The Pharma Innovation Journal 2020; 9(6): 461-467

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2020; 9(6): 461-467

www.thepharmajournal.com
Received: 07-04-2020
Accepted: 09-05-2020

Nitish Kumar
Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Science and Research, New Delhi, India

Amrita Parle
Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Science and Research, New Delhi, India

Corresponding Author:
Amrita Parle
Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Science and Research, New Delhi, India

Synthesis, characterization and evaluation of 3-acetylindole derivatives evaluating as potential anti-inflammatory agent

Nitish Kumar and Amrita Parle

Abstract
In the present study a series of novel 3-acetylindole derivatives were synthesized by reacting 3-acetylindole and benzaldehyde. The synthesized 3-acetylindole derivatives were characterized physico-chemically and by spectral (IR and ^{1}H-NMR) analysis. All the synthesized compounds were screened for their *in-vitro* anti-inflammatory activity by inhibition of the albumin denaturation technique using diclofenac as standard. The results revealed that most of the compounds have better activity as compared with the standard diclofenac.

Keywords: Inflammation, 3-acetylindole, Albumin denaturation

Introduction
Inflammation is defined as the local response of the living mammalian tissues to injury due to any agent [1], which is frequently associated with pain and involves occurrences such as: the increase of vascular permeability, increase of protein denaturation and membrane alteration.
Inflammation is a critical homeostatic process that is activated by cellular injury regardless of the mechanism of the injury. Inflammation is essentially local in nature, although cellular mediators released during inflammation may initiate systemic responses as well. The agents causing inflammation may be:

a. **Physical agents:** Heat, cold, radiation and mechanical trauma.
b. **Chemical agents:** Organic and inorganic poisons.
c. **Infective agents:** Bacteria, virus and their toxins.

When tissue cells become injured they release kinins, prostroglandins and histamine. These work collectively to cause increased vasodilation and permeability of the capillaries. This leads to increased blood flow to the injured site. These substances also act as chemical messengers that attract some of the body's natural defense cells, a mechanism known as chemotaxis [2].
Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.
Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process [3].
NSAIDS commonly used as anti-inflammatory agents, for example Aspirin, paracetalmol, diclofenac, phenylbutazone etc. However, these agents have their own drawbacks: Aspirin causes hyperuricemia(contra-indicated in Gout) and anti-platelet action, Paracetamol is hepatotoxic, Phenylbutazone causes agranulocytosis [4]. Thus there is need to develop new anti-inflammatory agents.
Indole is a bicyclic heterocyclic system having m.p. 52-54 °C, molecular weight 117.151g/mol with empirical formula C_8H_7N in which the pyrrole ring is fused with benzene ring at α, β-position.
It is reported that there are various medicinal activities of compounds having indole nucleus *viz* insecticidal of 5-iodoindole [5], anti-viral activities of isatin and indole oximes and anti-inflammatory activity of indole-3-acetic acid [6-8], fungicidal activity of the oxime derivatives

of 2-substituted indoles and 3-substituted indoles [9], antibacterial activity of 3-aryl/ 3-heteroaryl substituted indoles, antioxidant activity of a series of 3-pyranyl indole derivatives [10], *in vitro* antitubercular activity of indoleamide derivatives [11], anticancer [12] of indole-2-carbohydrazides and thiazolidinyl-indole-2-carboxamide derivates etc.

3-Acetylindole derivatives are also reported to have various therapeutic activities *viz*, a series of 3-acetylindole derivatives, for example, *N*-arylsulfonyl-3-acetylindoles and oxobutenoic substituted-3-acetylindole acids were reported as anti-HIV agent [13-14], hetroaryl substituted-3-acetylindole were reported as anti-inflammatory and antibacterial activity [15]. Antileishmanial activity of derivative of bis(indolyl)-pyridines were reported [16].

In the present study 3-acetylindole derivatives were synthesized, characterized and evaluated for anti-inflammatory activity.

