Section A-Research paper
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SYNTHESIS OF SOME NOVEL BENZIMIDAZOLE DERIVATIVES ASPOTENTIAL THERAPEUTIC AGENTS

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ABSTRACT

Acute asthma is still a major medical issue in the modern world. Despite its prevalence, asthma remains a challenging condition to manage effectively, so continuous research efforts are necessary. Firstly, it is necessary to understand the underlying causes and mechanisms of asthma to develop effective prevention strategies and treatments. Exacerbations are a key factor in determining the severity of asthma in people of all ages. Additionally, research is needed to explore new therapeutic options and interventions that can improve the management of asthma, reduce symptom severity, and enhance the overall quality of life for individuals with asthma. Therefore, in this present work, we designed some novel Benzimidazole derivatives 1-(1H-benzimidazol-1-yl)-2-(substituted) ethanone (III-a to III-i) and synthesized by simple synthesis of Benzimidazol-1-yl-2-chloroethanone (II). Benzimidazol-1-yl-2- chloroethanone (II) is treated with different aromatic and aliphatic amines in ethanol, refluxed for 4-6 hrs to obtain final Benzimidazole derivatives 1-(1H-benzimidazol-1- yl)-2-(substituted) ethanone (III). The designed and synthesized novel derivatives were screened for invitro anti-asthmatic and anti-

inflammatory activities. *In- vitro* anti-asthmatic activity was performed by using the Isolated Goat Tracheal chain method. *In-vitro* anti-inflammatory activity was performed by the Gelatin Zymography method. Experimental results revealed that some of the derivatives showed good anti-asthmatic & anti-inflammatory activities along with the standard drug fexofenadine.

Keywords: Benzimidazole, Aromatic amines, Ethanol, anti-asthmatic activity, anti-inflammatory activity.

INTRODUCTION

Asthma, a chronic respiratory condition characterized by inflammation and narrowing of the airways, affects millions of individuals worldwide. By unraveling the intricate mechanisms underlying asthma, researchers have identified genetic, environmental, and immunological factors contributing to its development and progression [1]. Novel diagnostic techniques, including biomarkers and advanced imaging modalities, have emerged to improve asthma diagnosis and phenotyping [2]. Moreover, significant progress has been made in developing targeted therapies, such as biologics and small molecule inhibitors, that specifically modulate the underlying immune and inflammatory processes. Firstly, it is necessary to understand the underlying causes and mechanisms of asthma to develop effective prevention strategies and treatments. Additionally, research is needed to explore new therapeutic options and interventions that can improve the management of asthma, reduce symptom severity, and enhance the overall quality of life for individuals with asthma [3].

Benzimidazole, a heterocyclic compound consisting of a fused benzene and imidazole ring, has gained significant attention in the field of medicinal chemistry due to its versatile pharmacological properties and diverse biological activities [4]. The benzimidazole ring serves as a structural core in numerous bioactive compounds, making it a key scaffold for the development of novel therapeutic agents. The synthesis of benzimidazole derivatives can be achieved through various methods, including condensation reactions between ortho-diamines and carboxylic acids or acid derivatives, as well as cyclization of o-phenylenediamine derivatives with appropriate carbonyl compounds [5]. These synthetic approaches have been extensively explored, enabling the generation of diverse benzimidazole libraries for structure-activity relationship (SAR) studies and biological evaluations. Structurally, the benzimidazole ring possesses unique properties that contribute to its pharmacological potential. The presence of nitrogen atoms in the imidazole moiety allows for hydrogen bonding interactions with target proteins, enhancing binding affinity and specificity. Additionally, the fused benzene ring provides rigidity to the structure, allowing optimal spatial orientation for molecular recognition and receptor interactions.

In the realm of drug discovery, benzimidazole-based compounds have demonstrated a wide range of therapeutic activities. Several benzimidazole derivatives have shown promising anticancer effects by targeting key enzymes and receptors involved in tumor growth and metastasis [6].

