, University of Delhi (Institutional Animal Ethics Committee (IAEC) Protocol No.2011/05) and performed in accordance with the Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

3.2 Anti-Microbial Activity:

The anti-bacterial activity of the synthesized compounds was evaluated by paper disc diffusion method using nutrient agar medium against following micro-organisms: *Staphylococcus aureus, Bacillus subtilis* (Gram positive) and *Escherichia coli, Pseudomonas aeruginosa* (Gram negative) and *Candida albicans* (fungus). In the paper disc-diffusion method, paper discs impregnated with compounds dissolved in DMSO at concentration of 50 & 100µg/ml were used. The microorganism culture was spread over nutrient agar media in petri-dishes and the disc impregnated with the solution was placed on the surface of the media inoculated with the bacterial strain. The plates were incubated at 35°C for 24 hrs.

Table 2: The percentage inhibition of oedema of test compounds and standard drug Diclofenac at 3 hours.

S.no	R	Dose(mg/kg, p.o)	% inhibition of oedema
1	p-dimethylamine	50	4.8
2	p-chloro	50	6.9
3	2-triflurомethyl	50	9.7
4	3,4-methoxy,p-methoxy	50	13.2
5	4-diethoxymethyl	50	25
6	p-methylthio	50	10.4
7	p-dimethylamine	50	11.2
8	p-chloro	50	9.7
9	2-triflurомethyl	50	11.8
10	3,4-methoxy,p-methoxy	50	11.6
11	p-chloro	50	14.4
A	Standard (diclofenac)	10	70
B	Control (CMC)		

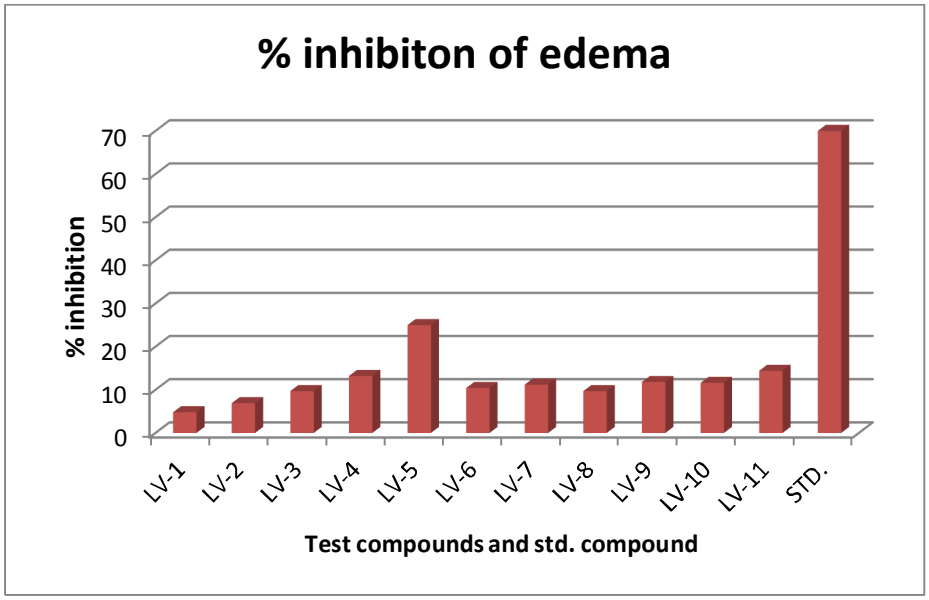


Fig 2: The percentage inhibition of oedema of test compounds (LV-1 to LV-11) and standard drug Diclofenac at 3hr (180 min).

Table 3: Anti-bacterial activity of synthesised compounds and standard drug Streptomycin against *B.subtilis* and *E.coli* determined by disc diffusion method.

Test samples	**Diameter of zone of inhibition in mm [mean (n=3)]**			
	B.subtilis		***E.coli***	
	50µg/ml	100µg/ml	50µg/ml	100µg/ml
LV-1	5.1	7.1	4.3	6.8
LV-2	4.2	6.3	4.1	5.0
LV-3	5.3	7.2	3.2	5.1
LV-4	6.3	7.6	3.0	4.6
LV-5	6.9	9.4	3.6	6.0
LV-6	5.2	6.8	2.8	3.3
LV-7	5.1	6.3	2.3	3.6
LV-8	4.2	5.1	4.2	4.6
LV-9	3.1	6.4	3.2	5.0
LV-10	2.8	3.3	1.3	3.2
LV-11	2.3	4.3	2.1	2.5
Std.	10.3	13.4	9.5	3.50

After incubation, the zone of inhibition around the disc was observed. The zone of inhibition indicates that the compounds inhibited growth of micro-organism. Each testing was done in triplicate. Streptomycin at concentration of 50 & 100 µg/ ml was used as standard drug for anti-bacterial activity. The results were interpreted in terms diameter (mm) of zone of inhibition. Table 3, 4 and Fig.3 shows the zone of inhibition (mm) of test samples and standard drug (Streptomycin) at a concentration of 50µg/ml.

Table 4: Anti-bacterial activity of synthesised compounds and standard drug Streptomycin against *S.aureus* and *P.aeruginosa* determined by disc diffusion method.

