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Synthesis and Pharmacological Evaluation of Some New Mannich Bases of 2-Substituted 4, 5-Diphenyl Imidazole Derivatives

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ABSTRACT

Mannich bases of 2-substituted 4,5-diphenyl imidazole derivatives have been synthesized. IR, 1H-NMR, Mass spectra, and elemental analysis, characterized the structures of all synthesized derivatives. The synthesized derivatives were also evaluated for their analgesic activity using Eddy's hot plate method and anti-inflammatory activity using formalin-induced paw edema method. Amongst them compounds **A_2, A_7, A_{13}, A_{15}**, and **A_{18}** have shown promising analgesic and compounds **A_2, A_3, A_8, A_{16}**, and **A_{18}** have shown significant anti-inflammatory activity.

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INTRODUCTION:

Many disease conditions are allied with pain and inflammation. Medical researchers have developed widely diverse compounds for treating pain, including some synthetic opioids that produce the analgesic effect that is much less likely to induce dependency. It is important to note that some pain is productive, acting as warning or injury and a guide to diagnosis and treatment; thus it is also important to realize that while analgesics relieve symptoms, they do not affect the underlying cause[1-2]. Inflammation is not a synonym for infection. Even in cases where inflammation is caused by infection, the two are not synonymous: infection is caused by exogenous pathogens, while inflammation is one of the responses of the organism to the pathogen. In the absence of inflammation, wounds and infections would never heal and progressive destruction of the tissue would compromise the survival of the organism. It is for that reason that inflammation is normally closely regulated by the body[3]. Among the all heterocyclic compounds discovered so far, nitrogen-containing heterocycle imidazole is the most important class of compounds in pharmaceutical industries. The study of the chemistry of compounds containing heteroatoms i,e. nitrogen has been and continues to be one of the most imperative, valuable and attractive areas of heterocyclic chemistry. As these moieties have remarkable biological and pharmacological activities such as antimicrobial[4], anticandida[5], fungicidal[6], analgesic[7], anti-inflammatory[8], antiepileptic[9], antileishmanial[10], and anthelmintic[11] activities. Subsequent to this and an extension of research on imidazoles, we attempted to synthesize new mannich bases of imidazoles in relation to molecular modification to illustrate certain pharmacological activity.

MATERIALS AND METHODS:

All the chemicals used in the synthesis of designed compounds were of synthetic grade and they were procured from Loba, High media and E. Merck. Thin layer chromatographic method was used for monitoring of progress of reactions and product formation. Thin layer chromatography for compounds was performed using silica gel-G on a glass plate in different solvents. Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker avance II 400 NMR Spectrometer, in DMSO-d_6 solvents using TMS as an internal standard. Mass spectra were recorded on Waters, Q-TOF Micromass. Elemental analysis was recorded on Perkin-Elmer Model 2400. Combustion analyses were found to be within the limits of permissible errors (±4).

Albino mice/rats were used for experimental purpose. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Sharadchandra Pawar College of Pharmacy, Otur, Pune, (IAEC, Approval no. 1197/PO/c/08/CPCSEA) before evaluation.

Analgesic activity[12]

The analgesic activity of synthesized compounds was evaluated by using hot plate method and the instrument used for the purpose was Eddy's hot plate. The Albino mice were used for the activity of either sex weighing 20-25 gm. The mice were divided into groups with six mice each. The one group for control, one for standard and rest of the groups were for the synthesized compounds. The standard Ibuprofen and test compounds were administered in mice were 20 and 50 mg/kg respectively by oral route using oral feeding tuberculin syringe. The stock suspensions of standard and synthesized compounds were prepared in a concentration of 10 mg/ml of 2% w/v CMC in distilled water. The basal reaction time, for jump response, when animals placed on a hot plate (maintained at constant temperature of 55±1.0 ºC) was observed and reaction time of animals on a hot plate at 0, 30, 60 and 90 minutes, after administration of the test and standard compounds, was noted. A latency period of 15 seconds was defined as complete analgesia as cut off time to avoid injuries to the paws. The formula used for calculating the percentage inhibition was-

$$\text{Percentage inhibition} = \frac{(\text{Post drug latency}) - (\text{Pre-drug latency})}{(\text{Cut off time} - \text{Pre-drug latency})} \times 100 \quad \text{--- (1)}$$

Anti-inflammatory Activity[13,14]

The synthesized compounds were screened for anti-inflammatory activity by using the formalin-induced paw edema method on albino rats (Wister strain) of either sex weighing 180-200 gm. The rats were divided into groups; each consists of six animals. One group for control, one for standard and rest of the groups were for synthesized compounds. The standard drug Diclofenac sodium (20 mg/kg) was administered for comparison. The dose of synthesized compounds administered in animals was 50 mg/kg oral route using oral feeding tuberculin syringe. The stock suspensions of standard and synthesized compounds were prepared in a concentration of 10 mg/ml of 2% w/v carboxymethyl cellulose (CMC) in distilled water. The control group was treated with vehicle CMC. After 30 minutes, the animals were injected with 0.1 ml of formalin in the sub-plantar region of left hind paw of rats. The paw volume was measured with the help of digital plethysmometer after 1 hr, 3 hr

and 5 hr of formalin injection. The formula used for calculating the percentage inhibition of edema was-

$$\text{Percentage Inhibition: } (Vc\text{-}Vt/Vc) \times 100 \qquad \text{--- (2)}$$

Where Vc represents the mean increase in paw volume in the control group of rats.