The extensive biological activities of benzimidazole compounds have spurred intensive research to develop novel derivatives with improved efficacy, selectivity, and reduced toxicity.

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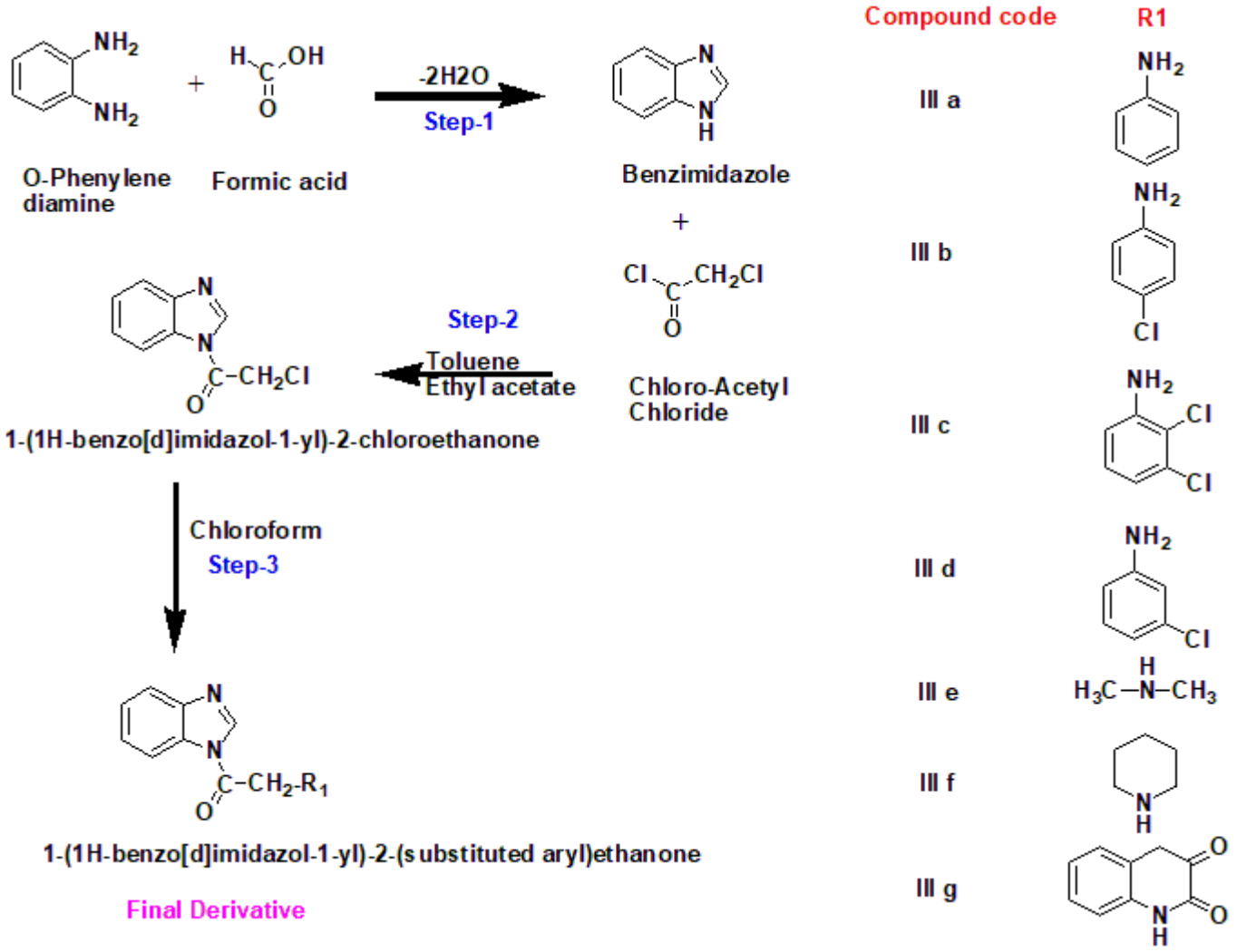
Through rational drug design approaches, researchers have focused on modifying different positions of the benzimidazole ring to optimize pharmacokinetic and pharmacodynamic profiles. This includes structural modifications at the N1, C2, C4, and C5 positions, leading to the synthesis of analogs with enhanced potency and selectivity against specific therapeutic targets [7].

