Microwave Synthesis of Novel Chalcone derived Pyrimidine-2-one Derivative: as an Anti-asthmatic agents

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ABSTRACT:

A new series of novel 4-(substituted-phenyl)-6-phenyl-pyrimidine-2(1H)-ones (4a-f) were synthesized and evaluated for their therapeutic potential as bronchodilators. These compounds were selected based on molecular characteristics and drug-likeness score, ensuring their suitability for oral bioavailability.Microwave-assisted synthesis, a rapid and environmentally friendly technique, was employed to efficiently produce the pyrimidine derivatives with Good yield and purity. The microwave irradiation method offered significant advantages over conventional synthesis, including reduced reaction time and improved product yield of 55% to 85%. This outcome highlights the value of employing green chemistry approaches in drug development.The structures of the derivatives were elucidated by FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS.All the compounds were given satisfactory reaction yields that represented the efficiency of the employed synthetic route.Clonidine-inducedcatalepsy model delayed the onset of catalepsy significantly3(a-f) when compared to an induction control group. In vitro evaluations confirmed that all test substances exhibited both broncho-dilatory and H1-antihistaminic activities, indicating their potential efficacy as anti-asthmatic drugs.Further investigations are underway to elucidate the precise mechanism of action for these compounds and explore other potential isosteres. The promising results from this study support the exploration of pyrimidine derivatives as a novel class of bronchodilators and encourage continued research in the development of effective anti-asthmatic medications.

KEYWORDS: Microwave-assisted, pyrimidine derivatives, green chemistry, anti-asthmatic drugs, TNF- α.

INTRODUCTION:

Asthma presently affects about 150 million people worldwide, and the number keeps risingevery day. Asthma prevalence, morbidity, and mortality rates have increased over the past 20 years, demonstrating how serious the condition is for the general population. In India, 30 million individuals are suffering from asthma. Airway remodeling, eosinophilia, airway

hyperreactivity, chronic inflammation of the bronchial airways, and persistent inflammation are all symptoms of allergic asthma. Allergic asthma also causes bronchial asthma. In allergic asthma, a large number of inflammatory and structural cells get activated, which releases inflammatory mediators such as histamine, prostaglandins, leukotrienes, and kinins.It can be diagnosed using restricted allergy tests,nitric oxide testing, sputum eosinophil testing, and provocative testing for exercise and cold-induced asthma.Although in many people the symptoms of asthma may disappear promptly with the use of recommended therapies, exposure to allergens may exacerbate the illness[1].Currently, a variety of drug classes are used to treat asthma, but none of them seems to be a great treatment**.**Asthma can be treated with Ayurvedicremedies including honey and cloves, herbal tea, adults, and curcumin. The drugs used to treat asthma-like β-agonist, corticosteroids, methyl xanthine, anticholinergic, leukotrienes,and most commonly antiasthmatics are used i.e. Fluticasone, Budesonide**,** Ciclesonide, etc [2]

Most pharmaceutical compounds are based upon a heterocyclic ring system. In recent years, researchers mainly focused on the modification of the pyrimidine-2-one ring system to obtain derivatives with a wide variety of pharmacological activities such as anti-inflammatory[3]antimicrobial [4] anticancer[5]anti-HIV[6]anti-neoplastic[7]antifungal[8]anesthetics[9] antiviral[10]antihypertensive[11]anticonvulsant[12]Anti-alzheimer[13]antiulcer[14] anticoagulant[15]antioxidant[16]antiarrhythmic[17].Pyrimidine fused chalcone showed good asthmatic activity.Chalcones areunsaturated ketones made up of two aromatic rings, such as rings A and B. A highly electrophilic three-carbon, unsaturated carbonyl system that adopts a linear or planar structure connects both rings[18,19].On both benzene rings, they have conjugated double bonds and an entirely delocalized Pi-electron system. Due to the presence of the chromophore keto ethylenic group (-CO-CH=CH-) in their structure, these compounds are coloured[20].By Claisen-Schmidt condensation of ketone with