2. Material and Methods

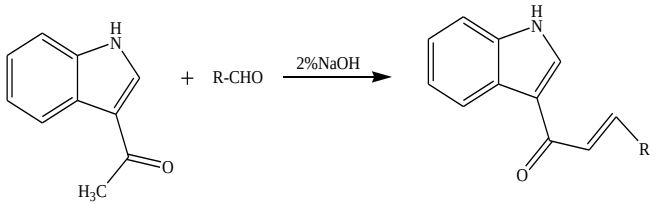
2.1 Experimental

All the commercially available reagent grade chemicals of Merck and Sigma Aldrich were used as received. Purity of the compound and progress of the reaction were monitored by thin layer chromatography (TLC) using by Ultra-violet (UV) light detector and/or by exposure to iodine vapors chamber. The melting point ranges of newly synthesized compounds were determined using visual melping point apparatus of Lab India model MR-VIS 10230308. Infra-red (IR) spectra were recorded using Bruker Alpha 1005151/06 ATIR spectrophotometer. Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on a Bruker using $CDCl_3$ or DMSO at 300MHz or 400MHz respectively. The Chemical shift values are reported in parts per million (ppm) relative to Tetra methyl silane as internal reference.

2.1 Synthesis

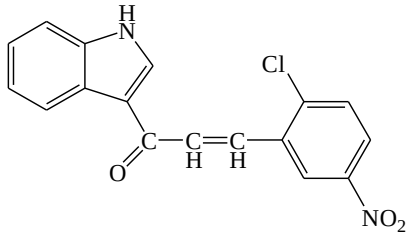
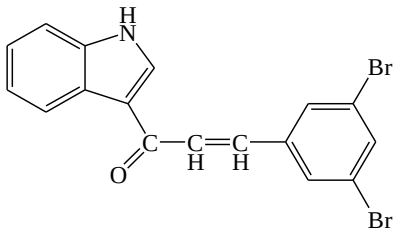
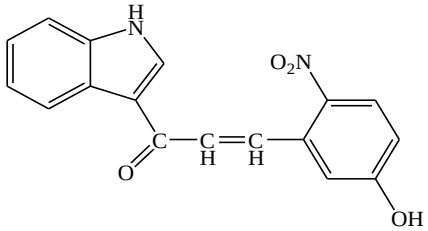
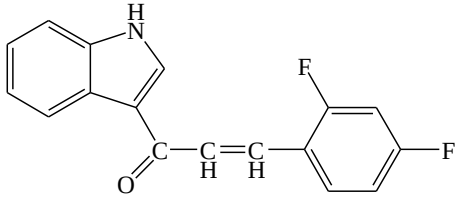
The title compounds were synthesized using synthetic strategy described in Scheme 1.

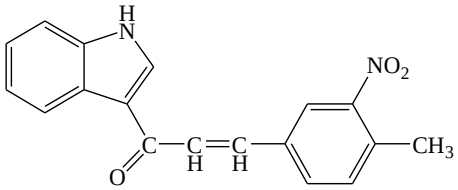
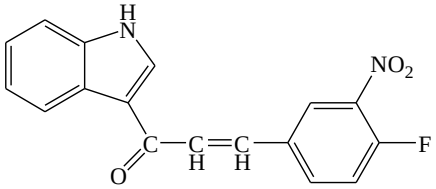
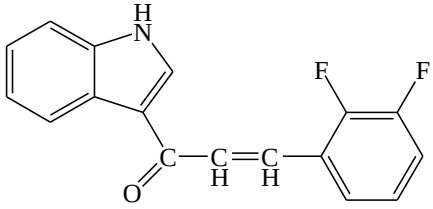
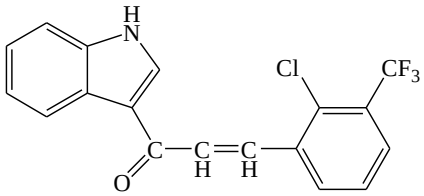
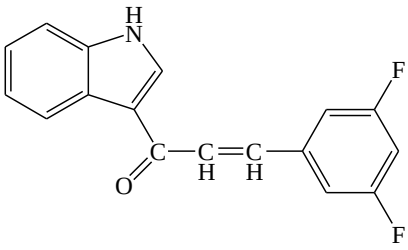
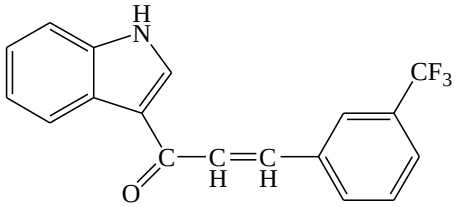
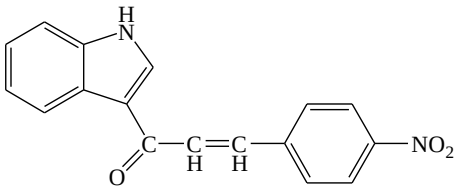
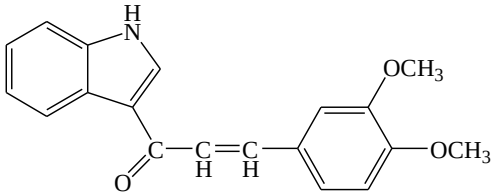
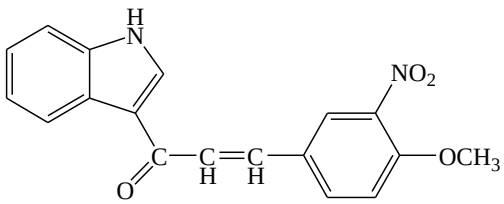
Scheme 1