This article provides on developing some novel small-molecule benzimidazole inhibitors for treatment, and prevention.

MATERIALS AND METHODS

Synthetic scheme:



Methodology [8]

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Step-1: Preparation of Benzimidazole (I):

In a 250 ml conical flask, 6g of o-phenylene diamine and 6 ml of 90% formic acid were combined. The reaction mixture was heated on a water bath for two hours before cooling. After cooling, 10% NaOH solution was gradually added while being constantly stirred to make litmus just alkaline. Cold water was used to filter and clean the precipitates. From ethanol, the product underwent recrystallization. The melting point was discovered to be between 178-180^{o} C.

Step-2: Preparation of Benzimidazol-1-yl-2-chloroethanone (II):

To a solution of Benzimidazole (6g, 0.05M) in toluene (60ml) was added chloroacetyl chloride (602ml, 0.076M) at 0^{o} C and then room temperature for 12h. The reaction mixture was concentrated under reduced pressure and the crude residue was dissolved in ethyl acetate (50ml), washed with water (2×30ml) dried over anhydrous Na_2SO_4 and evaporated to give 1-(1H-benzo[d]imidazole-1-yl)-2-chloroethane as pale yellow solid (805g,87.6%); mp= 107-109^{o} C.

Step-3: Preparation of final products (III) :

Take a mixture of 0.1M of 1-(1H-benzo[d]imidazole-1-yl)-2-chloroethanone and 0.1M of aromatic primary amine in a 30ml of ethanol and reflux for 6 hrs. Cool the residue and dried. Recrystallized from dry ethanol. 1-(1H-benzo[d]imidazole-1-yl)-2-chloroethanone (0.05M) was dissolved in 20ml of dry chloroform and 4 ml of pyridine. To which an equimolar amount of azole (aromatic secondary amine) was added and the reaction mixture was refluxed for 4 hrs, after cooling the viscous residue obtained was washed with DCM/Acetone and recrystallized from ethanol.

RESULTS

Anti Asthmatic activity:

Isolated Goat tracheal chain preparation [9-11].

An adult goat's trachea was isolated and collected from an abattoir. Trachea was divided into little rings and serially strung together to create a chain. Trachea was constantly aerated at 37°C while suspended in a Kreb's solution bath. Dose-response curves of histamine were obtained in Kreb's solution containing 5 mg/mL of test compounds. The percentage of maximum contractile response was plotted to record dose-response curves of histamine in the absence and presence of test substances (1, 2, 3). The biological activity was compared with the standard drug fexofenadine (1mg/ml).

