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SYTHESIS AND CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF NOVEL SUBSTITUTED INDOLE DERIVATIVES

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Abstract:

Today inflammation is becoming one of the major roots of all the disease leading to various pharmacological complications. Majorly anti-inflammatory drugs given to patients are NSAIDs. But they also have major side effects that initiated the work for developing safer drugs. Research is a continuous and a never ending process. Efforts are being made to synthesize and formulate newer drugs having ideal pharmacological parameters with least side effects. The present assessment is just a minor effort to synthesize a better drug in the class of anti-inflammatory agents. As a part of my dissertation work, synthesis of indole derivatives for anti-inflammatory activity is an interesting task because in present NSAIDs there does exists any drug that has inculcated indole scaffold . Since the ongoing research work favors the indole moiety for the anti-inflammatory activity, it guided me on the same path to research on the novelty of indole. Further after synthesizing the designed drug the purity of the all the intermediates and final compounds will be TLC monitored whereas structure conformation will be analyzed by IR, Mass spectroscopy and NMR. Synthesized drugs were pharmacologically screened by the carrageenan induced rat paw edema method. Some results also supported the research by inhibiting the inflammation.

Keywords: - Indole, Anti-inflammatory activity, Indole derivatives, NSAIDs.

INTRODUCTION

Inflammation is a protective immune-vascular response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair [1-2].

The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen [3]

Inflammation is tightly regulated by the body. Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (e.g. bacteria) and compromise the

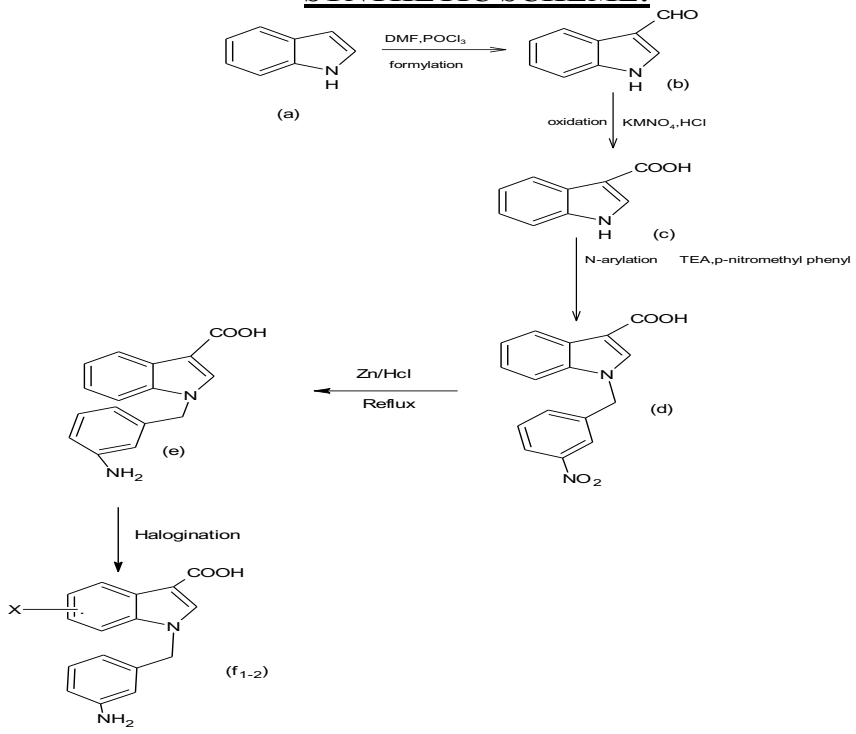
survival of the organism. In contrast, chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g. gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body [4]

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 [5], 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 [6-9].

MATERIALS AND METHODS:

All chemicals were provided from our college. 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. All the synthesized compounds were purified by recrystallization. Melting points were determined by using open capillary method.

SYNTHETIC SCHEME:



SYNTHETIC PROCEDURE:

Synthesis of 1H-indole-3-carboxylic acid:

The appropriate 1H-indole-3-carboxaldehyde (5 mmol) was dissolved in 100 ml of acetone and treated with a solution of $KMNO_4$ (15 mmol) in water (40 ml). The reaction mixture was stirred at room temperature for 5–16 h (according to a TLC test), discolored with 10% H_2O_2 and filtered [10]. Acetone was evaporated under reduced pressure and the resulting solution, filtered again, was acidified with 2 N HCl.