2.1.1 General procedure: To a solution of 3-acetylindole(2gm) (0.01 mole) in methanol (50ml), Ar aldehyde (2ml) (0.01 mole) was added in the presence of 2% sodium hydroxide (5ml). The reaction mixture was stirred for 9-10 h at room temperature and then the mixture was poured into ice water. The compound obtained was filtered, washed with water and recrystallized using methanol.

Table 1: List of synthesized compounds

Compound	Structure	IUPAC name
NK-1		3-(2-chloro-5-nitrophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-2		3-(3,5-dibromophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-3		3-(5-hydroxy-2-nitrophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-4		3-(2,4-difluorophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one

NK-5		1-(1*H*-indol-3-yl)-3-(4-methyl-3-nitrophenyl)prop-2-en-1-one
NK-6		3-(4-fluoro-3-nitrophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-7		3-(2,3-difluorophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-8		3-(2-chloro-3-(trifluoromethyl)phenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-9		3-(3,5-difluorophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-10		1-(1*H*-indol-3-yl)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-one
NK-11		1-(1*H*-indol-3-yl)-3-(4-nitrophenyl)prop-2-en-1-one
NK-12		3-(3,4-dimethoxyphenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-13		1-(1*H*-indol-3-yl)-3-(4-methoxy-3-nitrophenyl)prop-2-en-1-one

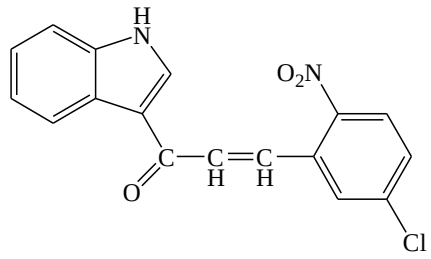
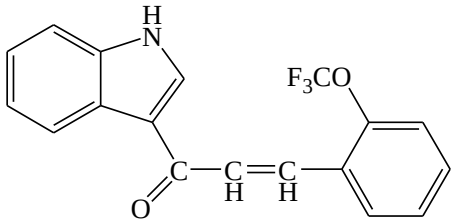
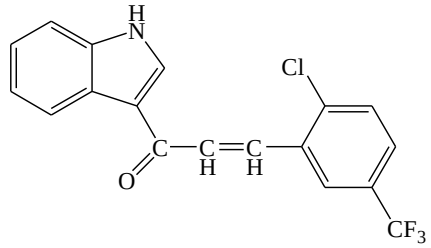
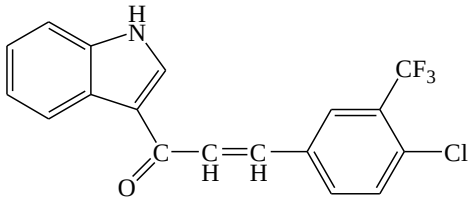
NK-14		3-(5-chloro-2-nitrophenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-15		1-(1*H*-indol-3-yl)-3-(2-(trifluoromethoxy)phenyl)prop-2-en-1-one
NK-16		3-(2-chloro-5-(trifluoromethyl)phenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one
NK-17		3-(4-chloro-3-(trifluoromethyl)phenyl)-1-(1*H*-indol-3-yl)prop-2-en-1-one

