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SYNTHESIS, STRUCTURAL CHARACTERIZATION OF SOME BENZIMIDAZOLO PYRIMIDINE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

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ABSTRACT

The synthesis of novel series of structurally related benzimidazolo pyrimidines is described. Preparation of 4-(2, 3-dihydro-1*H*-benzimidazol-2-yl)-1-phenylpropan-1-one by using Friedel Crafts reaction in which benzene and its derivatives reacted with cyclic anhydride such as succinic anhydrides in presence of aluminium trichloride, resulted solid reacted with ortho-phenylenediamine in presence of sodium hydroxide to form an active hydrogen containing building block, used for synthesis of benzimidazolo pyrimidine derivatives.

Twenty benzimidazolo pyrimidines derivatives was synthesized using Biginelli like reaction in which 4-(2, 3-dihydro-1*H*-benzimidazol-2-yl)-1-phenylpropan-1-one reacted with aldehydes and urea under acidic conditions in presence of ethanol. The acid used here was HCl.

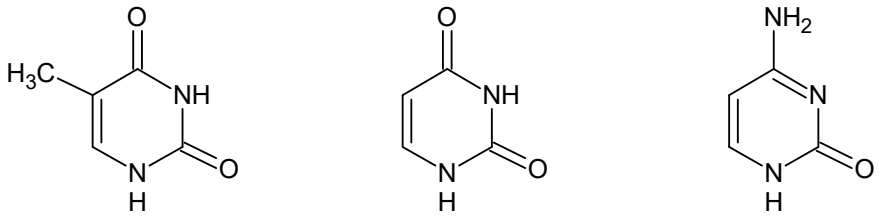
Progress of reaction was monitored by TLC. Reaction products were analysed with ^{1}H NMR and IR spectroscopy.

The anti-inflammatory activity of all synthesized derivatives was performed by Carrageenan induced rat paw oedema model. Indomethacin was used as an internal standard. All synthesized derivatives has tendency to show fall in oedema.

Keywords: Benzimidazolo Pyrimidine Derivatives, Anti-Inflammatory Agents

INTRODUCTION

Heterocyclic compounds carrying pyrimidine rings are of enormous importance because they represent a vital family of natural and synthetic products, several of which display valuable clinical applications and bioactivities **[1, 2]**. Substituted pyrimidines and purines are extensively found in living things and are among the leading compounds investigated by chemists **[3]**. Pyrimidines represent the most abundant members of the diazine class with thymine **(Figure 1a)**, uracil **(Figure 1b)**, and cytosine **(Figure 1c)** being key components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) **[4]**.



Thymine **Figure 1a** **Uracil** **Figure 1b** **Cytosine** **Figure 1c**

Non-steroidal anti-inflammmatory drugs (NSAIDs) have been used to treat various ailments for over 100 years. As a class, these drugs possess anti-inflammatory, anti-allergy, analgesic and antipyretic activity and are widely used to treat chronic inflammatory states such as arthritis, psoriasis and asthma **[5]**.

The literature indicated that compounds having pyrimidines nucleus possess broad range of biological activities, like 5-fluorouracil as anticancer **[6]**, idoxuridine and trifluoridine as antiviral **[7]**, zidovudine and stavudine as antiHIV **[8]**, trimethoprim, sulphamethiazine and sulphadiazine as antibacterial **[9]**, sulphadoxin as antimalarial and antibacterial **[10]**, minoxidil and prazosin as antihypertensive **[11]**, barbiturates eg. phenobarbitone as sedative **[12]**, propylthiouracil as antithyroid **[13]** and toxoflavin as antibiotics **[14]**.

All of NSAIDs are approximately equivalent in terms of anti-inflammatory efficacy but also cause untoward side effects (like in gastrointestinal), in a significant fraction of treated patients and this frequently limits therapy **[5]**.

