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Synthesis and Pharmacological Screening of Novel 5-Nitro Benzimidazole Derivatives as an Anti-Inflammatory Agents

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ABSTRACT
Anti-inflammatory illnesses are ailments or disorders that cause persistent inflammation in different body regions, the immune system's natural response to damage, infection, or foreign substances is inflammation. As a result, finding efficient and secure anti-inflammatory drugs is necessary since the treatment of inflammation is still a top focus in contemporary pharmacotherapy. In this present study, a new series of 5-Nitro Benzimidazole containing benzaldehyde moiety have been designed and synthesized and studied in vivo for their anti-inflammatory potential. 5-Nitro Benzimidazole is a bicyclic aromatic ring which is a flexible lead molecule for designing potent biologically active agents The in-silico research revealed several binding interactions of synthetic drugs in order to locate the binding receptors. The structure of the synthesized derivatives was elucidated by spectral analytical methods such as ^{1}H NMR, ^{13}C NMR, FT-IR, HRMS. In vivo anti-inflammatory activity has been carried out using the carrageenan induced paw oedema model. In vivo and in silico studies proved that all the synthesized derivatives show the promising anti-inflammatory activity, when compared with Indomethacin which is referred as standard.
***Keywords**: 5-nitro benzimidazole, Cyclooxygenase-2, Anti-inflammatory.*

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INTRODUCTION

The 3 out of 5 people die from chronic inflammatory conditions like diabetes, chronic respiratory ailments, heart problems, stroke, being overweight, and cancer globally. According to World Health Organization (WHO), around 1% of the worldwide population suffers from Rheumatoid arthritis, a type of chronic inflammatory disorder. The Global Asthma Report 2019 estimates that 339 million people globally suffer from asthma [1]. The human body's inflammatory reaction has an enormous effect on the treatment and rehabilitation of injuries, which can be referred to as inflammatory responses. Inflammatory illnesses come in both acute and chronic forms. Acute inflammation is the rapid reaction to tissue injury, and it is facilitated by the creation of several autacoid, such as histamine, serotonin, leukotrienes, and thromboxane. An acute case of inflammation often shows symptoms including discomfort, redness, swelling, heat, and immobility [2]. A particular component of the chronic inflammation process is the production of numerous mediators, particularly the development of tumours, interferon, interleukins, and cytokines. This sort of inflammatory response requires these mediators to function [3]. Inflammation that is ongoing can lead to the development of a number of disorders, including prolonged peptic ulceration, fatty liver, chronic obstructive pulmonary disease, diabetes, lung cancer, rheumatoid arthritis, allergic reactions, and cirrhosis of the liver [4]. Non-steroidal anti-inflammatory drugs (NSAIDs) taken for a prolonged amount of time can outcome in bleeds, gastrointestinal inflammation, and damage to the renal system [5]. The basic components for various bioactive compounds that have gained importance in medicinal chemistry are 5-nitro benzimidazole derivatives because of their significance as medicines in clinical applications. This makes them active substances because of their interactions with biomolecules and biomacromolecules [6]. Most of the pharmaceutical compounds are based upon a heterocyclic ring system. Heterocyclic compounds have a wide range of pharmacological actions. 5-nitro benzimidazole is a benzimidazole derivative with an NO_2 group attached at 5^{th} position of benzene ring. 5-nitro benzimidazole derivatives have a wide range of biological activities and therapeutic properties because of the adaptable core they contain. As a result, there are several synthetic techniques described in the literature, and interest in the synthesis benzimidazole