The precipitate was collected by filtration [11] and recrystallized from ethanol.

Synthesis of 2-methyl-1(3-nitrobenzyl)-1H-indole-3-carboxylic acid:

In a round bottom flask, fitted with dropping funnel and calcium guard tube. Took compound and dissolved in chloroform. Then added 1.5 equivalents of triethylamine (TEA). Stirred continuously for 0.5 hr. in cold condition [12]. Then added 1.5 equivalents of p- nitrobenzoyl chloride with continuous stirring during the period of 2 hrs. in cold condition. Then recovered the chloroform by distillation & recrystallized from ethanol [13-15].

Synthesis of 2-methyl-5-nitro-1(3-nitrobenzyl)-1H-indole-3-carboxylic acid.

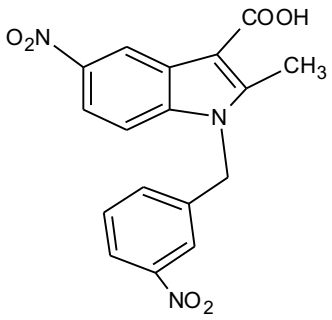
Placed 17.5 ml (25gm, 0.5mol) of concentrated nitric acid in 250ml round bottom flask, and added in portions with shaking 20ml (37gm) of concentrated sulphuric acid. Keeped the mixture cool during the addition by immersing the flask in cold water [16-18]. Stirred for 10min, then added compound in reaction mixture in small portions with continuous stirring in ice bath. Stirred for 1 hr and then added crushed ice in that solution. Filtered off the precipitates and recrystallized from ethanol.

Experimental design and procedure:-

Firstly we weighed the animals and numbered them. Then marked the animals with picric acid for individual animal identification. Divided rats into 5 groups of 6 rats each. Noted the initial paw volume of each rat by dipping just beyond tibio-tarsal junction by mercury displacement method, so that every time the paw was dipped in the mercury column up to the fixed mark to ensure constant paw volume [19-22]. 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 [23-26].

RESULT AND DISCUSSION:

Physical and spectral characteristics of compound (d-i)



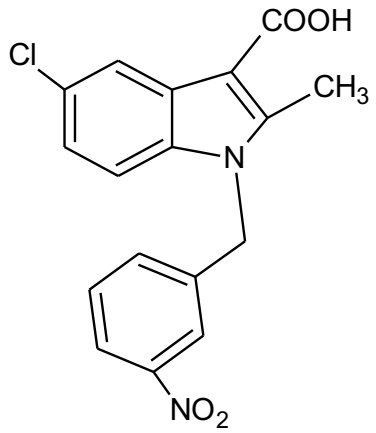
2-methyl-5-nitro-1-(3-nitrobenzyl)-1*H*-indole-3-carboxylic acid

Table no. 1: Physical Characteristics of compound-d-i

Molecular formula	% yield	Melting point range in (°C)	Rf value
$C_{17}H_{13}N_3O_6$	77.34	275-276	0.88

Solvent system for TLC:- Ethyl acetoacetate: n-Hexane (60:40)

Physical and spectral characteristics of compound (d-ii)



5-chloro-2-methyl-1-(3-nitrobenzyl)-1*H*-indole-3-carboxylic acid

Table no. 2: Physical Characteristics of compound-d-ii

Molecular formula	% yield	Melting point range in (°C)	Rf value
$C_{17}H_{13}ClN_2O_4$	74.36	289-290	0..92

Solvent system for TLC:- Ethyl acetoacetate: n-Hexane (60:40)

SCREENING OF ANTI-INFLAMMATORY ACTIVITY

Table 3:-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 (Indome thacin)	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 d-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 d-II	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

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

The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 27.58 to 37.93 % 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 –d ii was found to be nearly more potent then indomethacin which was used as standard drug. Compounds d-i shown more potent activity than compound –d-ii and indomethacin.

CONCLUSION:

The present work, which has undertaken is bonafied, and novel for the synthesis of 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 ^{1}HNMR spectra as well as Mass spectra. The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 27.58 to 37.93 % 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-(d-ii) was found to be nearly more potent then indomethacin which is used as standard drug. Compound-(d-i) shown more potent activity than compound-(d-ii) and Indomethacin. In conclusion, we have found some of the compounds prepared in course of this investigation were effective than the standard drug and some of them were 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.

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