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Synthesis and evaluation of new pyrazolines of benzimidazole as potent analgesic and antiinflammatory agents

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ABSTRACT

A series of 7-chloro-2-[3-(1h-benzimidazol-2-yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole (VI) was synthesized by the action of 7-chloro-6-fluoro-2-hydrazino-1,3-benzothiazole (V) on chalcones in the presence of catalytic amount of glacial acetic acid and ethanol. The structures of the synthesized compounds have been established on the basis of their elemental analysis and spectral (IR,[1]HNMR) studies. Further they have been screened for their anti-inflammatory and analgesic activity.

Keywords: Benzimidazole, Benzthiazole, Pyrazoles, Antiinflammatory, Analgesic.

INTRODUCTION

Benzimidaole is bicyclic in nature which consist of the fusion of benzene and imidazole. Benzimidazole have broad spectrum of biological activities, antibacterial[1], antiparasitic[2], antihypertensive[3], analgesic and anti-inflammatory activity[4]. Pyrazoles are one of the most active classes of compounds possessing wide spectrum of biological activities[5,6,7]. Many of therapeutically useful compound such as phenylbutazone[8], oxiphenabutazone[9], celecoxib[10]. Several pyrazole derivatives have emerged as group of compound possessing broad spectrum of useful medicinal properties[11,12]. Benzothiazole derivatives have been studied extensively and found to have diverse chemical activity and broad spectrum of biological activities like antimicrobial[13], antitumor[14], anthelmintic[15], antileishmanial[16,17], anticonvulsant[18] and anti-inflammatory activity. Hence in continuation[19, 20, 21]work on benzothiazoles, it is thought worthwhile to synthesize some new pyrazolobenzimidazole by incorporating 2-hydrazinobenzothiazole moieties in a single molecular frame work.

MATERIALS AND METHODS

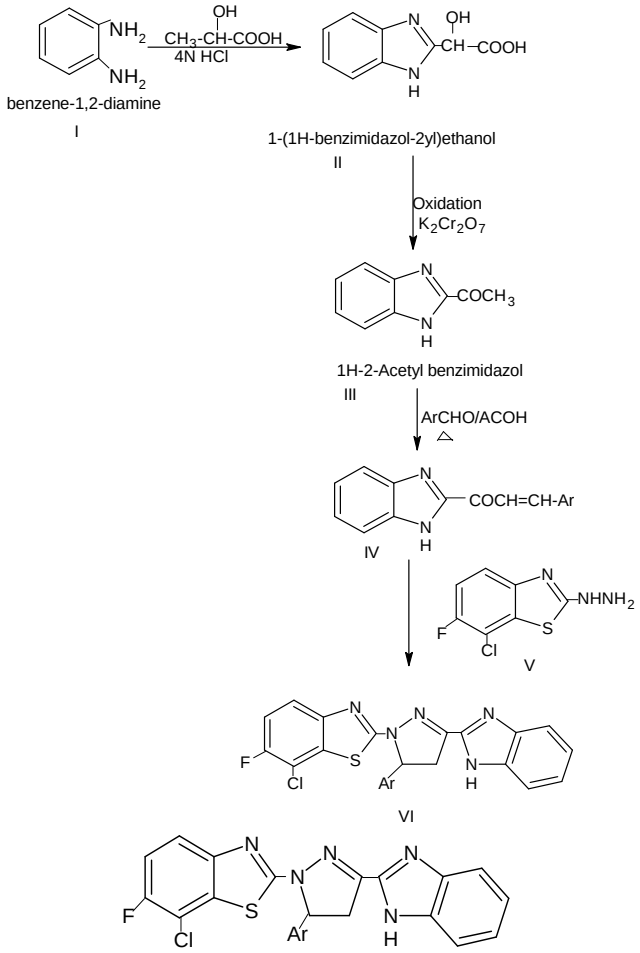
The identification and characterization of prepared compounds were carried out by thin layer chromatography, melting point, infrared spectroscopy and nuclear magnetic resonance spectroscopy. The melting point of organic compounds were determined by open capillary tube method which are uncorrected. The compounds were recorded on SHIMADZU FTIR- 8400S spectrophotometer by using KBr pallet technique.