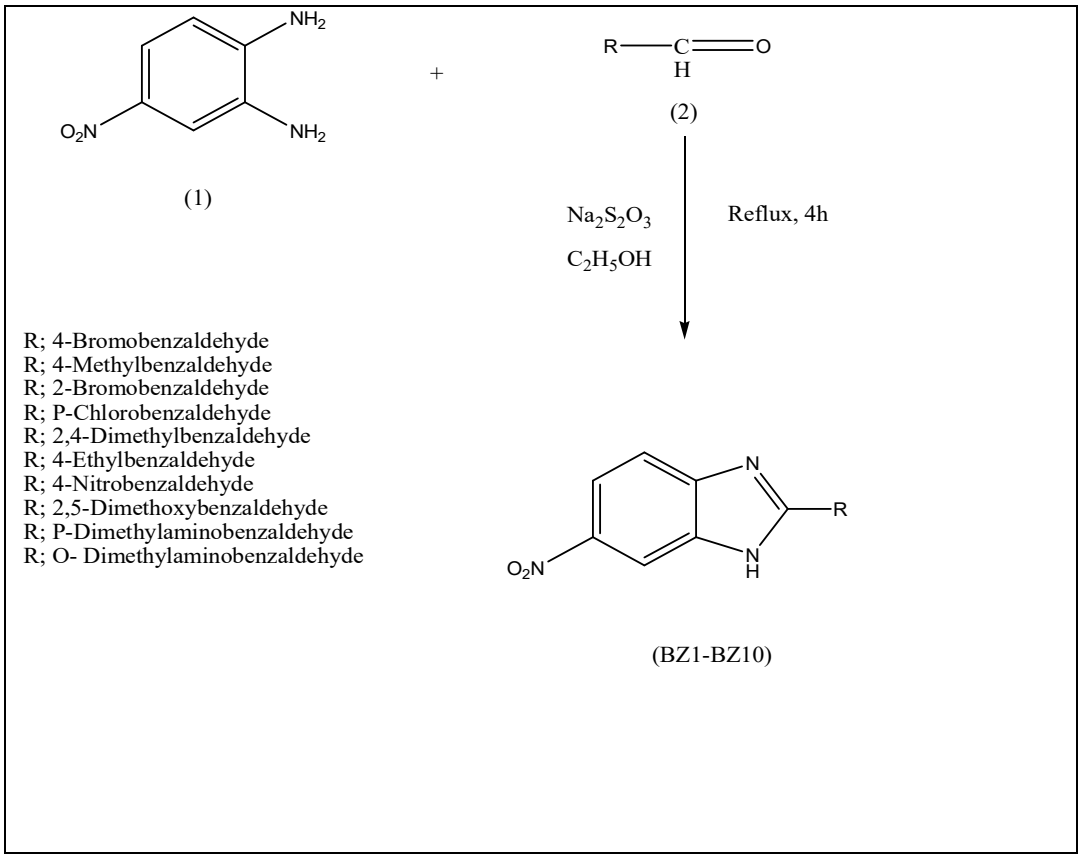
derivatives is constantly expanding [7]. Following that, preparation techniques and uses for this family of chemicals have undergone extensive research [8]. Several bioactive molecules have the nitrogen-containing heterocycle 5-nitro benzimidazole scaffold, which is vital for chemical and pharmaceutical chemistry [9]. Due to its many pharmacological uses, the 5-nitro benzimidazole became important class in the field of medicinal chemistry due to their various pharmacological and biological activities such as antiviral [9], anticancer [10], antitubercular [11], antidiabetic [12], antibacterial [13] anti-microbial [14], anti-muscarinic [15], anti-thyroid [16], anti-oxidant [17], anti-convulsant [18], antihypertensive [19], calcium channel blockers [20], proton-pump inhibitor [21], antiparasitic [22], anti-malarial [23], anti-inflammatory [24], anti-HIV [25], anti-analgesic [26], as well as inhibits enzymes like urease [26], acetylcholinesterase [27] and acts as an agonist on the GABA receptor [28].

MATERIAL AND METHODS

Chemistry

Analab Chemicals Pvt Ltd. and Sigma-Aldrich provided all the chemicals utilized in the experiment. Melting point equipment was used to determine the melting point using the open capillary tube method by utilizing a mobile phase, such as chloroform: methanol: (7:3 v/v) and iodine vapours, and a silica gel-coated plate, TLC was used to visualize the completion of reactions and the purity of the compounds. FT-IR spectra were recorded on Shimadzu, IR Affinity-1, Japan infrared spectrophotometer, ^{1}H NMR, and ^{13}C NMR spectra on a Bruker AVANCE III HD NMR Spectrometer DMSO-d6 the chemical shifts were recorded in parts per million (ppm) and was referenced with TMS. HRMS was performed on Impact II UHR-TOF Mass Spectrometer.