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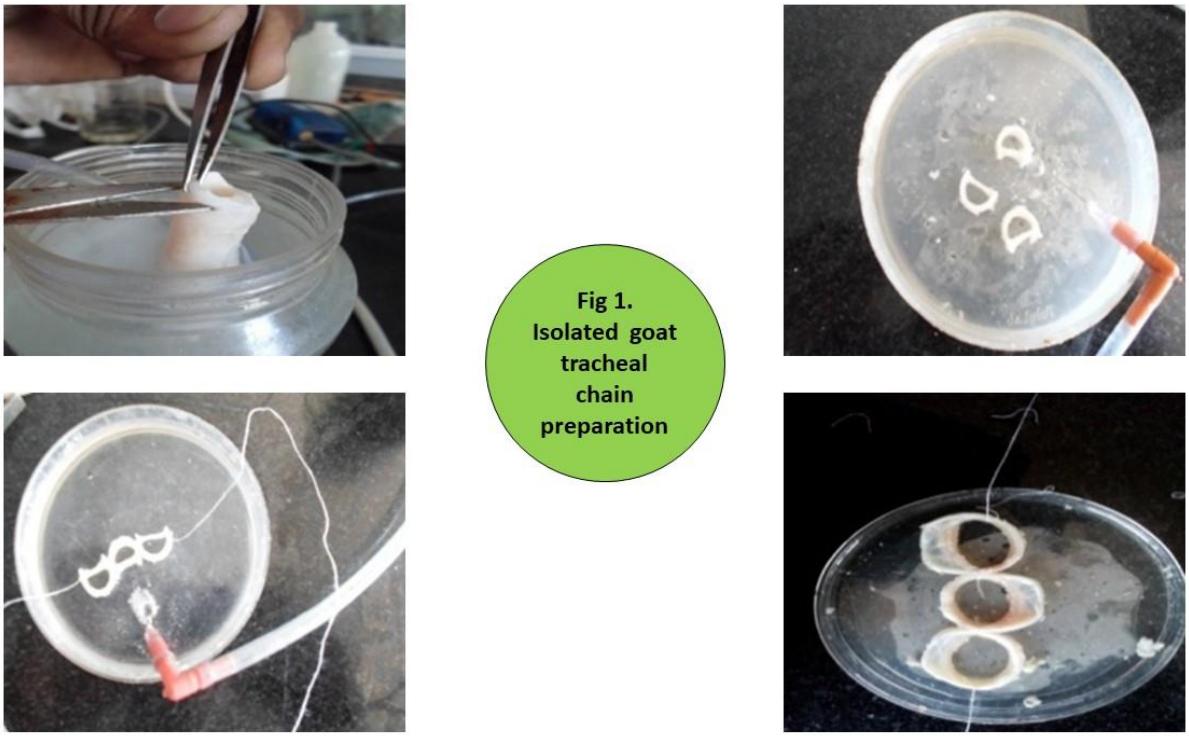