Vt represents the mean increase in paw volume in rats treated with test compounds.

Statistical Analysis

Data were represented as arithmetic Mean±SEM. Statistical analysis was performed by One Way Variance (ANOVA) followed by Dunnet's test. "p" value of less than 0.05 was considered as statistically significant.

Experimental:

General procedure for preparation of 2-substituted 4,5-diphenyl imidazoles[15]:

A mixture of benzil (25 mmoles), substituted benzaldehyde (25 mmol) and ammonium acetate 10gm were dissolved in glacial acetic acid and then refluxed for 3-5 hrs. After refluxing, the reaction mixture was kept overnight and filtered to remove any precipitate that may be present. Water was then added to filtrate & precipitate formed was collected. The filtrate was neutralized with ammonium hydroxide; the second crop of solid was collected. The two crops of precipitate were combined, dried and recrystallized from suitable solvents.

General procedure for preparation of mannich bases of 2-substituted 4,5-diphenyl imidazoles (A_1-A_{20})[16]:

A mixture of 0.001 moles of 2-substituted 4,5-diphenyl imidazoles & 0.001 moles of different aromatic amines and 0.001 moles of formaldehyde dissolved in 25 ml ethanol & refluxed for 3-5 hrs. The progress of the reaction was monitored by TLC using Benzene: Chloroform (1:4). The resultant mixture was poured on ice cold water and separated solid product **(A_1-A_{20})** was obtained, recrystallized from suitable solvents. A slight change in reaction time of each compound, completion of the reaction was confirmed by TLC.

A_1: 1-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl) piperidine

IR (KBr) cm^{-1}: 3196.08 (C-H Ar. Str.), 2970.70 (aliphatic C-H), 1501.11 (C=C Ar. Str.), 1451.39 (C=N str.) ^{1}H-NMR δ ppm: 7.24-8.11 (15H, m, Ar-H), 3.65 (2H of CH_2, piperidine), 2.55 (2H of CH_2, methylene) Mass M/Z: M^+ 388

A_2: 4-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)morpholine

IR (KBr) cm^{-1}: 3040.70 (C-H Ar. Str.), 2830.87 (aliphatic C-H), 1511.11 (C=C Ar, str.), 1471.04 (C=N str.) ^{1}H-NMR δ ppm: 7.26-8.11 (15H, m, Ar-H), 3.32 (2H of CH_2, Morpholine), 2.54-2.55 (2H of CH_2, methylene)

A_3: 1-methyl-4-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)piperazine

IR (KBr) cm^{-1}: 3198.91 (C-H Ar. str.), 2975.11 (aliphatic C-H), 1500.66 (C=C Ar. Str.), 1452.12 (C=N str.) Mass M/Z: M^+ 403

A_4: N'-((2,4,5-triphenyl-1H-imidazol-1-yl)methyl)isonicotinohydrazide

IR (KBr) cm^{-1}: 3430.20 (N-H str.), 3041.60 (C-H Ar. Str.), 2966.6 (aliphatic C-H), 1742.9 (C=O str.), 1599.0 (C=C Ar. Str.), 1461.0 (C=N str.) ^{1}H-NMR δ ppm: 6.93-8.03 (18H, m, Ar-H), 8.05 (1H of NH), 2.54-2.55 (2H of CH_2, methylene)

A_5: 4-((2,4,5-triphenyl-1H-imidazol-1-yl)methylamino)benzenesulfonamide

IR (KBr) cm^{-1}: 3426.4 (N-H str.), 3028.7 (C-H Ar. Str.), 2925.5 (aliphatic C-H), 1602.2 (C=C Ar. Str.), 1440.4 (C=N str.)

A_6: 4-(4,5-diphenyl-1-(piperine-1-yl methyl)-1H-imidazol-2-yl)phenol

IR (KBr) cm^{-1}: 3432.6 (O-H str.), 3062.0 (C-H Ar. str.), 2926.0 (aliphatic C-H), 1605.2 (C=C Ar. str.), 1485.4 (C=N str.) ^{1}H-NMR δ ppm: 9.51 (s, 1H, OH), 6.82-7.95 (14H, m, Ar-H), 3.35 (2H of CH_2, Piperidine), 2.55 (2H of CH_2, methylene)

A_7: 4-(-morpholinomethyl)-4,5-diphenyl -1H-imidazol-2-yl)phenol

IR (KBr) cm^{-1}: 3429.4 (O-H str.), 3067.3 (C-H Ar. str.), 2960.6 (aliphatic C-H), 1606.4 (C=C Ar. str.), 1445.4 (C=N str.)