Synthesis



Scheme 1: Synthesis of novel 5-nitro Benzimidazole derivatives

To a solution of 1equivalent of 4-nitro o-phenylenediamine and 1 equivalent of corresponding aldehyde in ethanol, 4 equivalent of Sodium Metabisulfite was added and the resulting mixture was refluxed for 4 hours. Diethyl ether was added once the reaction mixture had reached room temperature, and the unfiltered crude product was then filtered out. Up until the powder was achieved, the crude product was repeatedly suspended in an ethanol-diethyl ether combination. TLC was performed to check the completion of reaction.

RESULTS AND DISCUSSION

Chemistry

All the derivatives were properly separated from the reaction mixture and given satisfactory reaction yields, that signifying the efficiency of the employed synthetic route. The characterization of synthesized derivatives was carried out by using TLC, melting point, FTIR, ^{1}H NMR, ^{13}C NMR and HRMS for structure elucidation. The details are given below;

Synthesis of 2-(2-bromophenyl)-5-nitro-1H-benzo[d]imidazole (BZ-1)

Yield: 64%; MP: 228-232°C; Rf: 0.69; IR (KBr; ν cm^{-1}) 3752 (N-H), 3215 (C-H), 1329 (C-N), 1556 (C=N), 1161(C=S), 1412 (NO2), 1589(C=C) ^{1}H NMR: δ 7.12 (1H, td, J = 7.7, 1.4 Hz), 7.21-7.36 (3H, 7.28 (ddd, J = 8.1, 7.6, 1.6 Hz), 7.29 (ddd, J = 8.9, 1.3, 0.4 Hz)), 7.75 (1H, ddd, J = 7.7, 1.6, 0.5 Hz), 7.86-7.99 (3H, 7.92 (ddd, J = 8.9, 1.7, 0.4 Hz), 7.92 (ddd, J = 8.1, 1.4, 0.5 Hz)). ^{13}C NMR: δ 114.3 (1C), 118.4 (2C), 121.6 (3C), 126.3 (4C), 128.1-128.3 (5C) 128.2 (6C), 128.2 (7C), 128.2 (8C), 128.4 (10C), 132.4-132.7 (11C), 132.5 (12C), 137.9 (14C), 138.4 (13C), HRMS(m/z) [M+Z]; 319.13

Synthesis of 2-(4-ethylphenyl)-5-nitro-1H-benzo[d]imidazole (BZ-2)

Yield: 71%; MP: 207-213°C; Rf: 0.61; IR (KBr; ν cm^{-1}) 3560 (N-H), 3020 (C-H), 1235 (C-N), 1535(C=N), 3453(C-OH),1388 (NO2), 1586(C=C), ^{1}H NMR: δ 2.25 (3H, s), 7.03-7.17 (2H, 7.10 (ddd, J = 8.1, 7.9, 1.6 Hz), 7.10 (ddd, J = 7.9, 7.8, 1.6 Hz)), 7.35 (2H, ddd, J = 8.2, 1.2, 0.5 Hz), 7.62-7.93 (4H, 7.68 (ddd, J = 8.2, 1.8, 0.5 Hz), 7.75 (ddd, J = 8.1, 1.6, 0.5 Hz), 7.87 (ddd, J = 7.8, 1.6, 0.5 Hz)). ^{13}C NMR: δ 21.3 (1C), 114.3 (2C), 118.4 (3C), 127.3 (4C), 128.1-128.3 (5C), 128.2 (6C), 128.2 (7C), 129.1 (8C), 129.5 (9C), 137.9 (10C), 138.4 (12C), 141.5 (13C), HRMS(m/z) [M+Z]; 239.33