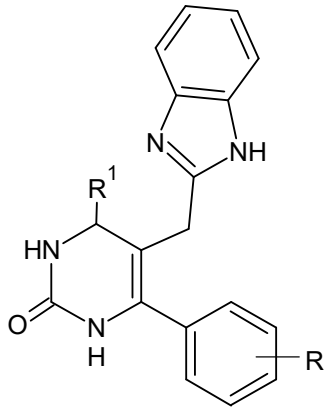
The main mechanism of action of NSAIDs is the inhibition of the enzymes possessing cyclooxygenase (COX) activity, which are involved in the formation of prostaglandins

and thromboxanes from arachidonic acid contained in cellular membranes **[15]**.

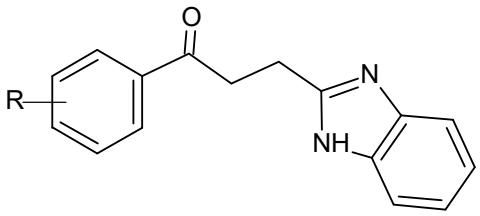
In this study synthesis of some new series of pyrimidines derivatives coupled with benzimidazole moiety using Biginelli like reaction and tested for their anti-inflammatory activity.

Present study is to provide a method for preparing pyrimidine-benzimidazole hybrid compound(s) of formula I, wherein the method comprises the steps of: (a) synthesising of a compound of Formula II (b) preparing a mixture comprising compound of formula II, urea and substituted aldehydes.

MATERIAL AND METHODS



Formula I



Formula II

(a) Synthesis of 3-(1*H*-benzimidazol-2-yl)-1-phenyl or substituted phenyl propan- 1-one (Formula II) **[16]** –

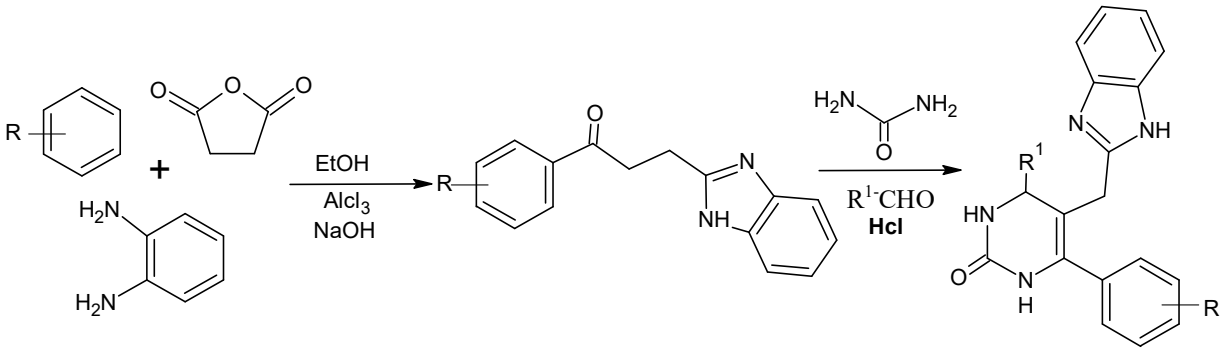
process for synthesis of the compound of formula II, wherein the process comprises the steps of: (i) preparing a mixture comprising substituted benzene, succinic anhydride and a catalyst in a solvent; (ii) heating the mixture at a temperature in the range of 75°C to 100°C for a time period in the range of 15mins to 45 min. under constant stirring; (iii) cooling the mixture and adding the water slowly to obtain a precipitated reaction mass; (iv) adding ortho-phenylenediamine to the precipitated reaction mass and then heating at a temperature in the range of 90°C to 100°C for a period in the range of 1hrs to 3 hrs to obtain a reaction mass; (v) cooling and basifying the reaction mass with a base to obtain an alkaline reaction mass; (vi) filtering the alkaline reaction mass and washing with ice cold water and drying it to obtain the compound of Formula II.