A_8: 4-(1-((4-methylpiperazin-1-yl)-4,5-diphenyl-1H-imidazol-2-yl)phenol

IR (KBr) cm^{-1}: 3429.4 (O-H str.), 3067.3 (C-H Ar. str.), 2960.6 (aliphatic C-H), 1606.4 (C=C Ar. str.), 1445.4 (C=N str.)

A_9: N'-((2-(4-hydroxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)isonicotino hydrazide

IR (KBr) cm^{-1}: 3353.21 (O-H str.), 3208.33 (N-H str.), 3048.19 (C-H Ar. str.), 2921.63 (aliphatic C-H), 1687.91 (C=O str.), 1500.60 (C=C Ar. str.), 1452.12 (C=N str.)

A_{10}: 4-((2-(4-hydroxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)benzenesulfonamide

IR (KBr) cm^{-1}: 3432.8 (O-H str.), 3175.8 (N-H str.), 3058.0 (C-H Ar. str.), 2928.3 (aliphatic C-H), 1610.3 (C=C Ar. str.), 1464.0 (C=N str.)

A_{11}: 4-(4,5-diphenyl-1-(piperidin-1-yl methyl)-1H-imidazol-2-yl)-2-methoxyphenol

IR (KBr) cm^{-1}: 3301.17 (O-H Str.), 3030.32 (Ar C-H Str), 2929.34 (aliphatic C-H), 1604.96 (Ar C=C Str.), 1456.25 (C=N Str.) Mass M/Z: M^+ 437

A_{12}: 2-methoxy-4-(1-(morpholine methyl)-4,5-diphenyl-1H-imidazol-2-yl)phenol

IR (KBr) cm^{-1}: 3490. 36 (O-H Str.), 3062.01 (Ar C-H Str), 2931.31 (aliphatic C-H), 1610.87 (Ar C=C Str.), 1449.68 (C=N Str.)

A_{13}: 2-methoxy-4-(1((4-methylpiperazin-1-yl)methyl)-4,5-diphenyl-1H-imidazol-2-yl)phenol

IR (KBr) cm^{-1}: 3377.69 (O-H Str.), 3060.04 (Ar C-H Str), 2824.24 (aliphatic C-H), 1600.36 (Ar C=C Str.), 1447.85 (C=N Str.)

A_{14}: N' ((2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)isonicotino hydrazide

IR (KBr) cm^{-1}: 3510.59 (O-H Str.), 3378.21 (N-H Str.), 3032.84 (Ar C-H Str), 2917.08 (aliphatic C-H), 1604.88 (C=O str.), 1499.60 (Ar C=C Str.), 1451.32 (C=N Str.) ^{1}H-NMR δ ppm: 8.99 (s, 1H, OH), 6.86-7.67 (17H, m, Ar-H), 7.92 (1H of NH), 3.92 (3H of CH_3), 2.55 (2H of CH_2, methylene)

A_{15}: 4-((2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)methylamino) benzene sulfonamide

IR (KBr) cm^{-1}: 3511.5 (O-H Str.), 2925.3 (Ar C-H Str), 2854.8 (aliphatic C-H), 1607.3 (C=O str.), 1498.5 (Ar C=C Str.), 1452.3 (C=N Str.) ^{1}H-NMR δ ppm: 9.06 (s,1H, OH), 6.88-8.01 (17H, m, Ar-H), 7.55 (1H of NH), 3.91 (3H of CH_3), 2.53 (2H of CH_2, methylene)

A_{16}: 1-((2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)piperidine

IR (KBr) cm^{-1}: 3062.1 (C-H Ar. Str.), 2925.2 (aliphatic C-H), 1505.8 (Ar.C=C Str.), 1450.9 (C=N str.), 773.0 (C-Cl) ^{1}H-NMR δ ppm: 6.82-7.92 (14H, m, Ar-H), 3.54 (2H of CH_2, piperidine), 2.54-2.55 (2H of CH_2, methylene)

A_{17}: 4-((2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl) methyl)morpholine

IR (KBr) cm^{-1}: 3044.04 (C-H Ar. str.), 2925.53 (aliphatic C-H), 1592.98 (C=C Ar. str.), 1452.75 (C=N str.), 768.31 (C-Cl)

A_{18}: 1-((2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl) methyl)-4-methyl piperazine

IR (KBr) cm^{-1}: 3032.84 (C-H Ar. str.), 2943.79 (aliphatic C-H), 1604.88 (C=C Ar. str.), 1451.32 (C=N str.), 770.87 (C-Cl) ^{1}H-NMR δ ppm: 7.28-8.11 (14H, m, Ar-H), 3.32 (2H of CH_2 Piperazine), 2.55 (2H of CH_2, methylene)