Table 2: Physical data of synthesized compounds

S. No.	Compound	Molecular Formula	State	Solubility	%Yield	Melting point
1.	NK-1	$C_{17}H_{11}N_2O_3Cl$	Solid	DMSO	56%	190-193ºC
2.	NK-2	$C_{17}H_{11}NOBr2$	Solid	DMSO	62%	142-145ºC
3.	NK-3	$C_{17}H_{12}N_2O_4$	Solid	DMSO	66%	187-190ºC
4.	NK-4	$C_{17}H_{11}NF_2O$	Solid	DMSO	57%	162-166ºC
5.	NK-5	$C_{18}H_{14}N_2O_3$	Solid	DMSO	70%	189-191ºC
6.	NK-6	$C_{17}H_{11}N_2O_3F$	Solid	DMSO	65%	190-193ºC
7.	NK-7	$C_{17}H_{11}NOF_2$	Solid	DMSO	57%	151-153ºC
8.	NK-8	$C_{18}H_{11}NClF_3O$	Solid	DMSO	69%	170-173ºC
9.	NK-9	$C_{17}H_{11}NOF_2$	Solid	DMSO	64%	150-154ºC
10.	NK-10	$C_{18}H_{12}NOF_3$	Solid	DMSO	66%	160-162ºC
11.	NK-11	$C_{17}H_{12}N_2O_3$	Solid	DMSO	59%	181-183ºC
12.	NK-12	$C_{19}H_{17}NO_3$	Solid	DMSO	68%	159-161ºC
13.	NK-13	$C_{18}H_{14}N_2O_4$	Solid	DMSO	72%	171-174ºC
14.	NK-14	$C_{17}H_{11}N_2O_3Cl$	Solid	DMSO	59%	176-178ºC
15.	NK-15	$C_{18}H_{12}NO_2F_3$	Solid	DMSO	65%	161-164ºC
16.	NK-16	$C_{18}H_{11}NClF3O$	Solid	DMSO	55%	168-170ºC
17.	NK-17	$C_{18}H_{11}NClF_3O$	Solid	DMSO	64%	159-162ºC

Table 3: Spectral study of synthesized compounds

Compound	IR spectra data	^{1}HNMR spectra data ($CDCl_3$)
NK-1	3271.55 cm^{-1}(Ar-H stretch), 1600.79 cm^{-1}(α,β unsaturated C=O stretch), 1518.89 cm^{-1}(Ar Nitro), 1433.75 cm^{-1} (Ar C-C stretch), 1341.34 cm^{-1} (Ar –N stretch), 1186.79 cm^{-1}-1139.50 cm^{-1}(Ar-Cl stretch), 742.92 cm^{-1}(Ar C-H out of plane).	*δ*11.916(1H, NH), *δ* 8.158(2H, CH=CH), *δ* 7.215-8.141 (7H, Ar-H)
NK-2	3181.48 cm^{-1}(Ar-H stretch), 1696.77 cm^{-1} (α,β unsaturated C=O Stretch), 1433.44 cm^{-1} (Ar C-C stretch), 1240.02 cm^{-1} (Ar –N stretch),1145.88 cm^{-1}(Ar-Br stretch), 749.62 cm^{-1}(Ar C-H out of plane)	*δ* 9.917(1H, NH), 7.688(2H, CH=CH), *δ* 7.286-7.607 (7H, Ar-H).
NK-3	3156.36 cm^{-1}(Ar-OH bonded), 3043.03 cm^{-1}(Ar-H stretch),1612.67 cm^{-1} (α,β unsaturated C=O stretch), 1523.97 cm^{-1}(Ar Nitro), 1432.91 cm^{-1}(Ar C-C stretch), 1314.62 cm^{-1}-1241.27 cm^{-1}(Ar-N stretch), 753.07 cm^{-1}(Ar C-H out of plane)	*δ*11.932(1H, NH), *δ* 8.074(2H,CH=CH), *δ* 7.023-7.492(7H, Ar-H), *δ*6.988(1H, Ar-OH).

