Synthesis, Characterization and Anti-Inflammatory Activity of Novel 1, 5-Disubstituted Indole Derivatives

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Abstract

A new series of 1,5-disubstituted indole derivatives such as 5-(acetylamino)-1-[(4-flurophenyl)carbonyl]-1H-indole-3-carboxylic acid, 1-[(4-fluorophenyl)carbonyl]-5-[(phenylcarbonyl)amino]-1H-indole-3-carboxylic acid, 1-(4-flurobenzoyl)-5-(4-ethylbenzamido-1H-indole-3-carboxylic acid, 5-(4-nitrobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid, 5-(4-bromobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid were synthesized. All the newly synthesized derivatives of 1,5-disubstituted indole derivatives are characterized by spectroscopically and analytically. All compounds were screened for their anti-inflammatory activity. The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 12.12 to 65.51 % inhibition. The compound I was found to be ne+arly more potent then indomethacin which is used as standard drug. A compound III has shown less activity then indomethacine. Compounds IV and V shown more potent activity than compound –I, II and Indomethacin.

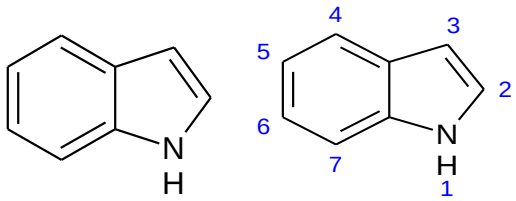
Key words: *1,5-disubstituted, Pharmacological screening, Indomethacin, Anti-inflammatory.*

1. INTRODUCTION:

1.1 Indole and its Derivatives: -

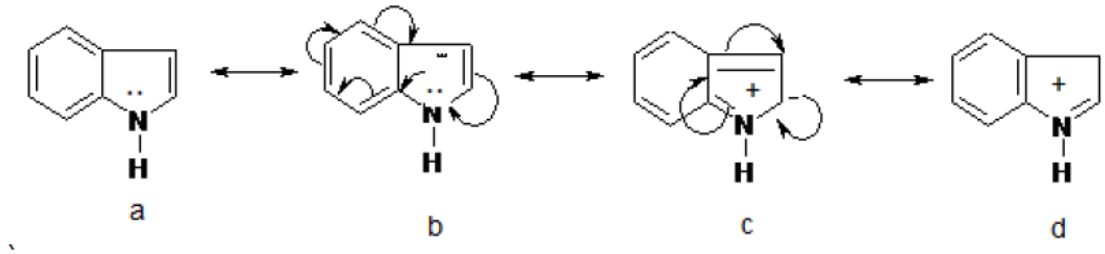
The word Indole is instituted from the word India, a blue color imported from India known as Indigo. Indigo can be changed over to isatin and afterward to oxindole At that point in 1866, Adolf von Baeyer decreased oxindole to indole utilizing zinc dust. In 1869, he proposed a formula for indole:

Indole is non-basic nitrogenous compound in which a benzene ring and a pyrrole nucleus are fused in 2, 3 positions of the pyrrole ring. It is aromatic heterocyclic organic compound. It has a bicyclic structure. Indole is colorless crystalline solid and melts at 52'C, soluble in alcohol, benzene and ether. It may be recrystallized from water.



Indole is a trivial name of benzopyrrole in which 2 and 3 carbon atoms of the nitrogen ring are members of a benzenoid nucleus. Indole is a planar molecule with 10 electrons. It's resonance energy is 47-49 K cal/mole. It is a very weak base with pKa value 3.63. The electrophilic attack results at third position since Presence of high electron thickness at third position. It has been like wise upheld by the estimation of electron thickness and by sub-atomic orbital strategy.

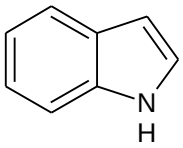
1.2 Resonance in indole molecule:-



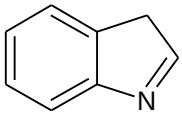
It undergoes all types of reactions for example: Protonation, nitration, sulfonation, acylation, halogenations, and formation of various metal complexes etc. it gives electrophilic as well as nucleophilic reactions. Indoles are probably the most widely distributed heterocyclic compound in nature. Tryptophan and essential amino acid assuchis constituent of most proteins.

Indole is a basic functional unit in plants as well as animals. It can be produced by bacteria as a degradation product of the amino acid tryptophan. It is found in jasmine and in certain citrus plant. Indole is a well known part of aromas and the antecedent to numerous pharmaceuticals At low fixations, in any case, it has a fancy smell, and is a constituent of many bloom fragrances, (for example, orange blooms) and perfumes. Indole and homologous of indole have been found in coal tar and in molasses tar. It is also found in liver, pancreas, brain and bile. Indole accompanied by its β-methyl homologue, skatole, is found in the feces of human, animal and in the content of intestine. Exacerbates that contain an indole ring are called indoles.