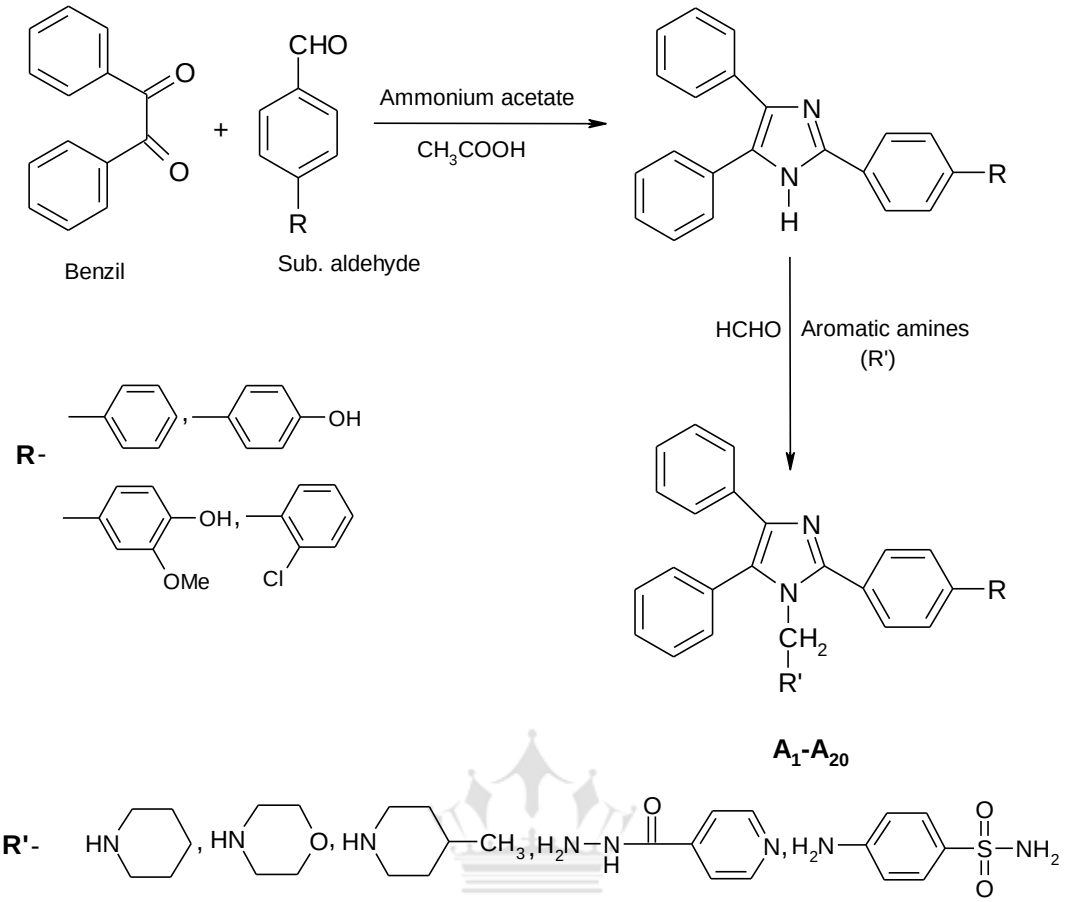
A_{19}: N'-((2-(2-chlorophenyl)-4,5,-diphenyl-1H-imidazol-1-yl)methyl)isonicotinohydrazide

IR (KBr) cm^{-1}: 3419.9 (N-H str.), 3058.0 (C-H Ar. str.), 2927.4 (aliphatic C-H), 1603.52 (C=C Ar. str.), 1729.8 (C=O str.), 1450.2 (C=N str.), 767.9 (C-Cl)

A_{20}: 4-((2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)methylamino)benzene sulfonamide

IR (KBr) cm^{-1}: 3431.9 (N-H str.), 3033.7 (C-H Ar. str.), 2921.2 (aliphatic C-H), 1601.1 (C=C Ar. str.), 1445.4 (C=N str.), 767.5 (C-Cl) ^{1}H-NMR δ ppm: 6.60- 8.04 (18H, m, Ar-H), 7.59 (s, 1H of NH), 3.83 (2H of CH_2, methylene)

SCHEME



RESULTS:

Table No. 1: Physical and Analytical Data of Synthesized compounds (A_1-A_{20})