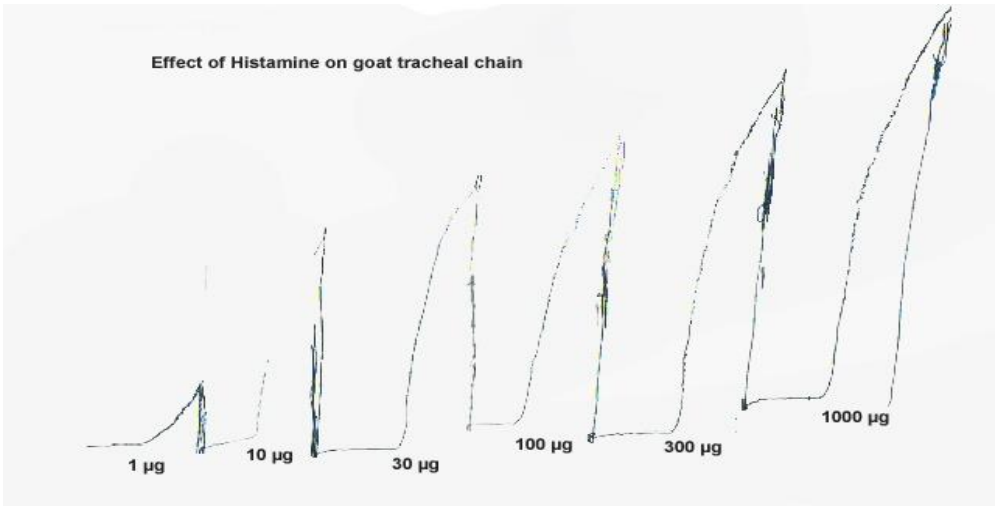

Fig 2: Effect of Histamine on isolated goat tracheal chain

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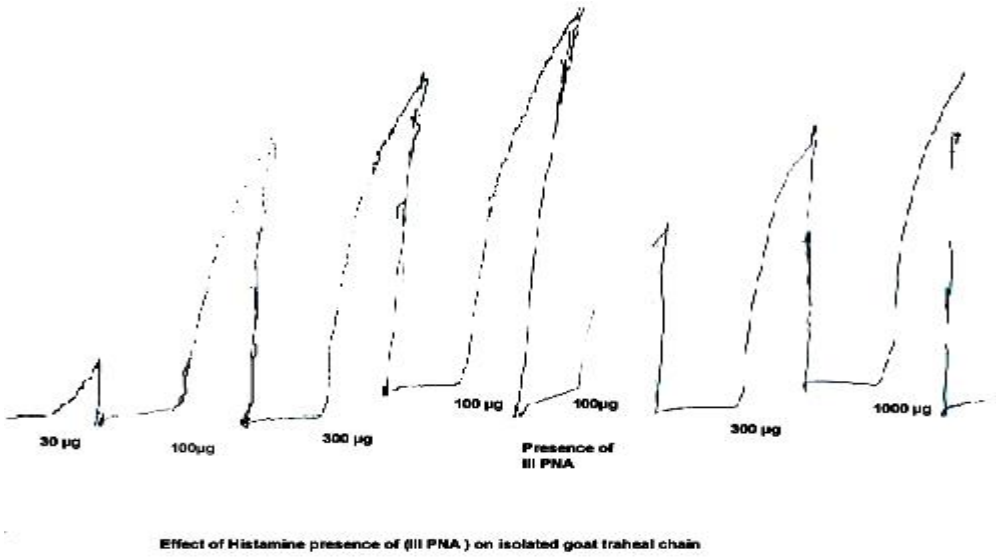

Fig3: Effect of Histamine presence of sample III PNA 5 mg/ml on isolated goat tracheal chain

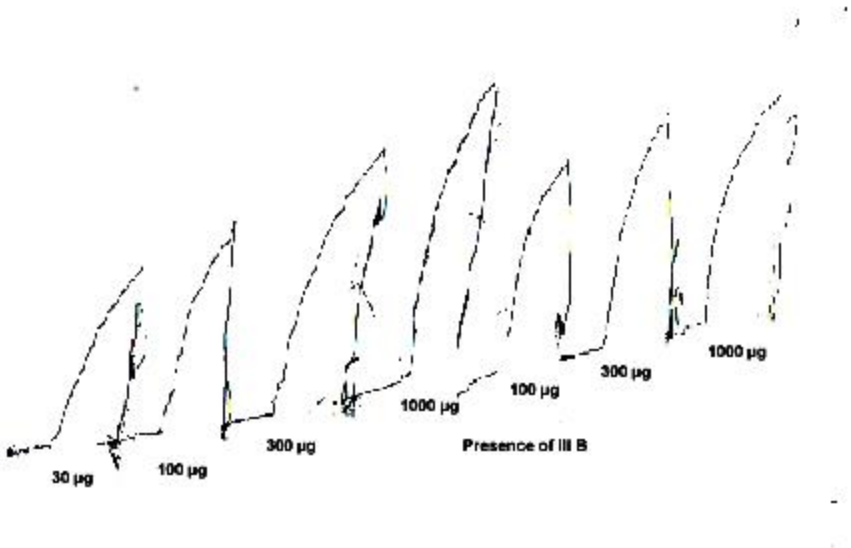

Fig 4: Effect of Histamine presence of sample (III B PCA) 5 mg/ml on isolated goat tracheal chain