(b) Synthesis of pyrimidine-benzimidazole hybrid (Formula I)[16] –

Preparing a mixture comprising compound of formula II, urea, substituted aldehydes in a solvent; (c) refluxing the mixture at a

temperature in the range of 78°C to 80°C for a time period in the range of 15 mins to 120 mins to obtain a reaction mixture; (d) cooling the reaction mixture at room temperature to obtain a solid mass; (e) dissolving the solid mass in a hot water and filtering to obtain a filtrate; (f) neutralising the filtrate with acid to obtain a crude pyrimidine-benzimidazole hybrid compound(s); (g) purifying the crude product to obtain pyrimidine-benzimidazole hybrid compound(s) of formula I

Scheme –



RESULT AND DISCUSSION

Physical properties of synthesized compounds –

Reaction progress checked by TLC using mobile phase (Benzene-ethyl acetate, 3:1). When the mobile phase has moved to appropriate distance, stationary phase removed, mobile phase is dried and spot detected using uv light. Rf value calculated for each synthesized compounds as mentioned in **Table 1**. Synthesized compounds are purified by recrystallisation using rectified alcohol. Melting point of compounds determined by using Veego (Model-VMP-DS) melting point apparatus after calibration. IR spectroscopy of compounds performed using Perkin Elmer spectrum 65 FT-IR Spectrometer and NMR on model Avance-II (Bruker).

Chemical properties of synthesized compounds –

PS1 – IR (KBr, cm^{-1})- **N-H str. - 3250, - Ar-CH.str. - 3072, -C-H methyl str. -2961, -C=O str. - 1715, -C=N str. - 1640, -C- H def.-1350,- C=C str. - 1570, -C-N str.-1119.**

PS2 - IR (KBr, cm^{-1}) **-OH str. - 3430, N-H str. - 3230, - Ar-CH str.- 3068, - C-H methyl str.- 2968, -C=O str. - 1720, -C=C str. -1572, -C= N str. -1674, -C-N str.-1109.** 1H NMR (400 MHz DMSO) - **6.5-8.3** -17H (s) of Ar-H, **3.9** -1H of OH(s), 1.2-2H(s) of CH_2, **2.1**-3H (s) of CH_3.

PS3 - IR (KBr, cm^{-1}) **N-H str. – 3250, - Ar-CH str. – 3072,- C-H methyl str. -2980, -C=O str. - 1695, -NO_2 str. - 1580,-C=N str. – 1664, -C=C str. - 1570, -C-N str.-1119.**

PS4 - IR (KBr, cm^{-1}) N-**H str. - 3253, - Ar-C-H.str. - 3078, C-H methyl str. -2966, C=O str. - 1715, NO_2 str. - 1585 -, -C=N str. - 1674, -C=C str. - 1575, -C-N str.-1119.**

PS5 - IR (KBr, cm^{-1}) - **N-H str. - 3250, - Ar-C-H.str. – 3072, -C=O str. - 1700, -C=N str. - 1674 -C=C str. – 1570, -C-N str.-1119.**

PS6 - IR (KBr, cm^{-1}) **-OH str. - 3580, -N-H str. - 3100, - Ar-C-H.str. - 3068,-C-H str. - 2966,-C=O str. - 1698, -C=C str. - 1580, -C-N str.-1121, -C=N str. – 1684.** 1H NMR (400 MHz DMSO) - **6.7-8.3** -17H (s) of Ar-H, **3.8** -1H of OH(s), 1.2-2H(s) of CH_2.

PS7 - IR (KBr, cm^{-1}) - **N-H str. - 3120, - Ar-C-H.str. - 3078,-C-H str. - 2966, -C=O str. - 1700, -NO_2 str. - 1581, -C=C str. - 1577, -C-N str.-1109, -C=N str. – 1674.**

PS8 - IR (KBr, cm^{-1}) **N-H str. - 3100, - Ar-C-H.str. - 3068, -C-H str. - 2966, -C=O str. - 1720, -NO_2 str.- 1581, -C=C str. - 1578,-C=N str. - 1664, -C-N str.-1118.**

PS9 - IR (KBr, cm^{-1}) **-N-H str. - 3140, - Ar-C-H str. – 3072,-C=O str. - 1720, -C=N str. - 1654, -C=C str. – 1570, -C-O str. - 1280, -C-N str.-1117.**

PS10 - IR (KBr, cm^{-1}) **-OH str. - 3430, - NH str. - 3230, - Ar-C-H str. - 3068, -C-H str. - 2966, -C=O str. – 1707, C=N str. – 1644, -C=C str.-1574, -C-O str. - 1280, -C-N str.- 1109.** 1H NMR (400 MHz DMSO) - **6.6-8.3** -17H (s) of Ar-H, **3.9**- 3H of OCH_3(s), **3.7** -1H of OH(s), **1.2**-2H(s) of CH_2.