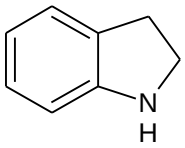
As isomer of indole in which the nitrogen atom takes part in the double bond is termed 3-pseudoindole or indolenin (1.2) and 2, 3 saturated compounds are known as indoline (1.3). There are some other oxygenated derivatives of indole are: oxindole (1.4), indoxyl (1.5), dioxindole (1.6) and indole 2, 3-dione or isatin (1.7).



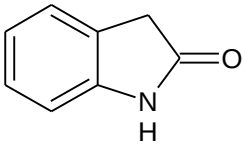
Indole (1.1)



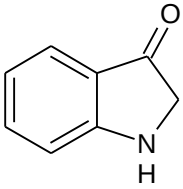
indolenin (1.2)



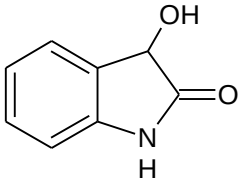
Indoline (1.3)



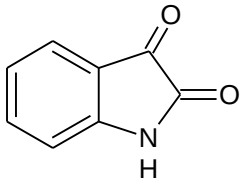
Oxindole (1.4)



Indoxyl (1.5)

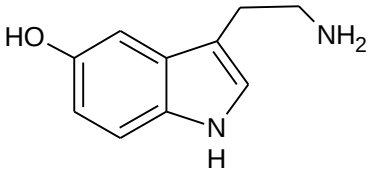


Dioxindole (1.6)

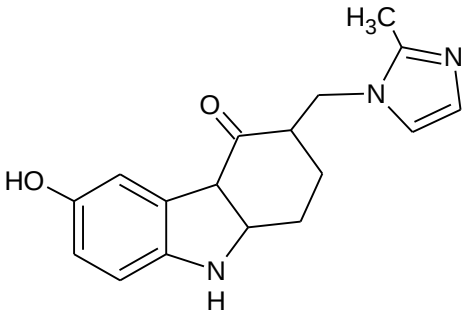


2,3-dione Indole (1.7)

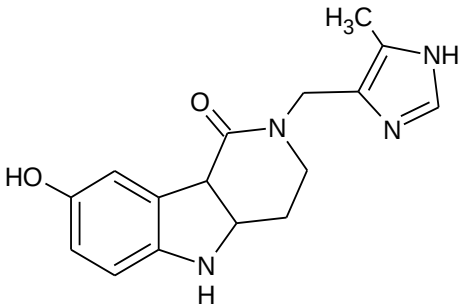
Indole derivatives derived from animals are serotonins (5-HT) and melatonin. Some widely used derivatives are ondansetron for the suppression of nausea and alosteron for treatment of irritable bowel syndrome.



Serotonin (1.8)



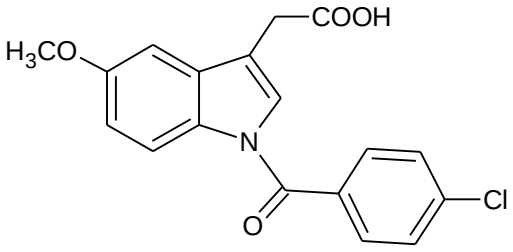
Ondensterone (1.9)



Alosetron (1.10)

From plant, tryptophan derived substances are also useful. Vincristine, an indole alkaloid is still extremely important in treatment of cancer. Brassinin, isolated from turnips is a phytoalexin. It prevents plants from microbial attack.

Indole moiety shows various biological activities like antimicrobial, CNS depressant, anti-HIV, anti-inflammatory, analgesic and many other activities e.g. indomethacin (1.11) is useful in treatment of rheumatoid arthritis, explains why indole and its derivatives are still a very interesting molecule since its synthesis in 1866



Indomethacin (1.11)

1.3 Inflammation:-

Inflammation (Latin. inflammatio; inflammare; to set on fire). Inflammation is the means by which the body deals with insult and injury. Insult may be caused: mechanically (e.g., by pressure or foreign bodies), chemically (e.g., by toxins, acidity, and alkalinity), physically (e.g., by temperature), by internal processes (e.g., uremia), and by microorganisms (e.g., bacteria, virus,). Inflammation is also defined classically as a protective reaction by the body, in response to some physical or chemical injury. It is characterized by following characteristic.

Pain, Heat, Redness, Swelling.

There are three significant elements of aggravation. To start with, aggravation is the initial phase in the mending or fix process after some physical or synthetic injury or stress. Second, inflammation prevents the spread of damaged cells to other areas of the body that could cause secondary problems and third, inflammation rids the body of damaged and dead cells. This very important task is more than just an act of housecleaning. There are two types of inflammation.

1.3.1 Types of Inflammation:-

A. Acute inflammation.

B. Chronic inflammation

A. Acute inflammation:

The intense incendiary reaction to a physical or compound pressure can last as long as three days, with the entire fix process taking as long as about a month and a half Components are vascular and cellular events. Which are mediated by chemical factors (mediators).