Synthesis of 5-nitro-2-p-tolyl-1H-benzo[d]imidazole (BZ-3)

Yield: 63%; MP: 193-199°C; Rf: 0.66; IR (KBr; ν cm^{-1}), 3331 (N-H), 3155 (C-H), 1423 (C-N),1620 (C=N), 1495 (C=S), 1450 (NO2), 1642(C=C), ^{1}H NMR: δ 2.25 (3H, s), 7.03-7.17 (2H, 7.10 (ddd, J = 8.1, 7.9, 1.6 Hz), 7.10 (ddd, J = 7.9, 7.8, 1.6 Hz)), 7.35 (2H, ddd, J = 8.2, 1.2, 0.5 Hz), 7.62-7.93 (4H, 7.68 (ddd, J = 8.2, 1.8, 0.5 Hz), 7.75 (ddd, J = 8.1, 1.6, 0.5 Hz), 7.87 (ddd, J = 7.8, 1.6, 0.5 Hz)). ^{13}C NMR: δ 21.3 (10C), 114.3 (9C), 118.4 (8C), 127.3 (7C), 128.1-129.3 (6C), 128.2 (5C), 125.2 (4C), 129.1 (2C), 129.5 (11C), 137.9 (12C), 138.4 (13C), 141.5 (14C), 149.3 (15C), HRMS(m/z) [M+Z]; 254.26

Synthesis of 2-(4-bromophenyl)-5-nitro-1H-benzo[d]imidazole (BZ-4)

Yield: 75%; MP: 210-213°C; Rf: 0.58; IR (KBr; ν cm^{-1}) 3488 (N-H), 3303 (C-H), 1244 (C-N), 1756(C=N), 2827(C-C2H5),1454 (NO2), 1521(C=C), ^{1}H NMR: δ 7.04-7.21 (2H, 7.11 (ddd, J = 8.1, 7.6, 1.6 Hz), 7.14 (td, J = 7.6, 1.3 Hz)), 7.63-7.94 (6H, 7.69 (ddd, J = 8.6, 1.5, 0.4 Hz), 7.74 (ddd, J = 8.6, 1.5, 0.4 Hz), 7.82 (ddd, J = 7.7, 1.6, 0.5 Hz), 7.88 (ddd, J = 8.1, 1.3, 0.5 Hz)). ^{13}C NMR: δ 114.3 (1C), 118.4 (2C), 122.3 (3C), 128.0-128.3 (4C), 128.1 (5C), 128.2 (6C), 128.2 (7C), 129.5 (8C), 131.7 (9C), 137.9 (10C), 138.4 (11C), 149.3 (12C), HRMS(m/z) [M+Z]; 319.13

Synthesis of 2-(2,4-dimethylpheny)-5-nitro-1H-benzo[d]imidazole (BZ-5)

Yield: 58%; MP: 200-222°C; Rf: 0.51; IR (KBr; ν cm^{-1}), 3311 (N-H), 3055 (C-H), 1323 (C-N),1720 (C=N), 1085 (C=S), 1350 (NO2), 1592(C=C), ^{1}H NMR: δ 2.15 (3H, s), 2.28 (3H, s), 6.99-7.26 (4H, 7.06 (ddd, J = 8.3, 7.9, 1.6 Hz), 7.10 (ddd, J = 8.2, 7.9, 1.7 Hz), 7.13 (dd, J = 1.4, 0.5 Hz), 7.20 (dd, J = 8.2, 1.4 Hz)), 7.63-7.93 (3H, 7.70 (ddd, J = 8.2, 1.6, 0.6 Hz), 7.82 (ddd, J = 8.3, 1.7, 0.6 Hz), 7.87 (dd, J = 8.2, 0.5 Hz)). ^{13}C NMR: δ 20.0 (1C), 21.3 (2C), 114.3 (3C), 118.4 (4C), 120.4 (5C), 127.8 (7C), 128.1-128.3 (8C) 128.2 (11C), 128.9 (13C), 129.1 (14C), 134.8 (15C), 137.9 (16C), 138.4 (17C), 153.1 (18C), HRMS(m/z) [M+Z]; 268.28