Comp.	Mol. Formula	Mol. Wt.	M.P. ˚C	Rf Value	% Yield	Elemental Analysis Calcd. (Observed)		
						C	H	N
A_1	$C_{27}H_{27}N_3$	393	252-254	0.53	76	82.41 (82.45)	6.92 (6.95)	10.68 (10.64)
A_2	$C_{26}H_{25}N_3O$	395	263-265	0.63	65	78.96 (78.99)	6.37 (6.41)	10.62 (10.65)
A_3	$C_{27}H_{28}N_4$	408	274-276	0.39	70	79.38 (79.41)	6.91 (6.94)	13.71 (13.74)
A_4	$C_{28}H_{23}N_5O$	445	216-218	0.46	72	75.49 (75.52)	5.20 (5.24)	15.72 (15.75)
A_5	$C_{28}H_{24}N_4O_2S$	480	197-199	0.58	57	69.98 (69.94)	5.03 (5.07)	11.66 (11.70)
A_6	$C_{27}H_{27}N_3O$	409	201-203	0.71	62	79.19 (79.22)	6.65 (6.67)	10.26 (10.30)
A_7	$C_{26}H_{25}N_3O_2$	411	230-233	0.54	66	75.89 (75.93)	6.12 (6.16)	10.21 (10.24)
A_8	$C_{27}H_{28}N_4O$	424	242-245	0.62	68	76.39 (76.42)	6.65 (6.68)	13.20 (13.23)
A_9	$C_{28}H_{23}N_5O_2$	461	231-234	0.48	64	72.87 (72.91)	5.02 (5.06)	15.17 (15.21)
A_{10}	$C_{28}H_{24}N_4O_3S$	496	257-259	0.35	53	67.72 (67.75)	4.87 (4.89)	11.28 (11.32)
A_{11}	$C_{28}H_{29}N_3O_2$	439	243-245	0.72	74	76.51 (76.54)	6.65 (6.61)	9.56 (9.53)
A_{12}	$C_{27}H_{27}N_3O_3$	441	224-226	0.67	58	73.45 (73.41)	6.16 (6.20)	9.52 (9.47)
A_{13}	$C_{28}H_{30}N_4O_2$	454	262-264	0.61	67	73.98 (73.95)	6.65 (6.70)	12.33 (12.36)
A_{14}	$C_{29}H_{25}N_5O_3$	491	238-241	0.58	52	70.86 (70.89)	5.13 (5.17)	14.25 (14.21)
A_{15}	$C_{29}H_{26}N_4O_4S$	526	218-221	0.35	63	66.14 (66.17)	4.98 (4.99)	10.64 (10.67)
A_{16}	$C_{27}H_{26}ClN_3$	427	230-233	0.45	60	75.77 (75.75)	6.12 (6.16)	9.82 (9.84)
A_{17}	$C_{26}H_{24}ClN_3O$	429	247-249	0.52	55	72.63 (72.66)	5.63 (5.67)	9.77 (9.80)
A_{18}	$C_{27}H_{27}ClN_4$	442	268-271	0.65	69	73.21 (73.25)	6.14 (6.17)	12.65 (12.68)
A_{19}	$C_{28}H_{22}ClN_5O$	479	226-228	0.42	65	70.07 (70.11)	4.62 (4.65)	14.59 (14.63)
A_{20}	$C_{28}H_{23}ClN_4O_2S$	514	259-261	0.49	57	65.30 (65.34)	4.50 (4.48)	10.88 (10.91)

Table No. 2: Analgesic activity of synthesized compounds (A_1-A_{20})

Comp.	Basal Time in seconds (Mean±SEM)	Reaction time (s) after drug administration			Percentage Inhibition
		30 min	60 min	90 min	
Control	4.78±0.148	4.79±0.159	4.80±0.151	4.79±0.154	00.00
Std	4.73±0.177	7.71±0.142***	8.31±0.189***	10.90±0.122***	**60.07**
A_1	4.48±0.111	5.33±0.097^{ns}	6.69±0.189***	6.93 ±0.184***	23.28
A_2	4.45±0.139	5.70±0.148***	6.80±0.101***	7.97±0.110***	**33.55**
A_3	4.59±0.126	6.61±0.162***	7.11±0.130***	7.15±0.097***	24.59
A_4	4.55±0.107	6.33±0.221***	6.83±0.190***	7.19±0.115***	25.26
A_5	4.53±0.189	6.48±0.153**	6.97±0.155***	6.99±0.100***	23.49
A_6	4.64±0.119	6.20±0.097***	6.88±0.163***	7.43±0.133***	26.93
A_7	4.42±0.126	5.74±0.246***	6.60±0.127***	8.06±0.158***	**34.40**
A_8	4.49±0.159	6.13±0.104***	7.05±0.110***	7.23±0.152***	26.07
A_9	4.44±0.119	5.30±0.176 ^{ns}	6.70±0.192***	7.26±0.103***	26.70
A_{10}	4.69±0.125	6.35±0.182***	6.92±0.118***	7.48±0.163***	27.06
A_{11}	4.60±0.146	6.28±0.157***	6.61±0.195***	7.76±0.161***	30.38
A_{12}	4.54±0.153	6.07±0.148***	6.79±0.143***	7.32±0.122***	26.57
A_{13}	4.38±0.097	5.82±0.170***	6.53±0.168***	7.91±0.141***	**33.23**
A_{14}	4.57±0.115	5.96±0.212***	6.94±0.110***	7.54±0.090***	28.47
A_{15}	4.67±0.147	6.58±0.133***	7.08±0.119***	7.99±0.172***	**32.13**
A_{16}	4.46±0.118	5.79±0.142***	6.73±0.123***	7.10±0.120***	25.04
A_{17}	4.74±0.125	6.50±0.087***	7.20±0.103***	7.56±0.156***	27.84
A_{18}	4.51±0.147	5.43±0.149*	6.42±0.164***	8.12±0.114***	**34.41**
A_{19}	4.56±0.206	5.89±0.220***	6.77±0.114***	7.08 ±0.168***	24.13
A_{20}	4.61±0.170	5.57±0.089**	6.59±0.158***	7.53±0.126***	28.10