B. Chronic Inflammation

Chronic inflammation is an abnormal condition that can associated with ill health and disease ceaseless irritation is a fiery reaction of delayed length - weeks, months, or even inconclusively - Whose all-inclusive time course is incited by industriousness of the causative upgrade to irritation in the tissue. The incendiary procedure unavoidably causes tissue harm and is joined by synchronous endeavors at recuperating and fix. The exact nature, extent and time course of chronic inflammation is variable, and depends on a balance between the causative agent and the attempts of the body to remove it.

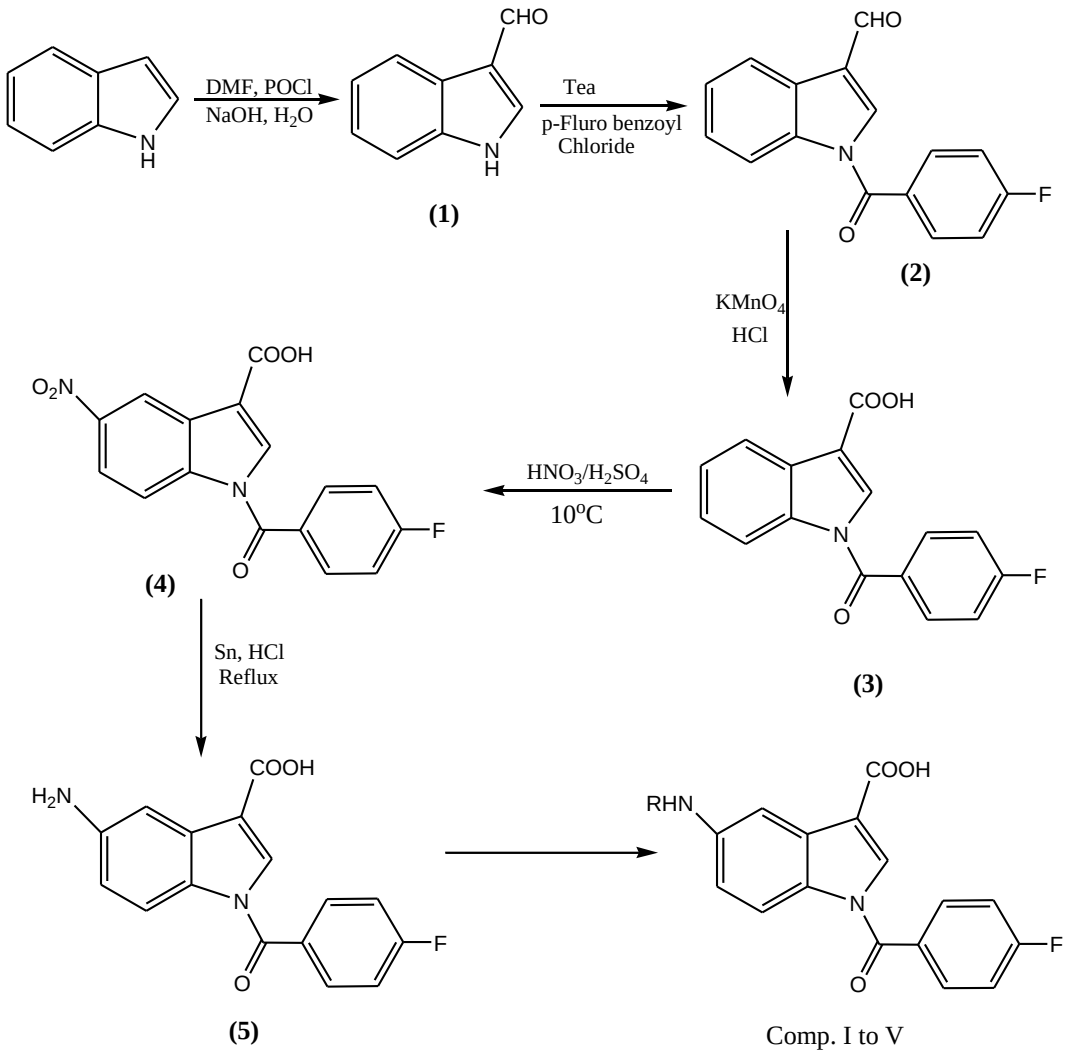
2. MATERIAL AND METHODS

Chemical and reagents

All chemicals were procured from, Rankem, E-Merck, Qualigens, Hi-Media, and S.D. Fine chemicals. All solvents were redistilled and dried before use. Reactions were routinely monitored by thin layer chromatography and spots were visualized by exposure to iodine vapour or UV light. All the synthesized compounds were purified by column chromatography followed by recrystallization. Melting points were determined by using open capillary method and are uncorrected.