NK-4	3161.97 cm^{-1}(Ar-H stretch),1615.17 cm^{-1}(α,β unsaturated C=O stretch), 1432.26 cm^{-1}(Ar C-C stretch), 1315.61 cm^{-1}-1241.68 cm^{-1}(Ar-N stretch), 1241.68 cm^{-1}-1178.18 cm^{-1}(C-F stretch), 753.24 cm^{-1}(Ar C-H out of plane)	*δ* 11.94(1H,NH), *δ* 8.223(2H, CH=CH), *δ* 7.180-7.504(7H, Ar-H).
NK-5	3168.49 cm^{-1}(Ar-H stretch),1615.07 cm^{-1} (α,β unsaturated C=O stretch), 1525.23 cm^{-1}(Ar Nitro), 1435.04 cm^{-1}(Ar C-C stretch), 1316.67 cm^{-1}-1242.19 cm^{-1}(Ar-N stretch), 753.37 cm^{-1}(Ar C-H out of plane)	*δ* 10.059(1H,NH), *δ* 7.956(2H,CH=CH), 7.183-7.555(7H, Ar-H).
NK-6	3165.81 cm^{-1}(Ar-H stretch),1612.77 cm^{-1} (α,β unsaturated C=O stretch), 1536.34 cm^{-1}(Ar –Nitro), 1428.23 cm^{-1}(Ar C-C stretch), 1351.65 cm^{-1}-1285.48 cm^{-1}(Ar-N stretch), 1078.83 cm^{-1}-1011.52 cm^{-1} (C-F stretch), 755.51 cm^{-1}(Ar C-H out of plane)	*δ* 10.014(1H,NH), *δ* 8.119(2H,CH=CH), *δ* 7.179-7.41(7H, Ar-H).
NK-7	3167.26 cm^{-1}(Ar-H stretch),1614.25 cm^{-1}(α,β unsaturated C=O stretch), 1431.38 cm^{-1}(Ar C-C stretch), 1316.68 cm^{-1}-1242.87 cm^{-1}(Ar-N stretch), 1179.17 cm^{-1}-1027.54 cm^{-1}(C-F stretch), 753.27 cm^{-1}(Ar C-H out of plane)	*δ* 8.37(1H, NH), *δ*8.225(2H, CH=CH), *δ* 7.191-7.506(7H, Ar-H).
NK-8	3247.89 cm^{-1}(Ar-H stretch),1596.10 cm^{-1} (α,β unsaturated C=O stretch), 1411.10 cm^{-1}(Ar C-C stretch), 1317.11 cm^{-1}(Ar-N stretch), 1130.54cm^{-1}(Ar-Cl Stretch), 1094.90 cm^{-1}-1014.31cm^{-1}(C-F stretch),798.21 cm^{-1}(Ar C-H out of plane)	^{1}HNMR(DMSO,400MHz)-*δ* 8.6 (1H, NH), *δ* 8.021(2H, CH=CH), *δ* 7.232-7.810(7H, Ar-H).
NK-9	3256.83 cm^{-1}(Ar-H stretch),1614.29 cm^{-1} (α,β unsaturated C=O stretch), 1434.75 cm^{-1}(Ar C-C stretch), 1316.72 cm^{-1}(Ar-N stretch), 1241.18 cm^{-1}-1143.86 cm^{-1}(C-F stretch), 754.34 cm^{-1}(Ar C-H out of plane)	^{1}HNMR(DMSO,400MHz)- *δ* 8.401(1H, NH), *δ* 8.012(2H,CH=CH), 7.031-7.432(7H, Ar-H).
NK-10	3157.58 cm^{-1}(Ar-H stretch),1612.31 cm^{-1} (α,β unsaturated C=O stretch), 1432.48 cm^{-1}(Ar C-C stretch), 1330.72 cm^{-1}(Ar-N stretch), 1176.16 cm^{-1}-1128.59 cm^{-1}(C-F stretch), 752.21 cm^{-1}(Ar C-H out of plane)	^{1}HNMR(DMSO,400MHz)- *δ* 8.421(1H,NH), *δ* 8.001(2H, CH=CH), *δ* 7.011-7.801(7H, Ar-H).