Mean±SEM (n=6); *** P<0.001; ** P<0.01; * P<0.05; ns- Non-significant

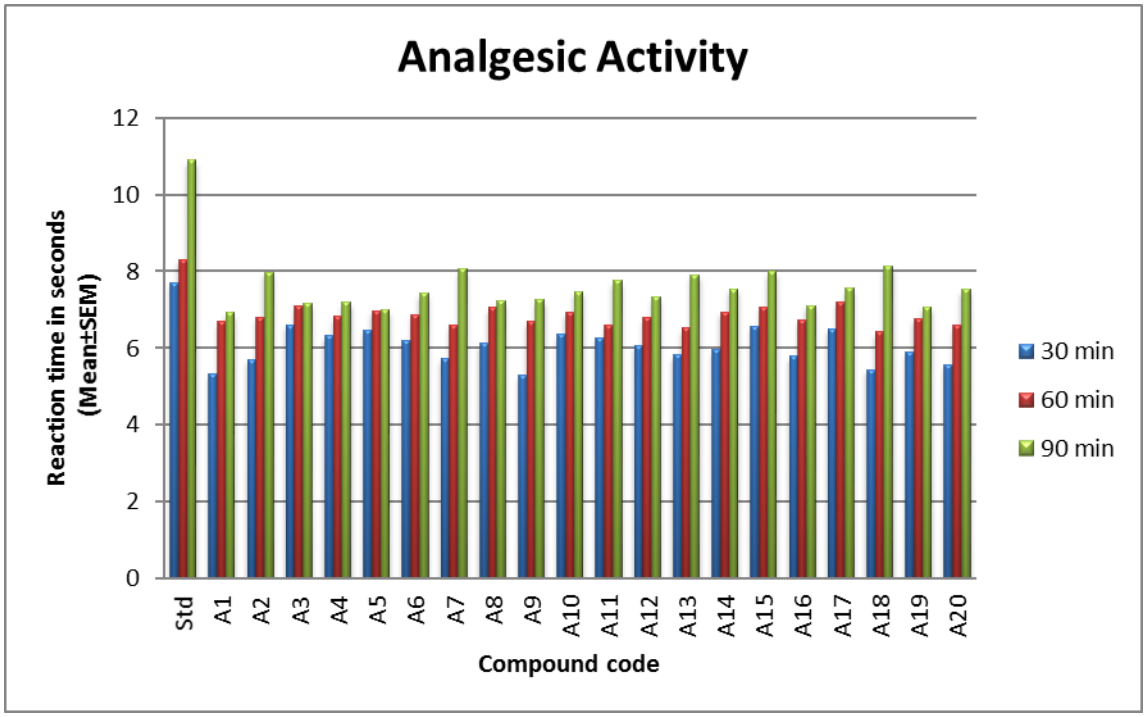


Figure 1: Graphical Representation of Analgesic activity (A_1-A_{20})

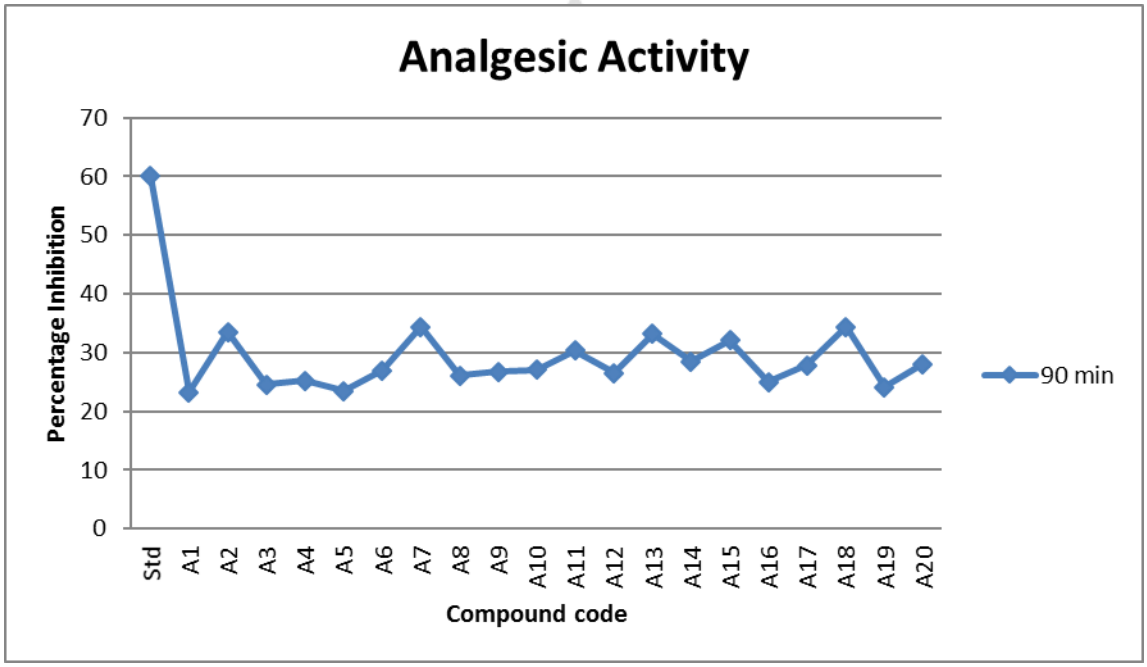


Figure 2: Percentage Inhibition (after 90 min) of Analgesic activity (A_1-A_{20})