PS11 - IR (KBr, cm^{-1}) **- NH.str. - 3264, - Ar-C-H str. - 3047,-C-H str. - 2957, -C=O str. - 1715, -C=N str. – 1640, -C=C str.-1558, -NO_2 str.-1328, -C-O str.- 1275, -C-N str. - 1115.**

PS12 - IR (KBr, cm^{-1}) **- NH str. - 3264, - Ar-C-H str. -3049,-C-H str. - 2957, -C=O str. - 1722, C=N str. – 1648, -C=C str.-1555, -NO_2 str.-1571, -C-O str.- 1275, -C-N str. - 1115.**

PS13 - IR (KBr, cm^{-1}) **-N-H str. - 3250, - Ar-C-H str. - 3047, -C=O str. - 1715, -C=C str.-1558, -C-N str.- 1120, -C-Cl str. - 662.**

PS14 - IR (KBr, cm^{-1}) **-O-H str. - 3480, -N-H str. - 3250,- Ar-C-H str. - 3034, -C=O str. - 1715, -C=C str.- 1558, -C-O str.** 1H NMR (400 MHz DMSO) - **6.6-8.3** -17H (s) of Ar-H, **3.9** - 1H of OH(s), 1.2-2H(s) of CH_2.- **1275, -C-N str.-1120, -C-Cl str.- 662.**

PS15 - IR (KBr, cm^{-1}) **-N-H str. - 3250, - Ar-C-H str. - 3049,-C=O str. - 1715, -C=C str.- 1558, -NO_2 str.- 1328, -C-N str.- 1120, -C-Cl str.-672.**

PS16 - IR (KBr, cm^{-1}) **N-H str. - 3270, - Ar-CH.str. - 3046, -C=O str. - 1715, -C=C str.-1558, - NO_2 str.- 1328, -C-N str.- 1120, -C-Cl str.- 666.**

PS17 - IR (KBr, cm^{-1}) **-N-H str. - 3250, - Ar-C-H str. - 3047, -C-H str. - 2957, -C=O str. - 1715, -C=C str.- 1558, -C-N str.- 1120, -C-F str.- 710.**

PS18 - IR (KBr, cm^{-1}) **-O-H str. - 3480, -N-H str. - 3250,- Ar-C-H str. - 3047, -C-H str. - 2957, -C=O str. - 1715, -C=C str.- 1558, -C-O str. - 1278, -C-N str.- 1120, -C-F str.- 718.**

PS19 - IR (KBr, cm^{-1}) **-N-H str. - 3250, - Ar-C-H str. - 3047, -C-H str. - 2957, -C=O str. - 1715, -C=C str.- 1558, -NO_2 str.- 1328, -C-N str.- 1120, -C-F str.- 710.** 1H NMR (400 MHz DMSO) - **6.6-8.4** -17H (s) of Ar-H, **3.7** -1H of OH(s), 1.4-2H(s) of CH_2.

PS20 - IR (KBr, cm^{-1}) **N-H str. - 3250, - Ar-C-H str. - 3047, -C-H str. - 2957, -C=O str. - 1715, -C=C str.- 1558, -NO_2 str.- 1328, -C-N str.- 1120, -C-F str.- 715.**

Pharmacological evaluation –

Animals -

Albino rats of either sex weighing 100–150 g were obtained from, Laxmi Biofarms Pvt. Ltd. (CPCSEA. 127) Alephata, Pune, India. All the animals were housed under standard ambient conditions of temperature (22 ± 3°C) and relative humidity of 50 ± 5%. A 12:12 h light:dark cycle was maintained. All the animals were allowed to have free access to water and standard laboratory animal diet 24 h prior to pharmacological studies. All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC).

Anti-inflammatory activity [17] –

Albino rats of either sex (100-150 g) were divided into 3 different groups, containing six animals each. Individual weight of animals determined before the test substance is administered.

