WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 6, 581-585. Research Article ISSN 2277–7105

SYNTHESIS AND EVALUATION OF SOME SUBSTITUTED BENZIMIDAZOLE DERIVATIVES FOR THEIR ANTI-INFLAMMATORY ACTIVITY.

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Article Received on
04 April 2017,

Revised on 25 April 2017,
Accepted on 15 May 2017

DOI: 10.20959/wjpr20176-8089

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ABSTRACT

A series of benzimidazole derivatives have been synthesized using substituted carboxylic acid and O-phenelyne diamine in presence of Protonic acid using magnetic stirrer. The synthesized compounds had been characterized using IR, ^{1}H NMR and CHN analysis. The resulting compounds have been extensively studied for their anti-inflammatory activity using Carageenan induced rat paw edema method. Diclofenac is used as a standard drug. The entire synthesized compound possesses promising biological activity.

KEYWORDS: Benzimidazole, anti-inflammatory activity, CHN analysis.

INTRODUCTION

Benzimidazoles are heterocyclic compounds that have awaked great interest during the last few years because of their proven biological activity as antiviral, antimicrobial, and antitumor agents. Benzimidazole is one of the commonly used nucleus. Role of Benzimidazole in medicinal chemistry is well known. The importance of Benzimidazole was realized when it was identified as a part of vitamin B_{12} structure.[1] Due to its widespread pharmacological activities, it has earned an important place in the list of chemotherapeutic agents. These findings stimulated great interest in the chemistry of imidazoles and related compounds and considerable success has occurred from these studies leading to a new antibacterial agent (Azomycin)[2], a trichomonoside[3] (Metronidazole) and a variety of benzimidazole derivatives of use as anthelmintic agents (Thiabendazole).[4] Further

exploitation of benzimidazole nucleus found its use in different therapeutic categories like; Domperidone (Janssen, 1978) as antiemetic, Albendazole (GSK, 1982) as anthelmintic, Bendazol (GSK, 1982) as coronary vasodilator, Omeprazole (Astrazeneca, 1988), Lansoprazole (Takeda, 1992), pantoprazole (Altana pharmaceuticals, 1994) as proton pump inhibitors and Pimobendan (Boehringer Ingelheim, 1994) as cardiotonic.[4]

MATERIALS AND METHODS

Carrageenan Induced Rat hind Paw Edema[5,6]

Anti-inflammatory activity was determined by Carrageenan Induced Rat hind Paw method of winter et al. wistar rats (120-150 g) was used for the experiment. The conventional laboratory diet was fed with adequate supply of drinking water. The animals were randomly selected, marked to permit individual identification and kept in polypropylene cages for one week prior to dosing to allow acclimatization of them to laboratory conditions. The drugs were prepared as a suspension by triturating with water and 0.5% sodium CMC. The standard group received 50mg/kg body weight of Diclofenac Sodium, test group received 200mg/kg body weight of synthesized compounds and the control group received 1% w/v of CMC.

Experimental

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, $CDCl_3$ as solvent and TMS as internal standard. Combustion analyses were found to be within the limits of permissible errors.

Synthesis of 2-substituted -1H-benzimidazole (1a-1f)[7]

A mixture of 0.05 mole of o-phenylenedaimine in 1o ml of protonic acid (Conc. H_2SO_4) in presence of carboxylic acids were stirred over a period of 30-60 minutes. The solid was collected by suction filtration washed with water and recrystallized from ethanol to give 1a. Similarly 1a to 1f were prepared using substituted acids. Analytical data were given in the table.

Spectral Data

SCHEME

1a: IR Bands (cm^{-1}): 3275.34 -NH str.; 3110.24, Ar-CH str.; 1546.47,-C=N str.; 1225.67,-C-N str.

1b: IR Bands (cm^{-1}): 3320.34 -NH str.; 3250.24 –OH str; 3060.26, Ar-CH str.; 2760.84 –CH_3 str.; 1576.47,-C=N str.; 1248.67,-C-N str.; **^{1}H NMR (δ ppm):** 6.5-6.9, 4H of phenyl; 4.8 1H of –NH; 0.8-1.4 3H of –CH_3.

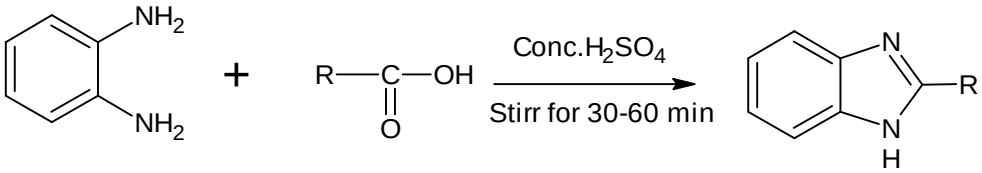
1c: IR Bands (cm^{-1}): 3315.1 -NH str; 3047.64, Ar-CH str.; 1550.2,-C=N str.; 1225.67,-C-N str.