Synthesis of 2-(4-Chlorophenyl)-5-nitro-1H-benzo[d]imidazole (BZ-6)

Yield: 68%; MP: 210-219°C; Rf: 0.68; IR (KBr; ν cm^{-1}) 3418 (N-H), 3093 (C-H), 1344 (C-N), 1656(C=N), 1119(C=S), 1299 (NO2), ^{1}H NMR: δ 7.08-7.22 (2H, 7.15 (ddd, J = 8.1, 7.6, 1.6 Hz), 7.14 (td, J = 7.6, 1.5 Hz)), 7.66-7.94 (6H, 7.72 (ddd, J = 8.7, 1.5, 0.4 Hz), 7.74 (ddd, J = 8.7, 1.5, 0.4 Hz), 7.86 (ddd, J = 7.7, 1.6, 0.5 Hz), 7.88 (ddd, J = 8.1, 1.5, 0.5 Hz)). ^{13}C NMR: δ 22.0 (1C), 21.3 (2C), 114.3 (3C), 118.4 (4C), 120.4 (5C), 127.8 (6C), 128.1-128.3 (12C), 128.2 (13C), 128.2 (14C), 128.9 (15C), 129.1 (7C,), 134.8-135.0 (8C), 134.8 (16C), 138.4 (17C), 153.1 (18C), HRMS(m/z) [M+Z]; 274.67

Anti-inflammatory Activity:

Acute Toxicity studies:

Acute oral toxicity studies were performed as per the OECD (Economic Cooperation and Development Organization) part 423 of the Guidelines. 12 Wistar rats weigh between 150 and 250 gm, grouped three in each and fasted overnight. The test BZ-1, BZ-2 and BZ-3 solutions of 50 and 200 mg/kg body weight of animal dose were prepared in 5% Dimethyl Sulfoxide (DMSO) and were administered orally to the animals, then the animals were observed for any changes in skin colour, changes in eyes, salivation, diarrhoea, tremors, convulsions, sleep, and coma at every 1 h/24 h and for every 24 h/14 day after treatment.

Anti-inflammatory Activity:

In this carrageenan-induced Paw oedema model 42 Wistar/Sprague-Dawley rats, either male or female, weighing between 150 and 250 g, are employed. With free an excess water, the animals are going to remain starving throughout a whole night. The rats will be divided into six groups (n=6), with groups 1 and 2 acting as a control and positive control respectively. The 3 group will receive standard drug treatment i.e., Indomethacin (2 mg/kg, s.c). and test samples (BZ-1, BZ-2, and BZ-3) will be administered to the rats in groups 4, 5, and 6. Oedema will produce by injecting Carrageenan (0.1 ml/100 g from a 10 mg/ml solution) into the planter aponeurosis of right hind paw of the rats 30 minutes later respective treatment. The left hind paw will serve as the control. The paw volume will be measure up to 4 hours using a plethysmometer.

Table 2: Treatment schedule of Carrageenan induced paw edema model

GROUP NO.	GROUP	DOSE TREATMENT	PARAMETERS TO BE EVALUATED
1.	Normal control	Will receive Distilled water (10 ml/kg, p.o)	Paw swelling and paw thickness
2.	Induction control (Carrageenan)	Will receive carrageenan (10mg/ml, i.p)	Paw swelling and paw thickness
3.	Reference Standard	Will receive indomethacin (2mg/kg, s.c)	Paw swelling and paw thickness
4.	BZ-1	Will receive Distilled water (10 ml/kg, p.o), carrageenan (10mg/ml, i.p), test compound-1.	Paw swelling and paw thickness
5.	BZ-2	Will receive Distilled water (10 ml/kg, p.o), carrageenan (10mg/ml, i.p), test compound-2.	Paw swelling and paw thickness
6.	BZ-3	Will receive Distilled water (10 ml/kg, p.o), carrageenan (10mg/ml, i.p), test compound-3.	Paw swelling and paw thickness

Effect of 5-nitro benzimidazole derivatives of carrageenan induced paw edema in rats:

The Paw edema (Paw volume) was found significantly increased from 30 minutes of carrageenan injection. ($p<0.001$); when it compared to normal control group and was significantly reduced ($p<0.001$) when it compared to treatment group after 30 minutes to carrageenan induction group. At 180 minute the test compound BZ-3 and BZ-2 showed less reduction ($p<0.01$) in paw edema than that of BZ-1, showed in **figure 3.** Values are expressed as mean ±SEM; n=6; Data analysed by one way ANOVA test followed by Tukey multiple comparison test.