Table No. 3: Anti-inflammatory activity of synthesized compounds (A_1-A_{20})

Comp.	Change in Paw Volume in ml (Mean ± SEM)			Percentage inhibition
	1 hr	3 hr	5 hr	
Control	0.768±0.006	1.237±0.006	1.642±0.005	00.00
Std	0.537 ±0.005***	0.681±0.006***	0.780±0.006***	**52.49**
A_1	0.682±0.004***	1.035±0.004***	1.282 ± 0.003***	21.92
A_2	0.672±0.003***	0.991±0.007***	1.182± 0.006***	**28.02**
A_3	0.697±0.004***	1.092±0.004***	1.137± 0.004***	**30.75**
A_4	0.713±0.007***	1.108±0.006***	1.502± 0.006***	08.52
A_5	0.680±0.004***	1.050±0.003***	1.321± 0.006***	19.54
A_6	0.702±0.006***	1.097±0.005***	1.251± 0.005***	23.81
A_7	0.695±0.005***	1.117±0.004***	1.416± 0.004***	13.76
A_8	0.685±0.005***	1.010±0.007***	1.128± 0.005***	**31.30**
A_9	0.683±0.005***	1.113±0.008***	1.364± 0.007***	16.93
A_{10}	0.692±0.008***	1.083±0.006***	1.436± 0.004***	12.54
A_{11}	0.705±0.004***	1.060±0.005***	1.348± 0.007***	17.90
A_{12}	0.677±0.005***	0.970±0.003***	1.232± 0.005***	24.97
A_{13}	0.710±0.006***	1.092±0.004***	1.266± 0.006***	22.89
A_{14}	0.715±0.008***	1.080±0.005***	1.401± 0.004***	14.67
A_{15}	0.722±0.006***	1.123±0.005***	1.473± 0.006***	10.29
A_{16}	0.667±0.007***	0.893±0.006***	1.110± 0.003***	**32.40**
A_{17}	0.718±0.004***	1.055±0.004***	1.370± 0.006***	16.56
A_{18}	0.707 ±0.004***	1.115±0.007***	1.132± 0.004***	**31.06**
A_{19}	0.690±0.005***	1.040±0.005***	1.376± 0.007***	16.20
A_{20}	0.693±0.006***	1.062±0.004***	1.392±0.004***	15.22

Mean ± SEM (n=6); *** P<0.001; ** P<0.01; * P<0.05

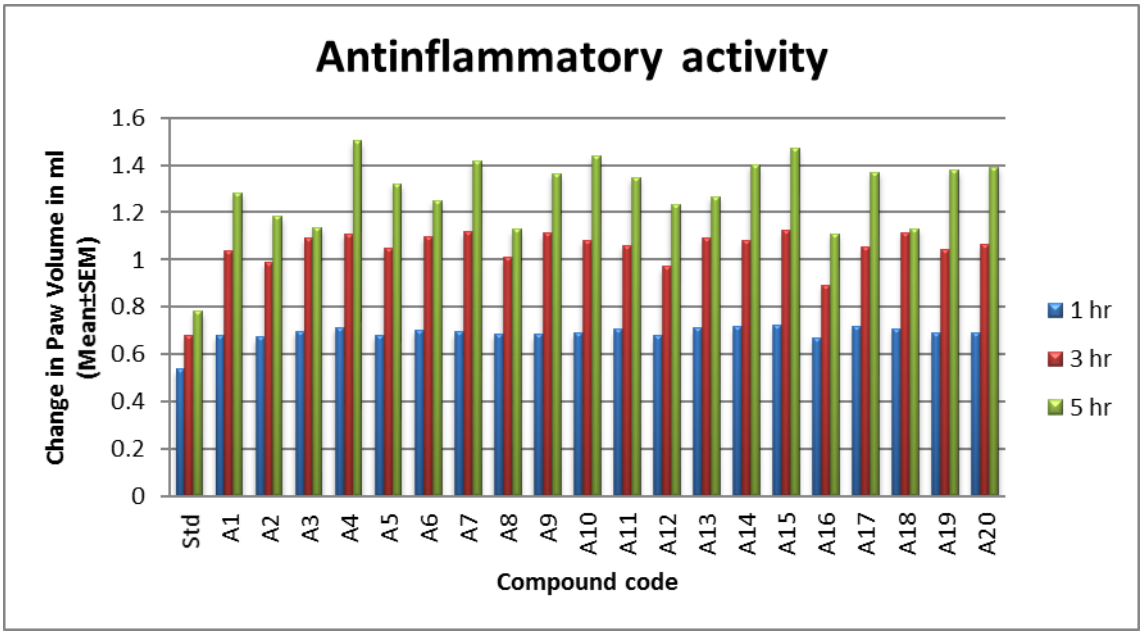


Figure 3: Graphical Representation of Anti-inflammatory activity (A_1-A_{20})