Synthesis of 7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole (VI):
General procedure:
A mixture of 7-chloro-6-fluoro-2-hydrazino-1,3-benzothiazole (2.02gm,0.01 mol) and 1H-2- Acetyl benzimidazole chalcone (0.01mol) was refluxed for two hrs. in ethanol (20 ml) containing few drops of acetic acid, kept at room temperature for 4-5 hrs. Separated solid was filtered washed with water, dried and crystallized from ethanol. Physical and analytical particulars of 7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole are given.(m.p- 185^{0}C, % Yield- 65.79 %)It's IR spectrum (VI) PD5 in KBr showed peak

(absorption frequency in cm^{-1}) at 3050(-NH),(-CH_2),1623(C=N),1180(C-F) and (C-Cl) at743.It's ^{1}HNMR spectrum (VI) PD5 in $CDCl_3$ showed characteristic proton signal (in $^{\delta}$ ppm) at 3.101(S,6H,-N(CH_3)$_2$,6.91(d,3H,CH_2 and 1H OF H_5 of pyrazolines),7.0125-8.419(m,10H,Ar-H) and 8.432(S,1H,-N-H)

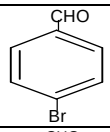
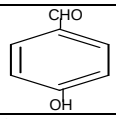
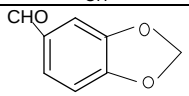
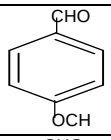
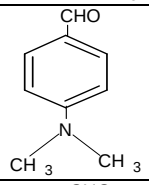
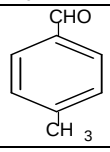
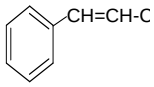
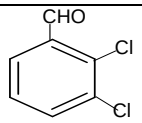
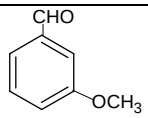
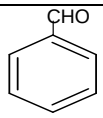
RESULTS AND DISCUSSION

The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in scheme. Treatment of o-phenylenediamine (I) with lactic acid in the presence of 4N HCl gave 2-hydroxyethyl-benzimidazole(II). Later on oxidation with acidic dichromate gave 2-acetylbenz-imidazole(III).Treatment of 2-acetylbenzimidazole on aromatic aldehydes in the presence of NaOH gave chalcones (IV). Condensation of chalcone with 7-chloro-6-fluoro-2-hydrazino-1,3-benzothiazole in presence of catalytic amount of ethanol and glacial acetic acid gave7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole(VI). The structures of the synthesized compounds have been established on the basis of their elemental analysis and spectral (IR , ^{1}HNMR Spectroscopy) studies. Amongst the compound tested for anti-inflammatory and analgesic activity some compound exhibited promising activity and some exhibited significant activity. Physical and analytical data of synthesized compounds are presented in TABLE NO.1



Physical and analytical data of 7-Chloro-2-[3-(1H-benzimidazol-2-yl)-5-aryl-4,5-dihydro-1H-pyrazole-1-yl]-6-fluoro-1,3-benzothiazole.

Table No. 1

Sr. No.	Compound code	Ar	Melting point	Yield %	Molecular formula	Molecular weight	C%	H%	O %
1	PB8		190^{0}C	62	$C_{23}H_{13}N_5SFClBr$	522	52.8	2.49	13.40
2	PH10		191^{0}C	60.50	$C_{23}H_{15}ON_5SClF$	384	71.8	3.9	18.22
3	PP9		199^{0}C	69.32	$C_{23}H_{12}O_2N_5SClF$	486	56.7	2.46	14.40
4	PA3		180^{0}C	61.20	$C_{24}H_{16}ON_5SFCl$	473	60.8	3.38	14.79
5	PD5		185^{0}C	65.79	$C_{25}H_{19}N_6SClF$	486	61.7	3.90	14.81
6	PT7		195^{0}C	68.28	$C_{24}H_{13}SClFN_5$	458	62.8	2.83	15.28
7	PC4		192^{0}C	66.82	$C_{25}H_{16}N_5SClF$	470	63.8	2.97	14.89
8	PD6		200^{0}C	67.23	$C_{23}H_{12}N_5Cl_3FS$	513	53.8	2.33	13.64
9	PM1		192^{0}C	66.14	$C_{24}H_{16}OSFClN_5$	474	60.7	3.37	14.76
10	PB2		195^{0}C	62.23	$C_{23}H_{12}N_5SClF$	444	62.1	2.70	15.76

BIOLOGICAL EVALUATION

Anti-inflammatory activity

Synthesized compounds were screened for anti-inflammatory activity(In vitro) by using inhibition of albumin denaturation technique[22].Diclofenac sodium was used as standard. The percentage of inhibition was calculated and compared with standard. The results are presented in TABLE NO 2.Some selected compounds were screened for anti-inflammatory activity(In Vivo) by Carrageenan induced rat paw edema method[23].Diclofenac sodium (0.1% per ml) at dose of 50mg/kg body weight served as standard. Statistical analysis was carried out to determine the percentage protection and the results are presented in TABLE NO 3.