NK-11	3211.25 cm^{-1}(Ar-H stretch),1626.84 cm^{-1} (α, β unsaturated C=O stretch),1520.92 cm^{-1} (Ar -Nitro), 1439.07 cm^{-1}(Ar C-C stretch), 1343.59 cm^{-1}(Ar-N stretch), 748.57 cm^{-1} (Ar C-H out of plane)	^{1}HNMR(DMSO,400MHz)- *δ* 8.569(1H,NH), *δ* 8.094(2H, CH=CH), *δ* 7.142-7.801(8H, Ar-H).
NK-12	3157.20 cm^{-1}(Ar-H stretch), 2832.36cm^{-1}(O-CH_3 stretch), 1610.47 cm^{-1}(α,β unsaturated C=O stretch), 1430.06 cm^{-1}(Ar C-C stretch), 1343.93 cm^{-1}-1241.67cm^{-1}(Ar-N stretch), 752.69 cm^{-1} (Ar C-H out of plane)	^{1}HNMR(DMSO,400MHz)-*δ* 8.401(1H,NH), *δ* 8.099(2H,CH=CH), *δ* 7.012-7.410(4H, Ar-H), *δ* 2.512(3H, OCH_3).
NK-13	3064.79 cm^{-1}(Ar-H stretch), 2735.31cm^{-1}(O-CH_3 stretch), 1669.09cm^{-1}(α,β unsaturated C=O stretch), 1512.93cm^{-1}(Ar-Nitro), 1448.19cm^{-1}(Ar C-C Stretch), 1334.50cm^{-1}(Ar-N Stretch), 762.90cm^{-1}(Ar C-H Out of plane)	*δ* 9.761 (1H,NH), *δ* 7.638(2H, CH=CH), *δ* 6.633-7.366(7H, Ar-H).
NK-14	3059.76 cm^{-1}(Ar-H stretch), 2735.31cm^{-1}(O-CH_3 stretch), 1605.52cm^{-1} (α,β unsaturated C=O stretch), 1212.22cm^{-1}(Ar-Cl Stretch), (1493.60cm^{-1}(Ar-Nitro), 1448.80cm^{-1}(Ar C-C Stretch), 1336.39cm^{-1}(Ar-N Stretch), 749.94cm^{-1}(Ar C-H Out of plane)	*δ* 9.873(1H, NH), *δ* 7.437(2H, CH=CH), *δ* 5.986-7.419(7H, Ar-H).
NK-15	1690.09cm^{-1} (α,β unsaturated C=O stretch), 1449.01cm^{-1}(Ar C-C Stretch), 1345.03cm^{-1}(Ar-N Stretch), 754.19cm^{-1}(Ar C-H out of plane).	*δ* 10.170(1HNH), *δ* 7.260-7.644(8H, Ar-H), *δ*5.743(2H,CH=CH).
NK-16	2966.88 cm^{-1}(Ar-H Stretch), 1682.13cm^{-1}(α,β unsaturated C=O stretch), 1448.67cm^{-1}(Ar C-C Stretch), 1308.99cm^{-1}(Ar-N Stretch), 1143.30cm^{-1}(Ar-Cl Stretch), 1077.58cm^{-1}(C-F Stretch), 761.22cm^{-1}(Ar C-H Out of plane).	*δ* 9.981(1H, NH), *δ* 8.057(2H, CH=CH), *δ* 7.240-7.846(7H, Ar-H).
NK-17	3063.14 cm^{-1}(Ar-H Stretch), 1664.91cm^{-1}(α,β unsaturated C=O stretch), 1448.12cm^{-1}(Ar C-C Stretch), 1352.59cm^{-1}(Ar-N Stretch), 1201.55cm^{-1}(Ar-Cl Stretch), 1074.73cm^{-1}(C-F Stretch), 752.25cm^{-1}(Ar C-H Out of plane).	*δ* 9.970(1H,NH), *δ* 7.472(2H, Ar-H), *δ* 6.819(2H, CH=CH).