Experimental:

The reaction scheme employed for the synthesis of lead compound. Intermediate 1H-indole-3-Carbaldehyde was synthesized by the formylation of 1-H indole with DMF and Phosphorous oxychloride. Then 1-[(4-flurophenyl) carbonyl]-1H-indole-3-carbaldehyde was obtained by benzoylation of 1H-indole-3-Carbaldehyde with p-flurobenzoyl chloride which is obtained by the reflux of p-flurobenzoic acid and thionyl chloride for 2hrs. 1[-(4-flurophenyl)carbonyl]-1H-indole-3-carboxilic acid obtained by the oxidation of 1-[(4-flurophenyl) carbonyl]-1H-indole-3-carbaldehyde with the help of $KMnO_4$ and Hydrochloric acid. Key Intermediate 1-[(4-flurophenyl) carbonyl]-5-nitro-1*H*-indole-3-carboxylic acid is found by the nitration of 1[-(4-flurophenyl)carbonyl]-1H-indole-3-carboxilic acid then reduction of key intermediate gives 5-amino-1-(4-flurophenyl) carbonyl]-1*H*-indole-3-carboxylic acid



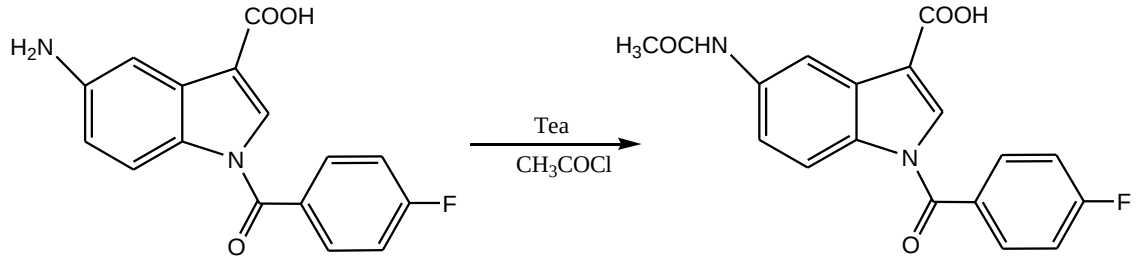
(1) **(2)** **(3)** **(4)** **(5)**

Comp. I to V

Where: R=CH_3CO, C_6H_5CO, $C_2H_5C_6H_4CO$, $NO_2C_6H_4CO$, BrC_6H_4CO

Synthesis of compound I to V

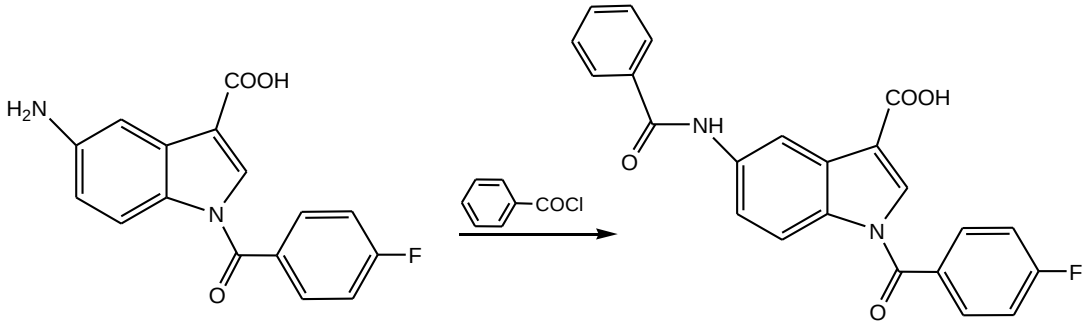
Synthesis of 5-(acetylamino)1-[(4-flurophenyl)carbonyl]-1H-indole-3-carboxylic acid



5-amino-1-(4-fluorobenzoyl)-1*H*-indole-3-carboxylic acid

5-(acetylamino)-1-[(4-fluorophenyl)carbonyl]-1*H*-indole-3-carboxylic acid

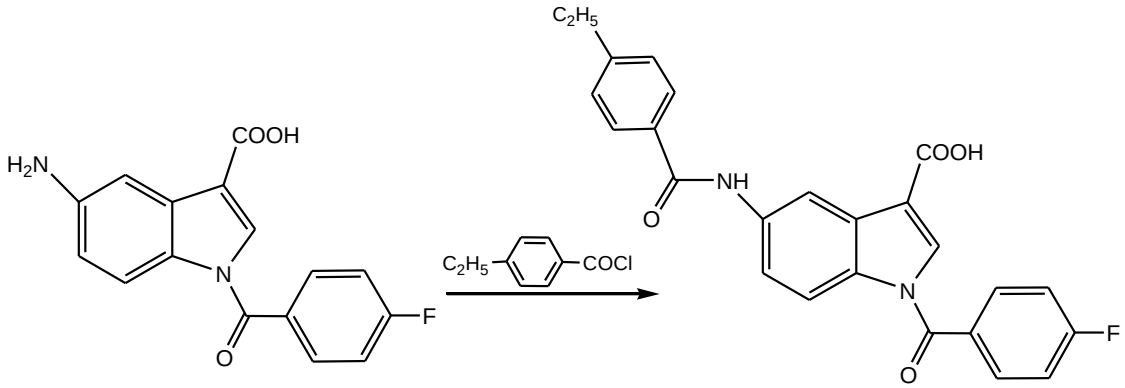
Synthesis of 1-[(4-fluorophenyl) carbonyl]-5-[(phenylcarbonyl)amino]-1*H*-indole-3-carboxylic acid