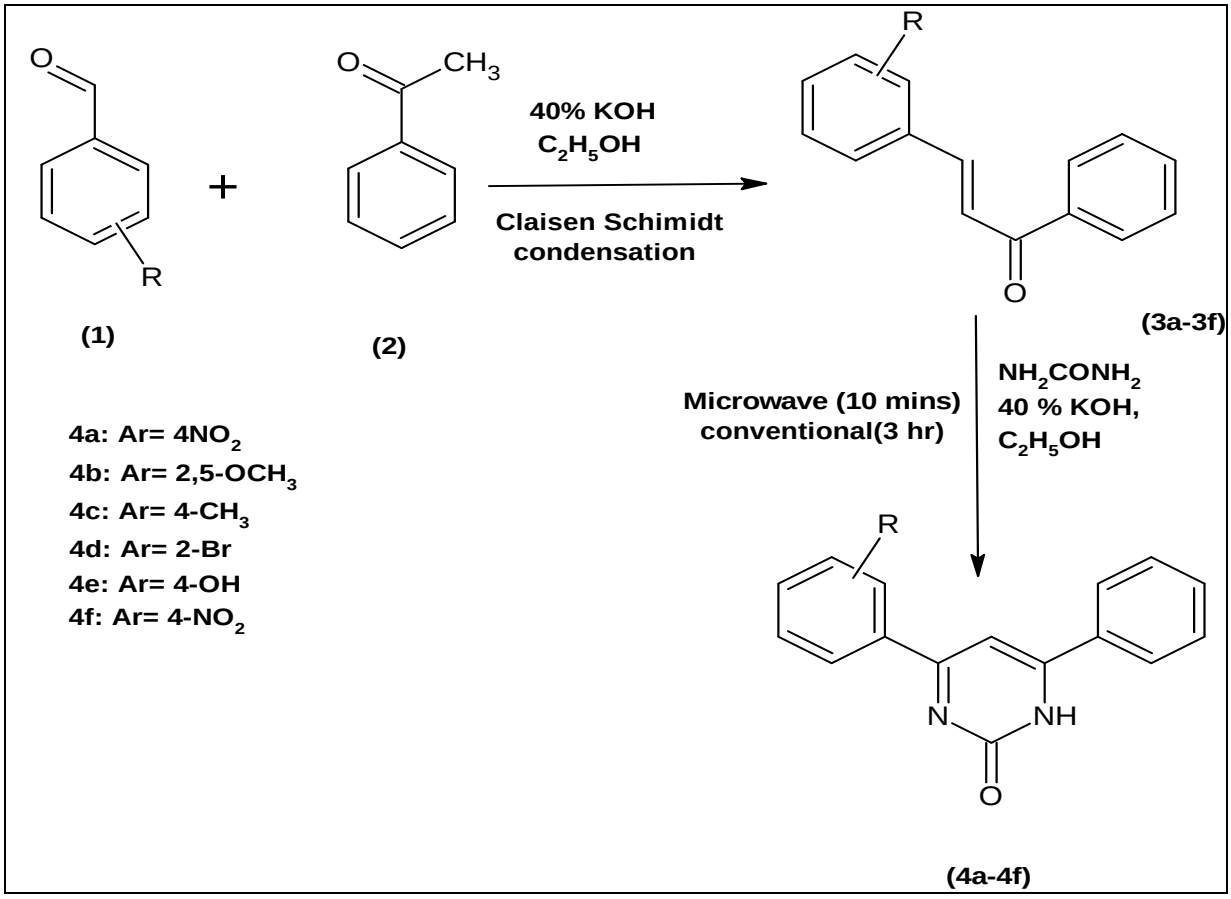
various aromatic aldehydes catalysedby strong bases (NaOH/KOH) or acids and followed by a dehydration procedure, chalcones are prepared[21,22].It is discovered that the biological activity of chalcones is produced by the presence of reactive,unsaturated keto groups[23].pyrimidine derivatives were prepared by using a microwave-assisted method [26-30].These Synthetic methods have limitations such as a longer reaction time,use of acids or bases, and hazardoussolvents[31,32].The aim of this work is to synthesizepyrimidine derivatives using microwave-assisted methods and to study their antiasthmatic activity[39-41].

2.MATERIAL AND METHODS

2.1Chemistry:

All The chemicals and solvents employed in the synthetic work were purchased from Sigma-Aldrichand Analab ChemicalsPvt. Ltd., Mumbai.The help of pre-coated Silica gel-G plates and ascending TLC, the length of time needed for the reaction to be completed as well as the purity of the compounds were tested using chloroform: Ethanol (70:30). The melting point was determined using the open capillary tube method with a digital melting point apparatus. 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 ppm and were referenced with TMS. HRMS was performed onImpact II UHR-TOF Mass Spectrometer.