3. Pharmacological evaluation

3.1 Anti-inflammatory activity

All the synthesized compounds were evaluated for *in vitro* anti-inflammatory activity at concentrations of 20µg/ml, 40µg/ml, 80µg/ml and 100µg/ml by inhibition of the albumin denaturation technique [17] using diclofenac as standard.

3.2 Procedure

The synthesized compounds are analyzed for anti-inflammatory activity by *in-vitro* method using the inhibition of the albumin denaturation technique. All the synthesized compounds and standard drug were dissolved in DMF (Dimethyl formamide) and diluted with saline phosphate buffer (pH 7.4) in such a way that DMF concentration in all solutions was less than 2.5%. The test solution (1ml, 100ug/ml) was mixed with 1 ml of 1% albumin solution in saline phosphate buffer and incubated at 27±1 ºC in an incubator for 15 minutes. Denaturation was induced by keeping the reaction mixture in a 60±1 ºC water bath for 10 minutes. After cooling, the turbidity was measured at 660 nm with a UV spectrophotometer. The denaturing inhibition rate was calculated from the control in which no drug was added. Diclofenac sodium was used as a standard drug. The inhibition percentage was calculated.

% Inhibition of denaturation= $[1-(V_t/V_c)] \times 100$

Where

V_t = absorption of test compound,

V_c= absorption of control

Table 4: Anti-inflammatory activity of synthesized compounds and standard drug Diclofenac

Compounds	Percentage inhibition of denaturation			
	20µg/ml	40µg/ml	80µg/ml	100µg/ml
NK-1	49.86	52.26	62.69	65.79
NK-2	34.28	44.11	61.24	61.60
NK-3	31.16	50.31	64.18	66.49
NK-4	22.36	24.20	35.21	38.87
NK-5	15.40	53.44	67.86	69.13
NK-6	36.85	62.93	73.28	81.62
NK-7	34.83	52.55	64.75	61.67
NK-8	32.08	48.84	54.01	56.71
NK-9	44.91	62.48	76.77	79.41
NK-10	22.73	45.38	50.52	52.09
NK-11	38.68	41.67	47.00	54.64
NK-12	29.70	52.30	62.38	68.26
NK-13	45.83	47.49	71.51	79.54
NK-14	42.80	44.81	64.79	69.13
NK-15	13.38	38.45	46.85	42.35
NK-16	20.71	37.96	51.41	53.90
NK-17	27.68	38.98	55.28	56.51
Diclofenac	57.65	61.10	74.68	80.48

4. Results and Discussion

A series of 3-acetyl indole derivatives were designed, synthesized, characterized and evaluated for their anti-inflammatory activity. Based on the work done, it can be said that

I. Yield- All compounds were synthesized in appreciable yield.

II. Spectral data were found to be in agreement with assigned structure.

III. Anti-inflammatory

- NK-1, NK-9, NK-13 and NK-14 showed equal anti-inflammatory activity as compared to standard diclofenac at 20µg/ml.
- NK-6 and NK-9 showed better anti-inflammatory activity as compared to standard diclofenac and NK-1, NK-3, NK-5, NK-7 and NK-12 showed equal anti-inflammatory activity as compared to standard diclofenac at 40µg/ml.
- NK-9 showed better anti-inflammatory activity as compared to standard diclofenac and NK-1, NK-2, NK-3, NK-5, NK-6, NK-7, NK-12, NK-13 and NK-14 showed equal anti-inflammatory activity as compared to standard diclofenac at 80µg/ml.
- NK-6 showed better anti-inflammatory activity as compared to standard diclofenac and NK-1, NK-3, NK-5, NK-9, NK-12, NK-13 and NK-14 showed equal anti-inflammatory activity as compared to standard diclofenac at 100µg/ml

5. Comparison amongst doses

- NK-6 and NK-9 at 40µg/ml showed better anti-inflammatory activity as compared to standard diclofenac at 20µg/ml.
- NK-1, NK-2, NK-3, NK-5, NK-6, NK-7, NK-9, NK-12, NK-13 and NK-14 at 80µg/ml showed better anti-inflammatory activity as compared to standard diclofenac at 40µg/ml.
- NK-6, NK-9 and NK-13 at 100µg/ml showed better anti-inflammatory activity as compared to standard diclofenac at 80µg/ml.

6. Discussion

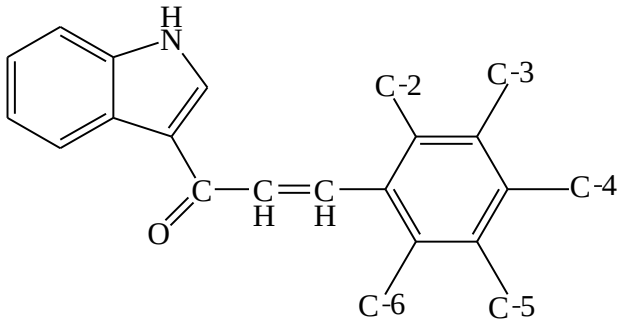


Fig 1: SAR positions of phenyl ring substituted on 2nd position of 3-acetyl indole

From the results it was observed that compounds NK-6 and NK-9 showed better activity as compared to standard diclofenac, it may be due to presence of fluoro group at *meta* or *para* position.