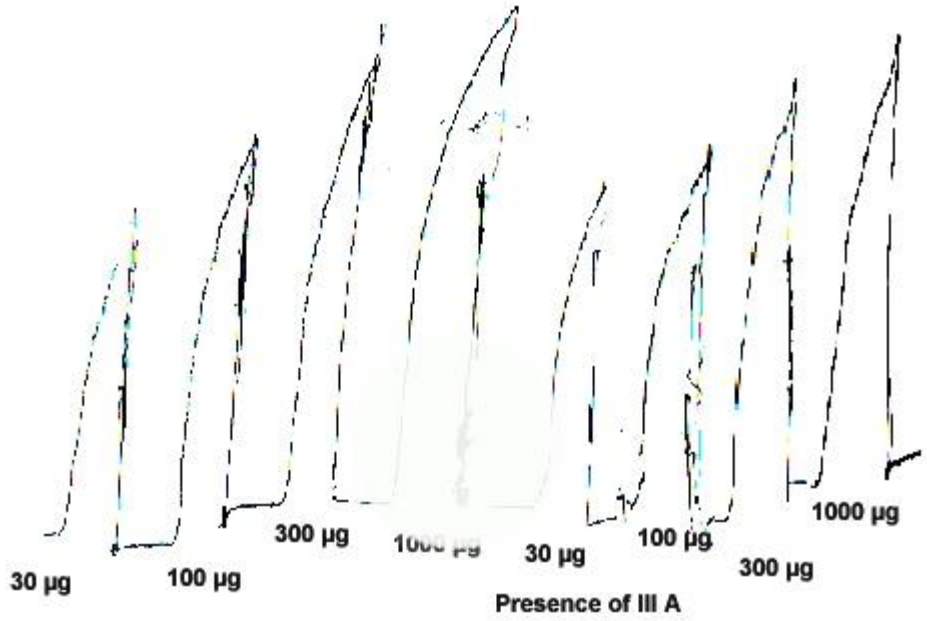

Fig 5: Effect of Histamine presence of sample (III A Aniline) 5 mg/ml on isolated goat tracheal chain

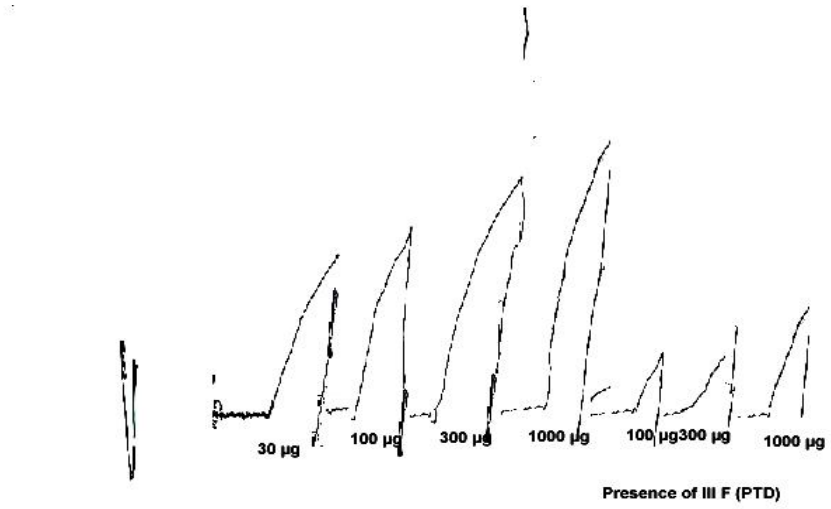

Fig 6: Effect of Histamine presence of sample (III F) on isolated goat tracheal chain