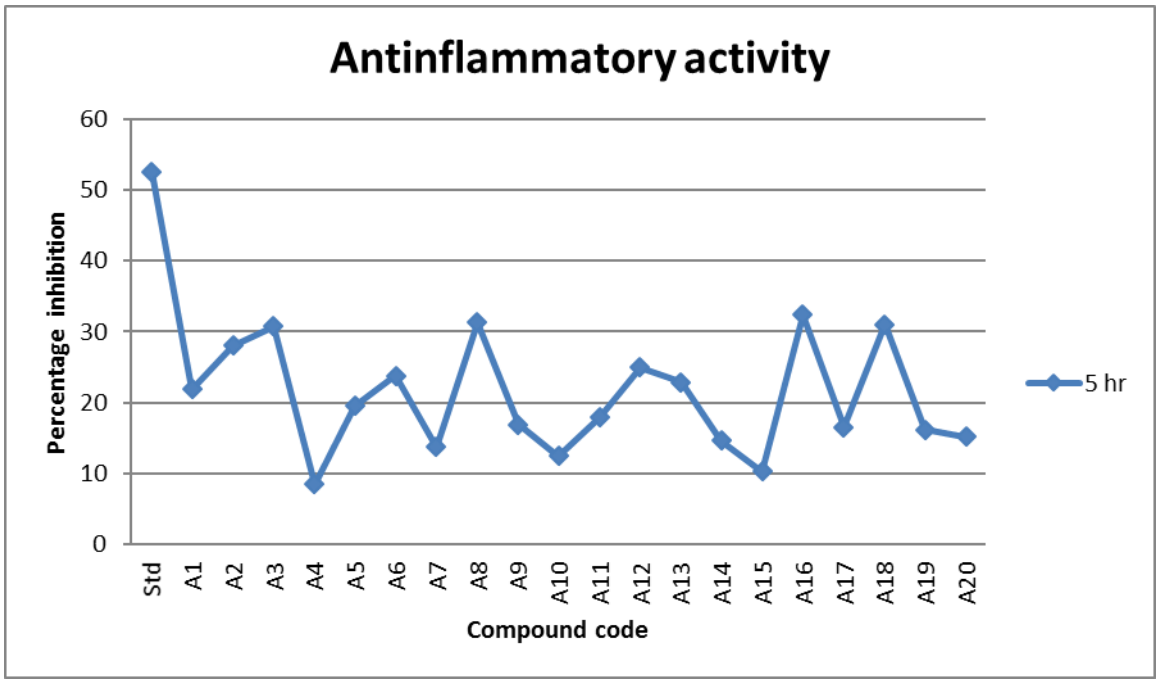


Figure 4: Percentage Inhibition (after 5 hr) of Anti-inflammatory activity (A_1-A_{20})

DISCUSSION:

Mannich bases of 2-substituted 4,5-diphenyl imidazoles (A_1-A_{20}) were synthesized by reacting equimolar quantity of benzil, substituted benzaldehyde and ammonium acetate to form 2-substituted 4,5-disubstituted imidazoles, which were then reacted with different aromatic amines to yield mannich bases. The structure of all synthesized compounds was recognized from their physical, analytical and spectral data. The IR spectra of all synthesized compounds showed normal absorption band of OH functional group in the range of 3301-3511 cm^{-1}. An absorption band observed for synthesized compounds in the range of 3028-3196 cm^{-1} may be attributed to aromatic stretching vibration, aliphatic stretching vibration showed in the range of 2824-2975 cm^{-1}, strong C=O group absorption band observed between 1687 cm^{-1} while that seen 1445-1485 cm^{-1} corresponds to C=N linkage. In ^{1}H-NMR spectra of synthesized compounds generally, the protons of hydroxyl group were observed at 9.51 ppm and aromatic protons showed multiplet at 6.82-8.11 ppm.

The synthesized compounds were evaluated for analgesic activity by following Eddy's hot plate method. The mice of either sex weighing 25-30gms were used for the study. Ibuprofen was used as a standard drug for comparison of analgesic activity. All of the compounds have shown better activity ranging from 23-34%, whereas the standard compound showed 60.07%. The compounds which exhibited the significant activity were A_2, A_7, A_{13}, A_{15}, and A_{18}. All the synthesized compounds have also been evaluated for anti-inflammatory activity by using the formalin-induced paw edema method on albino rats (Wister strain) of either sex. Diclofenac sodium was used as a standard drug for comparison of activity. It was apparent that compounds afforded 8-33% protection against induced paw edema, whereas standard drug showed 52.49% inhibition. Among the compounds tested, compounds A_2, A_3, A_8, A_{16}, and A_{18} have shown excellent activity. The remaining compounds were shown moderate to good anti-inflammatory activity.

CONCLUSION:

In the present work, reported the synthesis of mannich bases of 2-substituted 4,5-diphenyl imidazole derivatives. The synthesized compounds were screened for substantial analgesic activity by Eddy's hot plate method and anti-inflammatory activity using formalin-induced paw edema method. Several of the synthesized compounds showed promising analgesic and anti-inflammatory activities as compared to the standard drug. It was noted that presence

piperidine, morpholine and 1-methyl piperazine in imidazole derivatives may contribute for the enhancement of pharmacological activity.

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