2.2 Synthesis



Scheme 1: Synthesis of pyrimidine-2-one derivatives

2.3 Microwave Synthesis

First, 0.01 mol of the appropriately substituted benzaldehyde and 0.01 mol of the appropriately substituted acetophenone were dissolved in 20 ml of ethanol. After that, the mixture was stirred for 20 minutes at a temperature then added 10 ml of 40% aqueous KOH dropwise and stirredconstantly, after that precipitate was separated by filtration, and characterization by TLC, and subjected to further reaction**.**

A mixture of chalcone (3a-f) (0.01 mol), urea (0.01 mol, 0.6 g) was dissolved in ethanol (10 mL, 95%). To this, 40% aqueous potassium hydroxide solution (10 mL) was added slowly with constant stirring. The reaction mixture was placed in the microwave and irradiated at power 210 W for 7-10 min. In between, TLC was monitored to check the completion of the reaction condition. After completion of the reaction, the reaction mixture was cooled to room temperature and then poured into ice-cold water and neutralized by adding dilute HCl. The precipitate obtained was filtered, washed with water, and dried. The product (3a-f) was recrystallized from rectified spirit.

3. Anti-asthmatics Activity

3.1 Acute toxicity study:

As per the OECD 423 guidelines. An acute oral toxicity study was conducted on female Swiss albino mice which were fasted overnight and administered a single dose of 0.5% normal saline solution (control group)(n=3) or 2000mg/kg of (4a-4f) was dissolved in 0.5% normal saline solution (n=3)orally. Thereafter the mice were monitored continuously for 14 days.on the last 14th day, the mice were euthanized

3.2: Clonidine induces catalepsy in mice:

Swiss Albino mice were divided into five classes, each with five animals. Saline solution (10 ml/kg) was given as the normal control (Class 1), and the remaining classes (Classes 3 to Class 5) each received a single dose of the extract (100, 200, or 400 mg/kg body weight). Class 2 mice received a typical dose of the antihistamine chlorpheniramine maleate (10 mg/kg, i.p.). All classes received clonidine (1 mg/kg s.c.) one hour after the medication was consumed, and the catalepsy duration was measured at 15, 30, 60, 90, 120, 150, and 180 minutes.[42-46].

3.3Estimation of TNF-α in test Serum Sample

Preliminary research on limited numbers of patients has shown that anti-TNF medication improves lung function, airway hyperresponsiveness, asthma quality of life, and exacerbation rate. TNF- is a potentially significant cytokine in refractory asthma. A suitably powered large-scaleclinical research is required to determine the potential role of TNF- antagonism in refractory asthma.

4.RESULTS AND DISCUSSION:

4.1Chemistry:

All the derivatives were properly separated from the reaction mixture and given satisfactory reaction yields, 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;

6-(4-aminophenyl)-4-(4-nitrophenyl)Pyrimidine-2(1H)-one(PD1)

Yellow colour,% Yield: 85,Mp: 242-245°, Rf value:0.54, IR (KBr) v (cm^{-1}): 3150-3026 (NO2),1700-1725(C=O),1720-1740(CHO), 3500-3400(N-H),^{1}H NMR ($CDCl_3$) δ (ppm): δ 6.75 (1H, s), 7.43-7.64 (4H, 7.49 (ddd, *J* = 1.6, 8.9, 0.5 Hz), MS m/z:308.29 [M^{+}], NMR ^{13}C (100 MHz, DMSO*d6*) δ(ppm): 121.7, 130.6, 139.1(3C,BenzeneCH), 150.5(1C), 127.1, 128.4,

133.1 (3C BenzeneCH) 164.3 (1C) 134.7 (1C, chloride), 106 (1C), 163.5, 164.9 (2C, 1-Amide), 123.1, 125.8 (4C, Benzene CH), 156.5,(1C, Benzene C); HRMS (EI, m/z): 325$[M+H]^+$

6-(4-Chlorophenyl)-4-(2,4-dimethylpheny)Pyrimidine-2(1H) One(PD2)