Kale M.A. *et al.* (2017) in his studies have also shown that 3-acetyl indole derivatives with para chloro phenyl group substituted at 2nd position showed maximum anti-inflammatory activity. Verma L. *et al.* (2016) in his studies have shown that in the 3-acetyl indole derivatives if the phenyl group placed at second position is substituted with electron withdrawing group (diethoxymethyl) at C-4 position, it exhibited better anti-inflammatory activity. Thus our study is in concurrence with outcomes of Kale *et al.* but not in concurrence with the outcome of Verma *et al.*

7. Conclusion

Amongst all the title compounds, NK-6, NK-9, NK-13 and NK-14 showed better or equal anti-inflammatory activity. NK-9 exhibited highest activity making it the most potent amongst the series due to presence of fluoro group at *ortho* position of phenyl group substituted at 2 position of 3-acetyl indole. In future, these compounds can be subjected to toxicity studies and further for *in vivo* studies. These compounds can serve as a base for the future development of newer anti-inflammatory molecules having better anti-inflammatory activity.

8. Reference

1. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008; 454(7203):428-35.
2. Kuprash DV, Nedospasov SA. Molecular and Cellular Mechanisms of Inflammation. Biochemistry (Mosc). 2016; 81(11):1237-1239.
3. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y *et al*. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017; 9(6):7204-7218.
4. Lisowska B, Kosson D, Domaracka K. Positives and negatives of nonsteroidal anti-inflammatory drugs in bone healing: the effects of these drugs on bone repair.
5. Rajasekharan SK, Lee JH, Ravichandran V, Kim JC, Park JG and Lee J: Nematicidal and insecticidal activities of halogenated indoles. Scientific Reports, 2019, 1-14.
6. Radwan MAA, Ragab EA, Nermien M. Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents. Bioorg. Med. Chem. 2007; 15:3832-41.
7. Mazzei M, Giampieri M, Balbi A, Colla PL, Ibba C. Antiviral activity of indole derivatives. Antiviral Research. 2009; 83:179-85.
8. Liu K, Sun J, Lou H, Dai S, Xu H. Indole alkaloids from Nauclea officinal is with weak antimalarial activity. Phytochemistry. 2008; 69:1405-10.
9. Ryu CK, Lee JY, Park R, Ma M. Synthesis and antifungal activity of 1H-indole-4,7-diones. Bioorg. Med. Chem. Lett. 2007; 17:127-31.
10. Perumal T, Lakshmi NV, Thirumurugan P, Noorulla KM. $InCl_3$ mediated one-pot multi component synthesis, antimicrobial, antioxidant and anticancer evaluation of 3-pyranyl indole derivatives. Bioorg. Med. Chem. Lett. 2010; 20:5054-61.
11. Lun S, Tasneen R, Chaira T, Stec J, Onajole OK, Yang TJ *et al*. Advancing the therapeutic potential of indoleamides for tuberculosis. Antimicrob Agents Chemother. 2019, 00343-19.
12. Kazan F, Yagci ZB, Bai R, Ozkirimli E, Hamel E, Ozkirimli S. Synthesis and biological evaluation of indole-2-carbohydrazides and thiazolidinyl-indole-2-carboxamides as potent tubulin polymerization inhibitors. Comput Biol Chem. 2019; 80:512-523.
13. Ran JQ, Huang N, Xu H, Yang LM, Lv M, Zheng YT. Anti HIV-1 agents 5: synthesis and anti-HIV-1 activity of some N-arylsulfonyl-3-acetylindoles *in vitro*. Bioorg Med Chem Lett. 2010; 20(12):3534-6.
14. De Luca L, Ferro S, Gitto R, Barreca ML, Agnello S, Christ F *et al*. Small molecules targeting the interaction between HIV-1 integrase and LEDGF/p75 cofactor. Bioorg. Med. Chem, 2010, 1-7.
15. Verma L, Wakode S. Synthesis and Characterisation of 3-Acetylindole Derivatives and Evaluation of Their Anti-Inflammatory and Anti-Microbial Activity. Pharma Innovation. 2013; 2(5):41-50.
16. Khan FAK, Zaheer Z, Sangshetti JN, Patil RH, Farooqui M. Antileishmanial evaluation of clubbed bis(indolyl)-pyridine derivatives: One-pot synthesis, *in vitro* biological evaluations and in silico ADME prediction. Bioorganic & Medicinal Chemistry Letters. 2017; 27:567–573.
17. Osman NI, Sidik JN, Awal A, Athirah N, Adam M, Rezali NI. *In vitro* xanthine oxidase and albumin denaturation inhibition assay of *Barringtonia racemosa* L. and total phenolic content analysis for potential anti-inflammatory use in gouty arthritis. J Intercult Ethnopharmacol. 2016; 5(4):343–349.