5-amino-1-(4-fluorobenzoyl)-1*H*-indole-3-carboxylic acid

1-[(4-fluorophenyl) carbonyl]-5-[(phenylcarbonyl)amino]-1H-indole-3-carboxylic acid

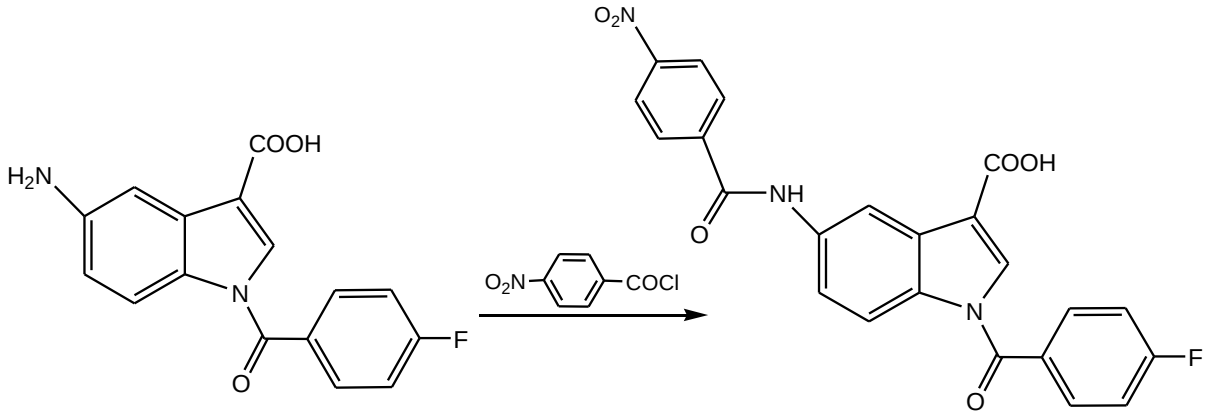
Synthesis of 1-(4-flurobenzoyl)-5-(4-ethylbenzamido)-1H-indole-3-carboxylic acid



5-amino-1-(4-fluorobenzoyl)-1*H*-indole-3-carboxylic acid

1-(4-flurobenzoyl)-5-(4-ethylbenzamido)-1H-indole-3-carboxylic acid

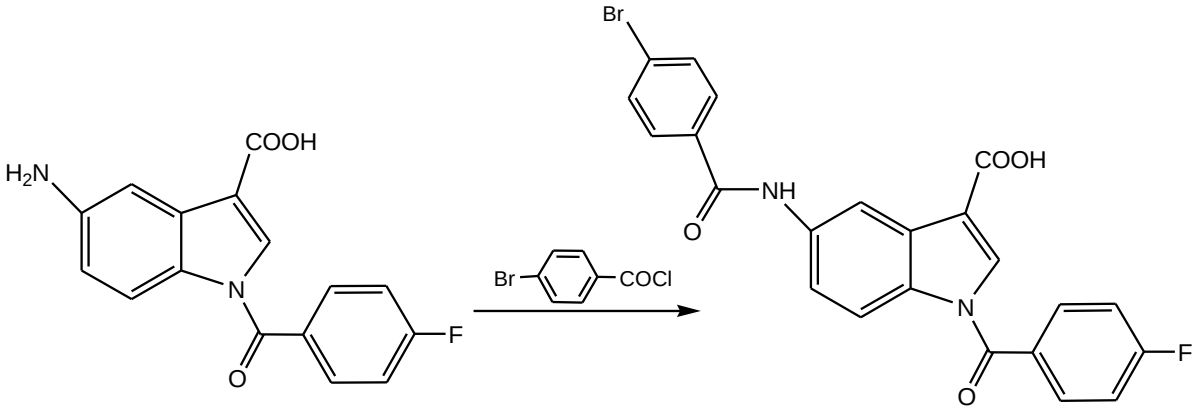
Synthesis of 5-(4-nitrobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid:



5-amino-1-(4-fluorobenzoyl)-1*H*-indole-3-carboxylic acid

5-(4-nitrobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid:

Synthesis of 5-(4-bromobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid:



5-amino-1-(4-fluorobenzoyl)-1*H*-indole-3-carboxylic acid

5-(4-bromobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid:

3. PHYSICAL AND SPECTRAL CHARACTERISTICS

3.1 Physical Characteristics

All the synthesized compounds were off white, light green to brown colored crystalline solids. All the compounds are freely soluble in chloroform and other solvents like methanol, ethanol. The melting point of the compounds was in the range of 70ºC to 300ºC.