Brownishcolour,% Yield: 75mp: 247-249°Rf value:0.6, IR (KBr) v (cm^{-1}): 1456-3099 (2,4dimethyl), 1700-1725(C=O),1720-1740(CHO), 3500-3400(N-H),^{1}H NMR ($CDCl_3$) δ (ppm):):^{1}H NMR: δ 2.27-2.39 (6H, 2.32 (s), 2.34 (s)), 6.71 (1H, s), 7.16 (1H, dd, *J* = 2.3, 0.6 Hz), 7.42-7.66 (6H, 7.48 (ddd, *J* = 8.6, 1.6, 0.5 Hz),NMR ^{13}C (100 MHz, DMSO*d6*) δ(ppm): 121.7, 131.6, 138.1(3C,BenzeneCH), 145.5(1C), 127.2, 128.5, 133.5 (3C BenzeneCH) 164.9 (1C) 134.7 (1C, chloride), 106 (1C), 163.4, 164.6 (2C, 1-Amide), 123.1, 125.8 (4C, Benzene CH), 156.5,(1C, Benzene C),HRMS m/z: 310.7$[M+H]^+$

6-(4-Chlorophenyl)-4-(4-ethyl phenyl)Pyrimidine-2(1H)-One(PD3)

Pale yellow color,% Yield: 90; mp: 250-252° ,Rf value:0.8 IR (KBr) v (cm^{-1}): 3374-3212 (4-CH_2CH_3), 1700-1725(C=O),1720-1740(CHO), 3500-3400(N-H),^{1}H NMR ($CDCl_3$) δ (ppm): ^{1}H NMR: δ 2.27-2.39 (6H, 2.32 (s), 2.34 (s)), 6.71 (1H, s), 7.16 (1H, dd, *J* = 2.3, 0.6 Hz), 7.42-7.66 (6H, 7.48 (ddd, *J* = 8.6, 1.6, 0.5 Hz),NMR ^{13}C (100 MHz, DMSO*d6*) δ(ppm):121.7, 131.6, 138.1(3C,BenzeneCH),32.4(4-ethyl), 145.5(1C), 127.2, 128.5, 133.5 (3C BenzeneCH) 164.9 (1C) 147.7 (1C,NH2), 106.3 (1C), 163.4, 164.6 (2C, 1-Amide), 123.5, 125.6 (4C, Benzene CH), 156.5,(1C, Benzene C),HRMS m/z: 315.78$[M+H]^+$

4-(2-bromophenyl)-6(4-Chloropheny)Pyrimidine-2(1H)-One(PD4)

Brawnish color,% Yield: 70; mp: 255-256°, Rf value: 0.9 IR (KBr) v (cm^{-1}): 3099-3000 (2,5 OCH3),

1700-1725(C=O),1720-1740(CHO), 3500-3400(N-H),^{1}H NMR ($CDCl_3$) δ (ppm): δ 2.27-2.39 (6H, 2.32 (s), 2.34 (s)), 6.71 (1H, s), 7.16 (1H, dd, *J* = 2.3, 0.6 Hz), 7.42-7.66 (6H, 7.48 (ddd, J = 8.6, 1.6, 0.5 Hz) ,7.53 (dd, J = 8.1, 0.6 Hz), 7.58 (dd, J = 8.1,2.3 Hz), 7.60 (ddd, J = 8.6, 1.5, 0.5 Hz)) NMR ^{13}C (100 MHz, DMSO*d6*) δ(ppm):121.6, 131.5, 138.2(3C,BenzeneCH), 145.4(1C), 127.2, 128.3, 133.7 (3C BenzeneCH) 164.9 (1C) 134.7 (1C, chloride),

106.3 (1C), 163.4, 164.6 (2C, 1-Amide), 123.5, 125.6 (4C, Benzene CH), 156.5,(1C, Benzene C)MS m/z: 361.6$[M+H]^+$

6-(4-Chlorophenyl)-4-(hydroxyphenyl)Pyrimidine-2(1H)-One(PD5)