Animals were fasted for 12 h before experiment and only water was allowed. While the first group was a control one and received vehicle (Tween 80 in propylene glycol (10% v/v), 0.5 ml per rat), the second group received Indomethacin (50 mg/kg). The entire remaining group received the test compounds at the 50 mg/kg dose orally. All the suspensions for oral dose were prepared in the vehicle mentioned above and administered in a constant volume of 0.5 ml per rat.

One hr. after the administration of the test compound and Indomethacin 0.1 ml 1% w/v suspension of carrageenan was injected in to the subplanater of left paw of control and test animals. Immediately, the paw volume was measured using plethysmometer (initial paw volume) there after the paw volume was measured after one, three and five hour. The difference between initial and subsequent readings gave the edema volume for the corresponding time. Percentage inhibition was calculated.

The results for present study as shown in following **Table 2**.

Table 1: Physical properties of synthesized derivatives

COMPOUND CODE	R	R^1	MOLECULAR FORMULA	MOLECULAR WEIGHT GM/MOLE	MP ^0C	% YIELD	TLC BENZENE & ETHYL ACETATE (3:1)
PS1	CH3	H	C25H22N4O	394.46	143-145	67	0.540
PS2	CH3	OH	C25H22N4O2	410.46	158-160	74	0.411
PS3	CH3	M-NO2	C25H21N5O3	439.46	167-169	77	0.578
PS4	CH3	O-NO2	C25H21N5O3	439.46	162-164	68	0.511
PS5	H	H	C24H20N4O	380.44	129-131	73	0.578
PS6	H	OH	C24H20N4O2	396.44	144-166	61	0.402
PS7	H	M-NO2	C24H19N5O3	425.43	156-158	59	0.425
PS8	H	O-NO2	C24H19N5O3	425.43	153-155	78	0.341
PS9	OCH3	H	C25H22N4O2	410.46	145-147	82	0.491
PS10	OCH3	OH	C25H22N4O3	426.46	157-159	63	0.421
PS11	OCH3	M-NO2	C25H21N5O4	455.46	141-143	77	0.547
PS12	OCH3	O-NO2	C25H21N5O4	455.46	155-157	69	0.445
PS13	Cl	H	C24H19ClN4O	414.88	157-159	72	0.354
PS14	Cl	OH	C24H19ClN4O2	430.88	139-141	69	0.432
PS15	Cl	M-NO2	C24H18ClN5O3	459.88	152-154	70	0.453
PS16	Cl	O-NO2	C24H18ClN5O3	459.88	151-153	64	0.542
PS17	F	H	C24H19FN4O	398.43	141-143	64	0.359
PS18	F	OH	C24H19FN4O2	414.43	146-148	67	0.472
PS19	F	M-NO2	C24H18FN5O3	443.43	158-160	75	0.517
PS20	F	O-NO2	C24H18FN5O3	443.43	155-157	72	0.489

Table 2: Results of anti-inflammatory activity of synthesized derivatives

Group	Dose	Carrageenan Induced Paw oedema					
		1Hr		3 Hr		5 Hr	
		EV	EI	EV	EI	EV	EI
Control	Saline	0.87	--	0.98	--	0.78	--
Indomethacin	50 mg/kg	0.48	44.82	0.21***	78.57	0.32	58.97
PS1		0.62	28.73	0.38**	61.22	0.36	53.84
PS2		0.53	39.08	0.30***	69.38	0.35	55.21
PS3		0.71	18.39	0.52*	46.93	0.54	30.76
PS4		0.68	21.83	0.49*	50	0.45	42.3
PS5	50 mg/kg	0.6	31.03	0.34**	64.28	0.37	52.56
PS6		0.64	26.43	0.38**	61.22	0.4	48.71
PS7		0.69	20.68	0.48*	51.02	0.44	43.58
PS8		0.7	19.54	0.50*	48.97	0.54	30.76
PS9		0.65	25.28	0.39**	60.2	0.41	47.43
PS10		0.5	42.52	0.25***	74.48	0.35	55.12
PS11		0.65	25.28	0.38**	61.22	0.41	47.43
PS12		0.63	27.58	0.37**	62.24	0.4	48.71
PS13		0.72	17.24	0.50*	48.97	0.52	33.33
PS14		0.6	31.03	0.37**	62.24	0.41	47.43
PS15	50 mg/kg	0.69	20.68	0.49*	50	0.52	33.33
PS16		0.75	13.97	0.53*	45.91	0.54	30.76
PS17		0.73	16.09	0.52*	46.93	0.55	29.48
PS18		0.62	28.73	0.38**	61.22	0.36	53.48
PS19		0.75	13.97	0.53*	45.91	0.54	30.76
PS20		0.73	16.09	0.52*	46.93	0.55	29.48