Test samples	Diameter of zone of inhibition in mm [mean (n=3)]			
	S.aureus		*P.aeruginosa*	
	50µg/ml	100µg/ml	50µg/ml	100µg/ml
LV-1	2.1	4.5	3.9	4.1
LV-2	2.8	2.3	2.3	2.6
LV-3	3.3	4.2	2.1	3.1
LV-4	3.9	4.9	4.2	4.6
LV-5	4.3	5.3	5.1	4.4
LV-6	3.2	5.1	4.4	5.8
LV-7	3.5	5.0	2.8	4.6
LV-8	2.8	4.2	3.9	5.5
LV-9	3.1	3.8	4.1	6.4
LV-10	2.9	4.2	3.4	6.8
LV-11	2.7	3.1	3.1	9.4
Std.	9.8	17.2	12.1	13.2

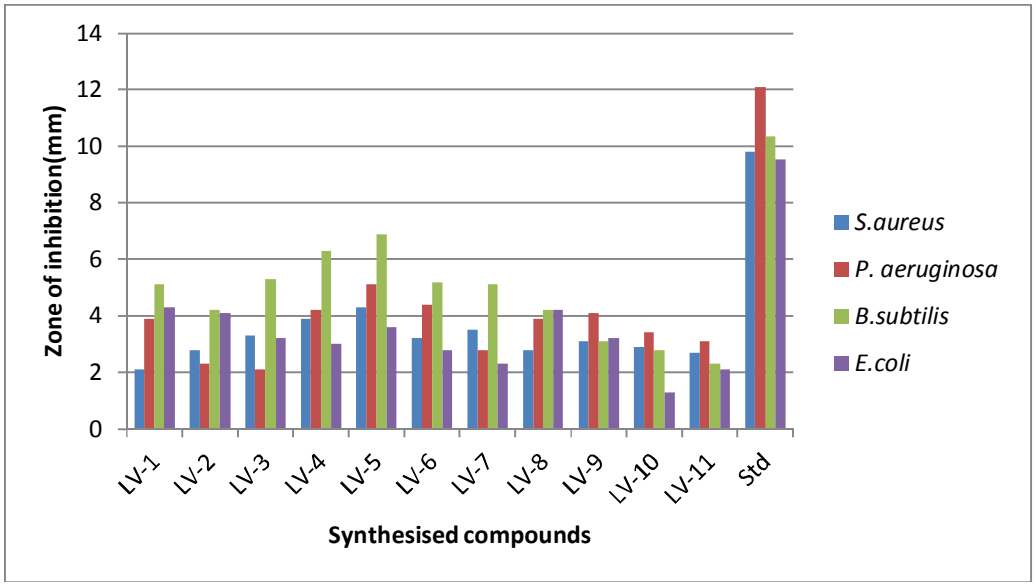


Fig 3: Zone of inhibition (mm) of test samples and standard drug Streptomycin at a concentration of 50µg/ml.

4. Results and Discussion:

The compounds were synthesized in moderate to good yield. Purity of compounds was determined by TLC on silica gel G plates. The spots were detected by exposure to iodine vapours. The yield and molecular weights of the synthesized compounds are given in Table 5. Synthesized compounds were characterized by spectral analysis (Fourier Transform Infra-red and 1H-NMR). The spectra were found to be in agreement with the assigned molecular structures. Amongst the synthesised compounds, LV-5 showed maximum inhibition of oedema i.e. 25% at the 3 hours interval as compared to the standard Diclofenac which showed 70% inhibition of oedema.

The compounds LV-4 and LV-5 showed maximum zone of inhibition against the *B.subtilis* while LV-5 and LV-8 showed maximum zone of inhibition against *E. coli*. The compounds LV-5 and LV-6 showed maximum zone of inhibition against *S.aureus* and *P. aeruginosa*. The compounds did not show any measurable activity against *C. albicans*.

Table 5: Physical properties of the synthesised compounds (LV-1 to LV-11)

S.no	Compounds	m.p.(°C)	% yield	Molecular formula	Molecular weight(atomic mass unit)	Rf
1	LV-1	186-188	55	C19H18N2O	290	0.66
2	LV-2	194-196	60	C16H12ClNO	269.7	0.69
3	LV-3	183-185	65	C18H12F3NO	315.2	0.73
4	LV-4	190-193	70	C19H17NO2	307.1	0.78
5	LV-5	145-147	67	C22H23NO3	349.4	0.65
6	LV-6	150-152	45	C18H15NOS	293.3	0.81
7	LV-7	198-200	25	C23H28N4O	346.4	0.79
8	LV-8	205-207	30	C19H16ClN3O	337.8	0.85
9	LV-9	187-189	35	C26H20F3N5O	371.3	0.67
10	LV-10	190-191	20	C21H21N3O3	363.4	0.77
11	LV-11	234-236	21	C25H20ClN5O	441.9	0.81

5. Conclusion

A series of 3-acetylindole derivatives were synthesized. All the synthesized compounds showed some anti-inflammatory activity. Among the compounds tested, compound LV-5 showed the highest activity and the activity was maximum at the time interval of 3 hours (180 min). The compounds LV-4 and LV-5 showed best activity against *B. subtilis* and LV-5 and LV-8 showed best activity against *E. coli*. The compounds LV-5 and LV-6 showed best activity against *S. aureus* and *P. aeruginosa*.

6. References

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