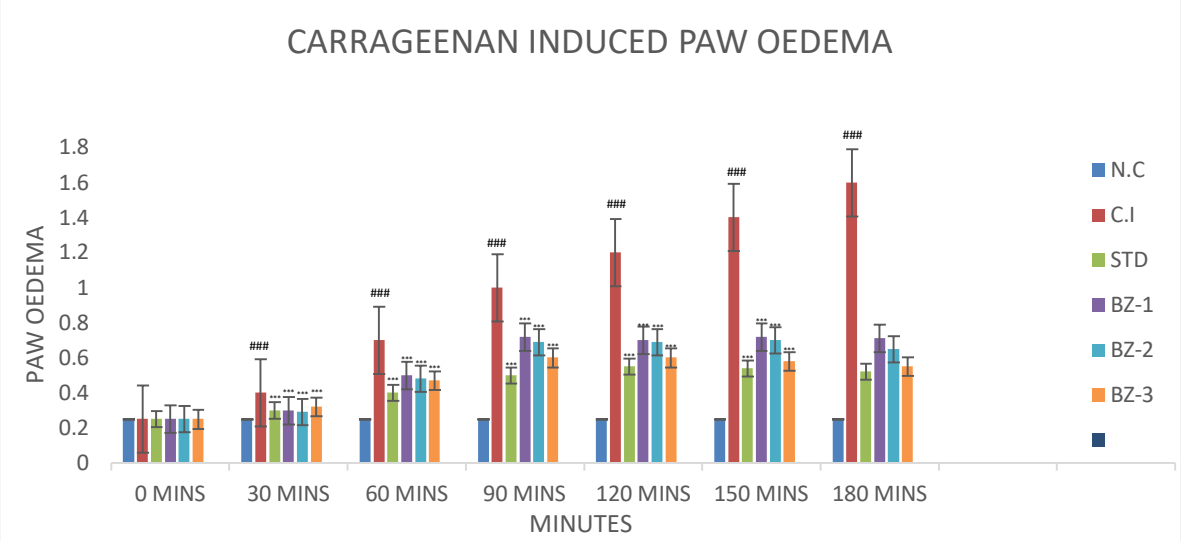


Figure 3: Effect of 5-nitro benzimidazole derivatives on carrageenan paw oedema in rats

Mean ± S.E.M = Mean values ± Standard error of means of experiments

CONCLUSION

A chemical or treatment's ability to diminish inflammation or swelling is referred to as its anti-inflammatory or antiphlogistic properties. About half of analgesics are anti-inflammatory medications, sometimes known as anti-inflammatories. This research highlights the importance of developing new drugs for the treatment of anti-inflammatory effect that have a better therapeutic effect. In the present study, a series of novel 5-nitro benzimidazole derivatives containing benzaldehyde were design and synthesized. According to their best docking result, ten novel 5-nitro benzimidazole derivatives were synthesized, out of which three derivatives were selected (BZ-1, BZ-2, BZ-3) and their anti-inflammatory activity were carried out using carrageenan induced paw edema model in rats. On the basis of biological activity results, it can be concluded that 5-nitro benzimidazole derivatives showed anti-inflammatory activity. All synthesized 5-nitro benzimidazole derivative showed prolonged and promising anti-inflammatory effect.

ETHICAL APPROVAL

The experimental procedures for the animal research were approved by the institutional animal ethics committee (Regd. No. DYPCOP/IAEC/2023/09).

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