Compound	Molecular formula	Molecular weight	% yield	Melting point (°C)	Rf value
I	$C_{18}H_{14}FN_2O_4$	331	65-70	172-176	0.54
II	$C_{23}H_{15}FN_2O_4$	392	55-60	248-251	0.61
III	$C_{25}H_{19}FN_2O_4$	420	46-48	271-273	0.58
IV	$C_{23}H_{14}FN_3O_6$	437	52-57	195-198	0.49
V	$C_{23}H_{14}FBrN_2O_4$	470	42-43	223-225	0.51

3.2 Spectral Characteristics:

Comp. I white micro crystals IR (cm^{-1}) C=O -1699, NH -3385, C-F -775, COOH(OH)- 3500, Ar-CH-2666-2955, ^{1}H-NMR Ppm Ar-CH (4H, m7.867-8.020), Ar-CH (4H, m6.607-6.647), NH(1H,s 5.017), CH_3CO(3H,s 2.787), COOH(1H,s11.008), Ar-F(s 3.086) Mass (m/e) 331 [M^+]

Comp. II Brown crystals IR (cm^{-1}) C=O -1680, NH-3379, COOH (-OH)3536, Ar-CH- 2853-3956, C-F -747, ^{1}H-NMR Ppm Ar-CH (4H, m7.064-7.170), Ar-CH Indole (4H, m7.180-7.182), Benz-CH (5H, m 7.6420-7.8386), NH(1H,s 5.881), COOH(1H, s11.441), Ar-F(s 4.7488), Ar-CO amide (0H,s 6.001), Mass (m/e) 393 [M+1], 394 [M+2]

Comp.III Light Green crystals IR (cm^{-1}) C=O -1662,1705, NH-3385, COOH (-OH)2590, Ar-CH- 2854-2951, C-F -765, CH_3- 1323-1340, ^{1}H-NMR Ppm Ar-CH (4H, m 7.036-7.183), Ar-CH (4H, m7.231-7.408), Benz-CH (5H, m7.417-8.434), NH(1H,s 5.0360 , 2.7603-2.7681), COOH(1H, s11.3686), CH_3(3H, t 2.7603-2.7681), CH_2 (2H,q 3.0176-3.2060) Mass (m/e) 420 [M^+]

Comp. IV Brown crystals IR (cm^{-1}) C=O -1651, 1705, NH-3292, COOH (-OH)3486, Ar-CH- 2854,2924, C-NO_2 -1529, C-F-742, ^{1}H-NMR Ppm Ar-CH (4H, m 7.030-7.176), Ar-CH (4H, m7.242-7.383), Benz-CH (4H, m7.776-8.291), NH(1H,s 5.0360), NO_2(1H,s 5.0218), COOH(1H, s 10.970), Ar-CONH (1H,s 4.898) Mass (m/e) 437 [M^+]

Comp. V Light Brown crystals IR (cm^{-1}) C=O -1618, 1678, NH-3159, COOH (-OH)3467, Ar-CH- 2949, 2974, C-Br -532, C-F- 752, ^{1}H-NMR Ar-CH (4H, m 7.036-7.183), Ar-CH (4H, m7.231-7.408), Benz-CH (5H, m 7.6420-7.8386), NH(1H,s 5.0360), Ar-Br (s 5.3488), COOH(1H, s 10.970), Ar-CONH (1H,s 4.898) Mass (m/e) 470 [M^+], 471 [M+1], 472 [M+2]

4. BIOLOGICAL EVALUTION:

Biological evaluation holds a great significance in screening the new chemical entities. The newly synthesized compounds were screened for anti-inflammatory.

4.1 Anti-Inflammatory Activity

Animals

For the biological evaluation Albino wistar rats, (200-300 g), were used. The animals were kept in colony cages (6 rats each), maintained on a standard pellet diet with water, and left for 2 days for acclimatization before the experimental session. They kept on fast for 16 hour before the experiment, but free access to water. Experiments were carried out according to the ethical guidelines for the care of laboratory animals.

Selection of experimental animals: - Healthy Albino wistar male rats weighing between 200-300 g. were used for the evaluation of anti-inflammatory activity. The animals were obtained from Zydus research centre, Ahmadabad.

Laboratory conditions: - The rats were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its top. Environmental room should be 22°C (± 3°C) relative humidity was at least 30 % and preferably not exceed 70 % other than during room cleaning the aim was to maintain between 50-60%. Lighting was to be artificial, the sequence being 12 hours light and 12 hours.

Food and water: - All creatures had free access to water and standard palletized research center creature diet.

Bedding: - In the present study, animals were provided with clean paddy husk bedding. Bedding was changed every alternate day to maintain proper hygienic conditions.