1d: IR Bands (cm^{-1}): 3320.34 -NH str.; 3250.24 –OH str; 3060.26, Ar-CH str.; 1576.47,-C=N str.; 1248.67,-C-N str.; **^{1}H NMR (δ ppm):** 6.8-7.4, 8H of phenyl; 4.8 1H of –NH; 5.8 1H of –OH.

1e: IR Bands (cm^{-1}): 3296.48 -NH str.; 3050.26, Ar-CH str.; 1650.38 NO_2 str.:1566.47,-C=N str.; 1238.67,-C-N str.

1f: IR Bands (cm^{-1}): 3330.34 -NH str.; 32750.24 –NH_2 str; 3045.26, Ar-CH str.; 1584.47,-C=N str.; 1264.67,-C-N str.; **^{1}H NMR (δ ppm):** 10.4 2 H of NH_2' 6.7-7.3, 8H of phenyl; 4.6 1H of –NH;

SCHEME



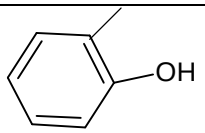
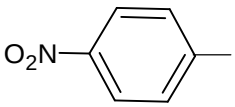
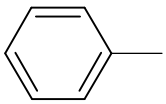
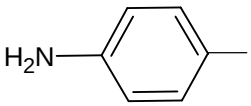
Comp	R	Comp.	R
1a	-H	**1d**	
1b	-CH_3	**1e**	
1c		**1f**	

Table No. 1: Analytical data of 2-substituted -1H-benzimidazole compounds (scheme).

Mol. Formula	Mol. Wt.	M.P ^{0}C	Rf Value	Yield %	Elemental analyses Calcd. (Found)		
					C	H	N
$C_7H_6N_2$	118.13	142-144	0.48	54	61.98	5.57	20.65
$C_8H_8N_2$	132.16	148-154	0.45	48	63.14 (60.24)	6.01 (5.98)	19.64 (18.32)
$C_{13}H_9N_2$	181.21	147-149	0.65	49	69.15	5.51	16.13

$C_{13}H_{10}N_2O$	210.23	210-214	0.68	68	74.27 (72.95)	4.79 (4.48)	13.33 (12.99)
$C_{13}H_{11}N_3$	209.23	184-186	0.67	67	73.45	5.49	21.41
$C_{13}H_9N_3O_2$	239.22	178-182	0.74	75	65.27 (64.88)	3.79 (3.99)	17.56 (17.96)

The combustion analyses of compounds synthesized were found to be within the limits of (±0.4).

Table No. 2: Anti-inflammatory activity of 2-substituted -1H-benzimidazole compounds.

Comp	Mean paw oedema volume ± SE					% inhibition at 4th hr
	0 hour	1 hour	2 hour	3 hour	4 hour	
Ct.	0.955±0.025	1.455±0.025	1.630±0.028	1.755±0.025	1.822±0.012	
Std.	0.945±0.025	1.235±0.025**	1.355±0.025**	1.340±0.028**	1.285±0.025**	45.57
1a	1.120±0.040	1.235±0.025**	1.580±0.040*	1.435±0.025**	1.525±0.025**	15.35
1b	1.012±0.021	1.250±0.028	1.325±0.045**	1.425±0.040**	1.525±0.047**	32.36
1c	1.020±0.041	1.450±0.042	1.545±0.025ns	1.595±0.0**	1.645 ±0.025*	14.25
1d	1.070±0.0	1.275±0.025	1.335±0.028**	1.540±0.025**	1.220±0.040**	41.25
1e	0.945±0.025	1.360±0.028	1.585±0.025ns	1.565±0.025**	1.645±0.028*	14.25
1f	0.965±0.025	1.300±0.041	1.390±0.025*	1.320±0.025**	1.264±0.028**	38.65

One way ANOYA followed by Dunnett's 't' test **P<0.01

RESULT AND DISCUSSION

The title compounds are synthesized by stirring method using water as solvent. The completion of reaction can be checked by TLC using proper solvent. The resulting compounds were purified by recrystallization from ethanol. All the compounds are characterized by IR, 1H NMR and CHN analysis. The resulting compounds are subjected to anti-inflammatory activity in well equipped pharmacology laboratory. All the compounds show significant pharmacological activity. These compounds with suitable modification can be explored as a drug candidate in future for the treatment of inflammatory disorders.

ACKNOWLEDGEMENT

Authors wish to express their sincere thanks to Mr. Uadyshing Patil, President Swami Vivekanand Nursing Home Trust's, Shrishivajinagar, (Rahuri Factory), Tal-Rahuri, and Dist-Ahmednagar Pin-413706 for their constant support and encouragement.

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