Analgesic activity-

The synthesized compounds were screened for Analgesic activity by Acetic acid-induced Writhing in mice[24] method. Aspirin I.P.at dose of 100 mg/kg body weight served as standard.% protection against writhing movement was taken as an index of analgesic and it was calculated. The results are presented in TABLE NO.4

Table No. 2 give information about Anti-inflammatory Activity (In vitro) of Synthesized compounds.

Table no.2

Compound	Mean absorbance ± S.D*.	% inhibition of denaturation
PD5	0.1980±0.024	21.26
PB2	0.3547±0.004	38.18
PD6	0.3180±0.001	38.18
PP9	0.3535±0.004	79.14
PC4	0.2221±0.006	61.16
PH10	0.3191±0.009	12.58
PM1	0.3547±0.004	44.09
PA3	0.2736±0.046	23.73
PD6	0.2626±0.004	60.60
PT7	0.2401±0.001	78.53
Control	0.1980±0.024	
Standard	0.3630±0.003	83.33

S.D. = Standard deviation (Average of three determination)*

Table No.3 gave information about Anti-inflammatory activity (In Vivo) of synthesized compounds PP9,PC4,PD6,PT7,PM1.

Table No.3

Sr.No.	Compounds	Dose mg/Kg	Mean difference in paw volume ± SE after 3 hrs.(ml)	% of inhibition
1	Control	50	3.48±0.045	
2	Standard(Diclofenac sodium)	50	1.02±0.016	70.68
3	PP9	50	2.19±0.016	41.37
4	PC4	50	2.12±0.076	37.06
5	PD6	50	2.04±0.087	
6	PT7	50	2.06±0.054	
7	PM1	50	2.044±0.058	

Table No.4 gave information of Analgesic activity of synthesized compounds.

Table No.4

Compound	Dose of Compound	No. of wriths per 30 minutes	% Inhibition
Control	0.3 ml normal saline	65±1.34	
PD5	50 mg/kg b.w	25.1±2.3	55.38
	100 mg/kg b.w	28±1.40	59.69
	200 mg/kg b.w	26.2±4.9	69.4
PB2	50 mg/kg b.w	29±1.41	56.92
	100mg/kg b.w	26.2±4.9	63.07
	200mg/kg b.w	24.4±3.1	61.53
PD6	50 mg/kg b.w	28±1.4	59.69
	100mg/kg b.w	24.2±2.1	61.53
	200mg/kg b.w	25.1±2.1	56.92
PP9	50 mg/kg b.w	24.4±3.1	62.4
	100mg/kg b.w	29±1.41	55.38
	200mg/kg b.w	28±1.40	56.92
PC4	50 mg/kg b.w	29.0±1.41	61.53
	100mg/kg b.w	26.2±4.9	56.92
	200mg/kg b.w	24.4±3.1	59.69
PH10	50 mg/kg b.w	28.2±4.9	55.38
	100mg/kg b.w	26.2±4.9	59.69
	200mg/kg b.w	24.4±3.1	62.4
PM1	50 mg/kg b.w	28±1.40	56.92
	100mg/kg b.w	25.1±2.3	63.07
	200mg/kg b.w	28±1.41	61.53
PA3	50 mg/kg b.w	24.4±3.1	62.4
	100mg/kg b.w	29±1.41	55.38
	200mg/kg b.w	28±1,40	56.92
PB8	50 mg/kg b.w	26.12±3.9	59.69
	100mg/kg b.w	28±1.41	56.92
	200mg/kg b.w	25.1±2.3	61.53
PT7	50 mg/kg b.w	29±1.41	55.38
	100mg/kg b.w	26.2±4.9	59.69
	200mg/kg b.w	24.4±3.1	62.4
Aspirin	100mg/kgb.w	30.2±1.8	53.53

CONCLUSION

Ten new compounds of 7-chloro-2-[3-(1H-benzimidazol-2-yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazoless(VI) were synthesized. All the synthesized compounds were characterized by IR,^{1}HNMR spectral properties. The synthesized compounds were screened for anti-inflammatory and analgesic activity. The results presented on above tables reveals that compounds show moderate to significant anti-inflammatory and analgesic activity.

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