Values are expressed as mean ± SEM (n=6); EV – Oedema volume, EI – Oedema inhibition
Significant at p<0.05, **highly significant at p<0.01,very highly significant at p<0.001**

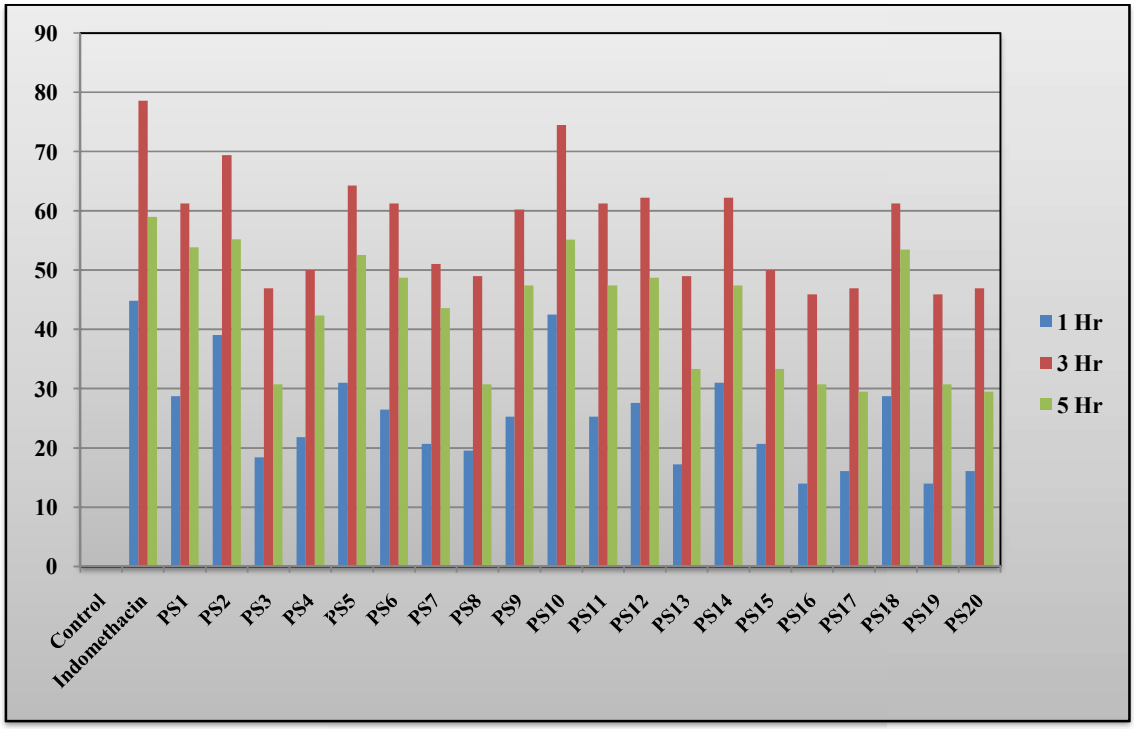


Figure 2: Graphical representation for anti-inflammatory activity

CONCLUSION

Twenty benzimidazole coupled pyrimidines derivatives were synthesized and screened for anti-inflammatory activity. Structures of all synthesized compounds were characterized by IR, ^{1H} NMR spectroscopy. It was interesting to note that all derivatives showed anti-inflammatory effect. Out of twenty derivatives PS2 and PS10 showed very highly significant fall in oedema. PS1, PS5, PS6, PS9, PS11, PS12, PS14, PS18 showed highly significant fall in oedema.

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