Acute toxicity studies

The acute toxicity of indole derivatives was determined by using Albino wistar rats (200-300 g) before taking the anti-inflammatory activity. The creatures were fasted for 24 hours before the examination and all over methodology (OECD Guideline no.425) technique for CPCSEA was embraced for intense

poisonousness considers. Newly synthesized compounds suspended in tween-80 was administered to the group of rats (n=3) up to dose level of 10 mg/kg. Animals were placed in individual plastic cage and observed at least once daily for the first 30 minutes and periodically for 24 hours to observe for sign of toxicity.

The anti-inflammatory activity of synthesized indole derivatives were carried out using carrageenan induced rat hind paw edema method.

Method: - carrageenan induced paw edema.
Animals used-Albino wistar rats
No. of animals used per group:-6 rats
Dose of test compound:-3 mg/kg
Dose of standard drug:-3 mg/kg (Indomethacin)
Route of administration:-Intra peritoneal (suspended in 1% tween-80 solution)
Requirements:-
Instruments:-Mercury displacement plethysmometer.
Inflammation inducing agent:-carrageenan solution (1%w/v) in saline solution was prepared and injected (0.1ml) in sub planter region to induce paw edema.
Chemicals:-Tween-80
Standard drug:-Indomethacin (3 mg/kg) aqueous suspension was prepared using solution of tween-80 as a suspending agent.
Test compounds:-suspension of compounds were prepared and administered intra peritoneal similar to that of standard drug.
Apparatus: -Syringes (1 ml, 2 ml), sample tubes (to prepare suspension of test compounds).

Experimental design and procedure:-
Weigh the animals and number them. Imprint the creatures with picric corrosive for singular creature distinguishing proof. Divide rats into 5 groups of 6 rats each. Note the initial paw volume of each rat by dipping just beyond tibio-tarsal junction by mercury displacement method, so that every time the paw is dipped in the mercury section up to the fixed imprint to guarantee consistent paw volume. The animals were deprived of food overnight (allowed free access to water) and synthetic compounds were administered once before 30 minutes the injection of carrageenan. Dose volume not exceeding 0.5ml/100gm intra peritoneal was administered.
Group I:-The solvent control received normal saline.
Group II:-Positive control received Indomethacin (3 mg/kg).
Group III:-Received indole derivative-4.7 at a dose of 3 mg/kg suspended in 1%w/v tween-80
Group IV:-Received indole derivative-4.8 at a dose of 3 mg/kg suspended in 1%w/v. tween-80
Group V:-Received indole derivative-4.9 at a dose of 3 mg/kg suspended in 1%w/v tween-80.
Group VI:-Received indole derivative-4.10 at a dose of 3 mg/kg suspended in 1%w/v tween-80.
After 30 minutes of test compound administration, 0.1ml of 1%w/v of carrageenan in normal saline was injected in to the sub planter region of the left hind paw of rat. Immediately after the carrageenan injection, the volume of its displacement was measured using plethysmometer.
The reading was recorded at 0, ½, 1, 2, 3 hrs.

The % inhibition of edema was calculated at the end of 3 hrs by using the formula.[30]

Percent (%) restraint = 1 – Vt/Vc X 100,
Where Vt: - edema volume in test group,
Vc: -edema volume in control group
Results were expressed as mean ± standard deviation.

5. RESULT AND DISCUSSION:

Screening of Anti-inflammatory activity in Albino wistar rat:

Compound code	Inhibition of inflammation in cm					% inhibition			
	0 hr	1 hr	2 hr	3 hr	4 hr	1 hr	2 hr	3 hr	4 hr
Control	0.36±0.02	0.33±0.02	0.31±0.02	0.30±0.02	0.29±0.02				
Standard (Indomethacin)	0.33±0.02	0.30±0.02	0.26±0.02	0.23±0.02	0.20±0.18	09.09	16.13	23.33	31.03
Comp-I	0.33±0.02	0.28±0.02	0.26±0.02	0.22±0.02	0.18±0.02	15.15	16.12	26.66	37.93
Comp-II	0.31±0.02	0.27±0.02	0.17±0.02	0.14±0.09	0.11±0.009	18.18	16.12	53.33	62.06
Comp-III	0.34±0.07	0.30±0.02	0.21±0.008	0.17±0.08	0.21±0.01	09.09	32.19	43.33	27.58
Comp-IV	0.32±0.02	0.31±0.1	0.21±0.02	0.14±0.02	0.10±0.01	12.12	19.09	53.33	65.51
Comp-V	0.32±0.02	0.32±0.02	0.25±0.01	0.15±0.007	0.13±0.02	13.13	20.13	27.77	37.58

No. of animals used in each Group (n) = 6, Values are expressed as Mean ± SEM
Dose of test compound = 3 mg/kg, Dose of Indomethacin = 3 mg/kg

Result:-

- The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 12.12 to 65.51 % inhibition of rat paw edema volume after 3 hours, whereas the standard drug Indomethacin showed 31.03 % inhibition of rat paw edema volume after 3 hours.