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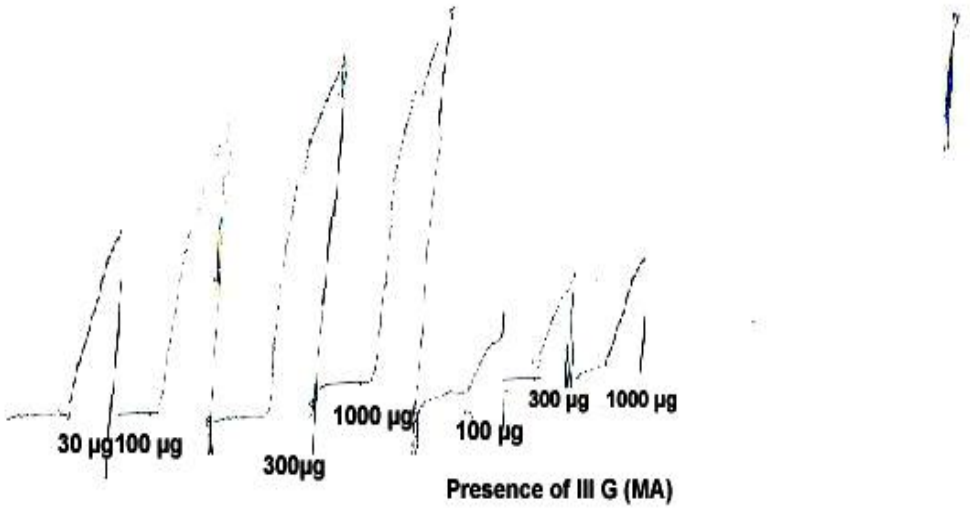

Fig 7: Effect of Histamine presence of sample (III g MA) 5 mg/ml on isolated goat tracheal chain

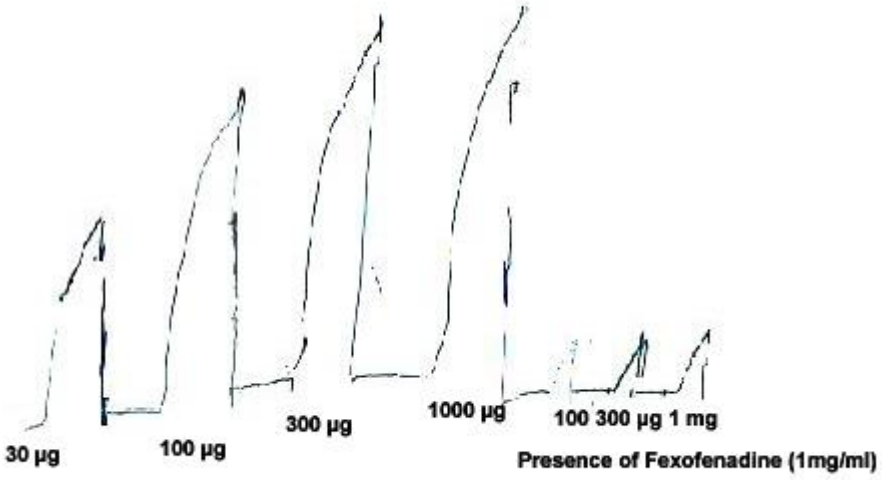

Fig 8: Effect of Histamine presence of Fexofenadine (1 mg/ml) on isolated goat tracheal chain

S. No	Conc. of Histamine (µg)	% of Response	% of Response of Histamine					
			III a (ANILINE)	III b (PCA)	III c (PNA)	III f (PTD)	III g (MA)	Fexofenadine (1 mg/ml)
1	100	60	57	58	52	7	5	2
2	300	70	67	68	61	11	8	3
3	1000	100	94	95	92	14	10	6

Table 1: Effect of Histamine Presence of synthetic samples on isolated goat tracheal chain