Yellow color% Yield: 65; mp: 272-274°,Rf value:0.7 IR (KBr) v (cm^{-1}): 3199-2789 (4-OH), 1700-1725(C=O),1720-1740(CHO), 3500-3400(N-H)^{1}H NMR ($CDCl_3$) δ (ppm): δ 2.26-2.38 (6H, 2.32 (s), 2.35 (s)), 6.71 (1H, s), 7.12 (1H, dd, *J* = 2.3, 0.6 Hz), 7.43-7.67 (6H, 7.48 (ddd, J = 1.6, 8.6, 0.6 Hz),7.53 (dd, J = 8.1, 0.6 Hz), 7.57 (dd, J = 8.1,2.3 Hz), 7.60 (ddd, J = 8.6, 1.5, 0.5 Hz))NMR ^{13}C (100 MHz, DMSO*d6*) δ(ppm): 116.7, 125.6, 130.1(3C, BenzeneCH), 160.5(1C), 127.1, 128.4, 132.1 (3C BenzeneCH) 163.4 (1C) 133.8 (1C, chloride), 116 (1C), 163.4, 164.8 (2C, 1-Amide), 125.1, 126.8 (4C, Benzene CH), 156.5(1C, Benzene C); HRMS (EI, m/z): 325$[M+H]^+$

6-(4-Chlorophenyl)-4-(4-nitrophenyl) Pyrimidine-2(1H)-One(PD6)

Yellow color,% Yield:87; mp: 280-282°,Rf value:0.9,IR (KBr) v (cm^{-1}): 3150-3026 (NO2), 1700-1725(C=O),1720-1740(CHO), 3500-3400(N-H),^{1}H NMR ($CDCl_3$) δ (ppm), ^{1}H NMR ($CDCl_3$) δ (ppm): δ 2.28-2.37 (6H, 2.26 (s), 2.34 (s)), 6.72 (1H, s), 7.11 (1H, dd, *J* = 2.3, 0.6 Hz), 7.42-7.68 (6H, 7.48 (ddd, J = 1.6, 8.6, 0.6 Hz),7.54 (dd, J = 8.1, 0.6 Hz), 7.58 (dd, J = 8.1,

2.3 Hz), 7.61 (ddd, J = 8.5, 1.6, 0.8 Hz)NMR ^{13}C (100 MHz, DMSO*d6*) δ(ppm): 116.9, 125.5,

130.5(3C, BenzeneCH), 160.4(1C), 127.1, 128.3, 132.1 (3C BenzeneCH) 163.5 (1C) 133.9 (1C, chloride), 116 (1C), 163.3, 164.9 (2C, 1-Amide), 125.1, 126.9 (4C, Benzene CH), 156.5(1C, Benzene C);MS m/z: 327.72$[M+H]^+$

5.Anti-asthmatics Activity

5.1 Clonidine induces catalepsy in mice:

Mice experienced catalepsy from clonidine (1 mg/kg, s.c.), which persisted for two hours. At 120 minutes following the injection of clonidine, the vehicle-treated group displayed a highest amount of catalepsy (216.2 7.76 sec.). The animals pretreated with PD (a-f) (180, 360, 720 mg/kg, p.o.) showed a significant inhibition *p0.001 of clonidine-induced catalepsy, and the duration of catalepsy was determined to be 135.4 15.347, 153.6 16.5, and 141.2 5.84 seconds, respectively, at 120 minutes after the administration of clonidine. At 120 minutes after the administration of clonidine, chlorpheniramine maleate (10 mg/kg, i.p.) significantly (p0.001) reduced the catalepsy that clonidine had caused in mice.

Duration of catalepsy(sec)at Mean ± SEM(Table:1)

		Duration of catalepsy(sec)at Mean ± SEM						
Sr.no	**Groups**	**15min**	**30min**	**60min**	**90min**	**120min**	**150min**	**180min**
1.	Distilled water (10 ml/kg, p.o.)	28.4±1.9	109.6±2.07	167.4± 20.57	201.1±8.21	135.6±15.34	216.8±7.76	197.6±14.14
2.	Chlorpheniramine maleate (10 mg/kg, i.p.)	14.0±0.70	22.6±0.67	65.4±10.7	71.8±1.72	88.8±13.1	94.8±6.46**	107.8±5.77
3.	PD1 (50 mg/kg, p.o.)	21.2±2.13	97.0±1.14	108.6± 3.58	137.2±7.72	171.8±11.9	152.8±6.74	146.4±5.93
4.	PD2(50 mg/kg, p.o.)	20.4±0.87	92.8±2.08	98.0±12.4	129.8±11.3	153.6±16.5	141.0±5.37*	131.4±4.10
5.	PD3(50 mg/kg, p.o.)	17.0±1.58	87.4±4.20	62.8±10.8	123.8±14.6	141.6±5.13*	132.2±3.83	126.2±3.98
6.	PD4(50 mg/kg	16.0±0.58	84.4±4.21	52.8±9.8	133.8±14.5	131.6±5.13*	134.2±3.33	127.2±3.96
7.	PD5(50 mg/kg	17.0±1.58	86.4±4.12	61.8±0.8	121.8±13.6	142.6±5.13*	133.2±3.53	129.2±3.97
8.	PD6(50 mg/kg)	18.0±0.58	88.4±4.2	63.8±10.9	124.8±14.6	143.6±5.23*	132.2±3.983	129.2±3.92