- The compound -I was found to be nearly more potent then indomethacin which is used as standard drug. A compound -III has shown less activity then indomethacine. Compounds IV and V shown more potent activity than compound –I, II and Indomethacin.

6. CONCLUSION

The present work, which has undertaken is bonafied, and novel for the synthesis of N-Benzoyl-5-substituted-indole, 3-carboxylic acid derivatives.

- In this view we have made an attempt in reviewing the literature on substituted indole for their medicinal significance with help of chemical abstract, journals and internet sites.
- All synthesize compounds were tested for the preliminary tests, physical constants and TLC.
- All structures of final compound were confirmed by IR and 1HNMR spectra as well as Mass spectra.
- The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 12.12 to 65.51 % inhibition of rat paw edema volume after 3 hours, whereas the standard drug Indomethacin showed 31.03 % inhibition of rat paw edema volume after 3 hours.
- The compound -I was found to be nearly more potent then indomethacin which is used as standard drug. A compound -III has shown less activity then indomethacine. Compounds IV and V shown more potent activity than compound –I, II and Indomethacin
- In conclusion, we have found some of the compounds prepared in course of this investigation are effective than the standard drug and some of them are found to be as active as the standard drug.
- The compounds which have been found to be more active than standard in anti inflammatory activity may be further investigated for the toxicity. .

REFERENCES

1. Bansal RK, Indoles, Heterocyclic Chemistry, 4th edition, New Age international Publishers; 2005; Pg no. 299-329.
2. Cigdem Karaaslan and Sibel Suzen; International Journal of Electrochemistry Volume 2011 , Article ID 154804, 10 pages
3. en.wikipedia.org/wiki/Inflammation
4. H.P. Rang; M.M. Dale; J.M. Ritter; R.J. Flower; “Pharmacology” Elsevier, 2007, 6th edition; Pg.- 232.
5. Burger's Medicinal Chemistry and Drug Discovery, 6th Edition-2003, Volume 3, page no.748.

6. Palwinder Singh, Anu Mittal, Current status of COX-2 inhibitors, Mini-Reviews in Med. Chem., 2008, 8, 73-90.

7. Srivastava, Anupam "indole" a versatile nucleus in pharmaceutical field, international journal of pharmaceutical review and research.Vol-1, issue-3, Nov.2010-Jan.2011.

8. Jaishree Badiger, Manjulatha K. Synthesis and biological evaluation of some *N*-substituted indoles General Paper ARKIVOC 2009 (xii) 217-231.

9. Amit S. Kalgutkar, Brenda C. Crews, Bioorganic & Medicinal Chemistry 13 (2005) 6810–6822.

10. Dharmendra Kumar, Narendra Kumar, International Journal of Engineering Science and Technology Vol. 2(7), 2010, 2553-2557.

11. Aldo Andreani , Massimiliano Granaiola European Journal of Medicinal Chemistry 39 (2004) 785–791.

12. Balasubramanian Narasimhan1, Ruma Saharan *Acta Pharmaceutica Sciencia 53: 117 – 126 (2011).*

13. Il Hwan Cho, United States patent, 1H-indole derivatives for cox-2 inhibition, patent no.US 6, 599, 929, B2 .date of patent: Jul.29, 2003.

14. Rodney W.Stevens**,** United States patent, indole derivatives as anti inflammatory and analgesic activity, patent no.US 5,290,788 date of patent: Mar. 1, 1994.

15. Douglas G. Batt, United states patent, substituted indole for lipoxygenase inhibition,anti inflammatory .Patent number: 5,093,351, date of patent: Mar. 3,1992.

16. Amit S. Kalgutkar, Brenda C. Crews, PNAS u January 18, 2000 vol. 97, no. 2, page no.925–930.

17. nagwa m. abdel gawad, International Journal of Pharmacy and Pharmaceutical Sciences, ISSN- 0975-1491 Vol 3 Suppl 3, 2011.

18. Palwinder Singh, Matinder Kaur, Bioorganic & Medicinal Chemistry Letters 19 (2009) 3054–3058. 20 formylation of indole, Org. Syn. Coll. Vol. 5, 656.

19. Sadik Al Mekhlafi, Hussein Alkadi, Synthesis and anti-inflammatory activity of novel Ketoprofen and Ibuprofen derivatives ,Journal of Chemical and Pharmaceutical Research, 2015, 7(2):503-510

20. Giuseppina sanna,silvia madeddu, Synthesis and Biological Evaluation of Novel Indole-Derived Thioureas,journal list, Molecules. 2018 Oct; 23(10): 2554.

21. Mashooq Ahmad Bhat, Mohamed A. Al-Omar *et al*, a review article of Indole Derivatives as Cyclooxygenase Inhibitors Synthesis, Biological Evaluation and Docking Studie,, Published: 24 May 2018.