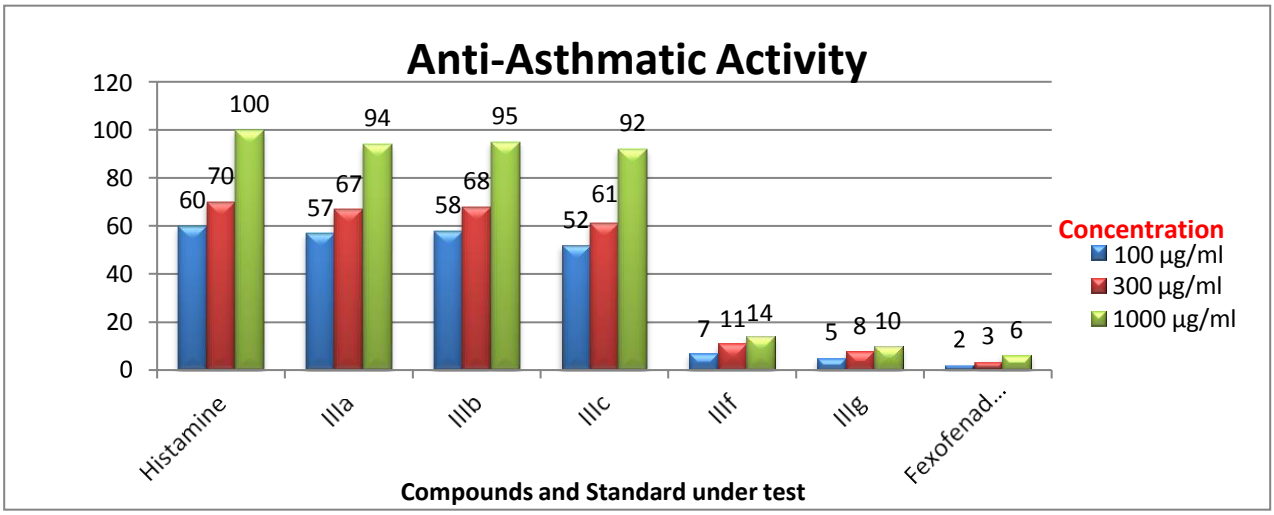

Fig 9: Bar diagram of effective designed compounds on isolated goat tracheal chain

Anti-inflammatory activity results:

S. No	Sample Name/No	Anti-inflammatory activity against MMP-2	Anti-inflammatory activity against MMP-9
1	III a	10%	12%
2	III b	30%	39%

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3	III c	62%	75%
4	III f	42%	48%
5	III g	15%	20%
6	III h	70%	82%
7	III i	80%	90%
8	Positive control	100%	90%
9	Negative control	Nil	Nil

Positive control: - Tetracycline hydrochloride

Negative control: - Tonsil sample (MMP-2 and 9 sample only)

DISCUSSION

Based on a thorough literature review, this current research work was designed with Seven novel benzimidazole derivatives that were easily synthesized in three steps. All reactions were purified by recrystallization technique, and reaction completion was monitored by TLC.

Among all the designed derivatives seven derivatives were subjected to *in-vitro* anti-asthmatic and anti-inflammatory activity.

***In-vitro* anti-asthmatic activity:**

Histamine exhibited dose-dependent responses on the goat tracheal chain. These responses were not significantly altered by III c (PNA), III b (PCA), III a(ANILINE) but the responses were decreased by III f(PTD) and III g (MA). This activity was compared with fexofenadine (1 mg/ml), histamine responses were also significantly inhibited.

Test derivatives: III g (MA) > III f (PTD) > III c (PNA) > III a (ANILINE) > III b (PCA)

Standard drugs: Fexofenadine

***In-vitro* anti-inflammatory activity:**

Among all the compounds III i (ISTN), III h (PN), and III c (PNA) showed very potent activity as the standard Tetracycline. The remaining compounds showed relatively significant anti-inflammatory activity.

Conclusion:

In conclusion, this research article investigated the synthesis of seven novel compounds and evaluated their *in-vitro* asthma activity as well as anti-inflammatory activity with the standards. The results obtained shed light on the potential therapeutic efficacy of these compounds in managing asthma-related symptoms. Through in-vitro experimental procedures and data analysis, we identified compounds **……** that exhibited promising inhibitory effects on key asthma-related parameters, such as bronchoconstriction and inflammation. Overall, the synthesized compounds demonstrate potential as future candidates for the development of novel asthma therapeutics, offering hope for improved treatment options for individuals suffering from this chronic respiratory condition.

Future Scope:

These potent leads finding contribute to the growing body of knowledge in the field of asthma research and provide a foundation for further studies, including in-vivo evaluations and clinical trials.

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