*The data are presented as mean ± SEM. The data wereanalysed by one-way ANOVA followed by Dunnet's test. *p<0.05, **p<0.01 and ***p<0.001 was considered significant.*

Estimation of TNF-α in test Serum Sample(Table.2)

Sr No	Compound Code	Observed Optical Density at 450 nm	Concentration (pg/mL)
1.	DW	0.835	209.14
2.	PD1	0.79	192.68
3.	PD2	0.799	195.97
4.	PD3	0.755	284.71
5.	PD4	0.745	195.67
6.	PD5	0.891	192.44
7.	PD6	1.13	384.71

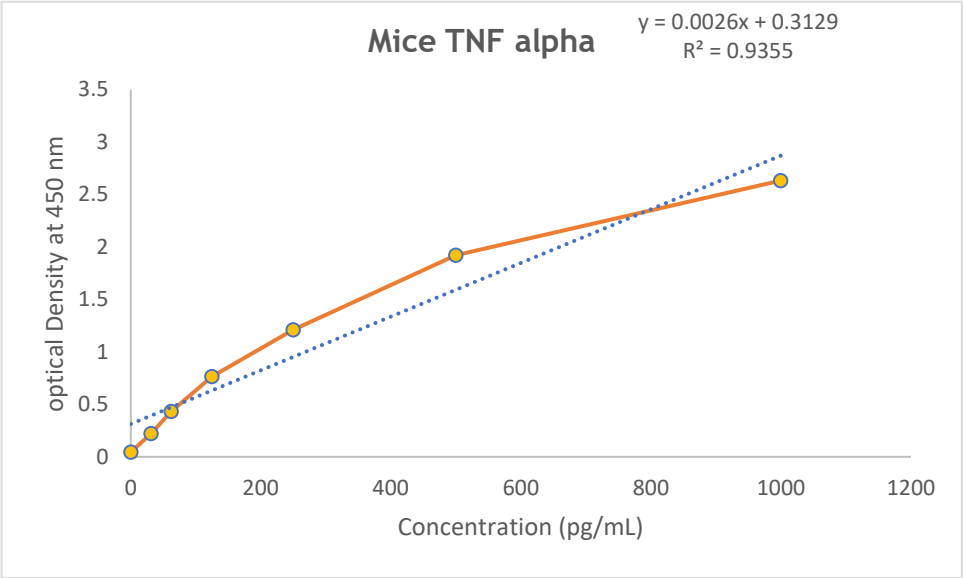
8.	Cetirizine	1.02	276.81
9.	Chlorpheniramine	0.915	238.40

Standard graph (Fig.1)

CONCLUSION:

Asthma remains a common respiratory tract disease forindividuals of all ages. However,the numerous phenotypes of asthma.Although the processes in the diagnosis of asthma are not difficult,the growing understanding that asthma is varied and has unique phenotypes will assist to improve the current limits.In addition, treatment that isby guidelines offers a structure for an evidence-based strategy that, for many patients, is very successful and effective.Clonidine induced catalepsy model is an experimental model. Clonidine isan α -Adrenoreceptor agonist which induced significant catalepsy conditions in mice andintervened by histamine through H1 receptors. Histamine can discharge by clonidine from mast cells and the presence of such mast cells now evident brain obvious clonidine induced catalepsy may be due to the releaseof histamine from brain mast cell duration of catalepsy was significantly reduced in mice pretreated with 4(a-f) this catalepsy possible due to the prevention of the release of histamine from the brain. and thena demonstration of antihistamines4(a-f). 4a showed good asthmatic activity as compared to 4(b-f) due to the presence of the NO2 group which is an electron-withdrawing group at para- position.

Ethical approval:



This project was approved by the Animal Ethics Committee in Dr .D, Y, PATIL COLLEGE OF, PHARMACY, AKURDI[DYPCOP/IAEC/2023/13/06]

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