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Design, Synthesis and Pharmacological Evaluation of Novel Substituted Benzimidazole Derivatives as Analgesic and Anti-Inflammatory Agent

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ABSTRACT

A series of newly substituted 2-amino benzimidazole derivatives were synthesized starting with Ortho phenylenediamine (OPD) potassium hydroxide & carbon disulphide (CS2) resulting 1 h benzimidazole 2 thiol derivatives which further was refluxed with hydrochloric acid and substituted aniline gives series of newly substituted 2 amino benzimidazole. Structures of newly synthesized substituted benzimidazole derivatives were verified by TLC, Melting point, FTIR & NMR analysis. Substituted 2 amino benzimidazole was tested for analgesic activity & anti-inflammatory activities. 2 amino benzimidazole compounds 57a, b, c, e, g, h, i and k showed good analgesic activity where as other compounds possess significant analgesic activity with compared to standard drug Tramadol while the compounds 57a, b, c, e, g, i, and k showed good anti-inflammatory activity where as other compounds possess significant activity with compared to standard drug diclofenac sodium.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly used as a first choice of drug for treating of several inflammatory diseases as well as to relieve aches and pain of day to day life[1]. However, prolonged use of NSAIDs results in common side effects like platelet dysfunction, hepatotoxicity and bleeding disorders[2-4]. But one of the most potential side effect associated with long term use of NSAIDs is gastrointestinal (GI) ulcerations due to inhibition of cyclooxygenase (COX) in tissues where prostaglandins show their physiological functions, i.e. gastric mucosal defense and renal homeostasis[5]. The two COX isoforms, namely COX-1 expressed in most tissues such as kidney and gastro intestinal (GI) tract, while COX-2 is active at the sites of inflammation, causes development of selective COX-2 inhibitors, with the assuming that they significantly reduce the gastric toxicity associated with acute and chronic use of NSAIDs. However, with the clinical results of physiological roles of COX-2 enzyme in various tissues, like stomach and kidney, some selective COX-2 inhibitors are lead to withdrawal from the market because of cardiovascular toxicity, have questioned the benefits of selective COX-2 inhibition[6]. Consequently, the need of alternative studies to reduce GI side effects associated with NSAIDs has raised. The novel researches were pursued in desire of GI-sparing NSAIDs such as addition of chemical moieties that release gastro protective mediators like nitric oxide (NO)-releasing or hydrogen sulphide (H_2S)-releasing NSAIDs, microsomal prostaglandin E synthase-1 inhibitors or dual cyclooxygenase/5-lipoxygenase [7,8]. But these approaches also have their own limitations, [9-14] so the need of hour is to develop an anti-inflammatory, analgesic agents with better efficacy, less toxicity and lesser side effects of gastric ulceration. According to reported literature, oxidative stress components or reactive oxygen species (ROS) are involved in pathophysiology of NSAIDs-induced ulcerations. On synthesis of novel chemical moiety or chemical modifications of existing molecules may lead to neutral molecules with prominently reduced acidic nature and oxidative stress as a useful result to explore safer and potent anti-inflammatory and analgesic agents[15]. Benzimidazoles and its derivatives substituted at 1, 2, 5 and 6-positions to meet the required structural requirements for anti-inflammatory, analgesic and antioxidant activity[20, 23].

It is found that benzimidazoles and its derivatives possess diverse biological activities[24]. They have been found to be active often with high potency. Benzimidazoles are comparatively non-toxic[25]. The literature also shows benzimidazole moiety like 5,6-

dimethyl benzimidazoles is a part of vitamin B_{12} chemical structure [26-27]. This shows the chances of an anticancer activity exhibited by benzimidazole derivatives. Some benzimidazoles do have vitamin B_{12} like activity while some benzimidazoles are reported to be ant pernicious anemia factor [28-32].

MATERIALS AND METHODS

The chemicals used in the present project work were purchased from Loba, Merck and Fisher scientific chemicals. The melting point of the synthesized compounds was determined in open capillary using LABHOSP melting point apparatus. TLC was performed on silica gel plates using Butanol: Ethanol: Water (9:1:1) solvent system. Visualization was done in UV light chamber at 254 nm, iodine chamber. The infrared spectra of the synthesized compounds were recorded using SHIMADZU-FTIR 8400 spectrophotometer using potassium bromide pellet technique and sodium chloride cells for liquid samples. ^{1}H-NMR spectra of the synthesized compounds were taken using Bruker ACF-300 MHz spectrometer using tetramethyl silane (TMS) as an internal standard. ^{1}H-NMR spectra were recorded with pyridine/chloroform as a solvent and the chemical shift data were expressed as δ values relative to TMS.

SYNTHESIS OF COMPOUNDS

The synthesis of compounds is illustrated in Scheme 1. Details are described as follows.

SCHEME 1

2.1.3.1 Preparation of 1*H*-benzimidazole-2-thiol derivative (Comp. 55a-55c)

A mixture of 10.7g(0.1mol) of o-phenylenediamine (OPD), 19.5g (0.1 mol) of potassium hydroxide and 26 mL (0.1 mol) of carbon disulphide, 300 mL of 95% ethanol and 45 mL of water in round bottom flask and reflux for 3 h. Then norit was added cautiously and further heated for 10 next min, filter the resultant mixture. A yellowish filtrate of potassium 1*H*-benzimidazole 2-thiolate derivative was collected in conical flask and mixed with 300mL of water and 25mL of acetic acid stirred for another hour at 60-70^{0}C. The crude product of 1*H*-benzimidazole 2-thiol derivative starts separating as glisten white crystal at cold temperature, then kept in refrigerator for 3 h for complete crystallization. Using above procedure comp. 55a-55c were synthesized by using different derivative of o-phenylenediamine.

2.1.3.1 Preparation of 2-amino 1*H*- benzimidazole derivative (Comp. 56a-56l)

A mixture of 1*H*-benzimidazole-2-thiol derivative (Comp. 55a-55c) (0.1mol) was refluxed for 2 h along with hydrochloric acid and substituted aniline (0.1mol) to yield the crude product of 2-amino 1*H*-benzimidazole derivative. The crude products were recrystallized from ethanol to obtain pure product. Using same procedure twelve derivatives (Comp. 56a-56l) were synthesized by using aniline derivatives.

2.1.3.1 Preparation of 1-alkyl-2-amino benzimidazole derivative (Comp. 57a-57l)

To a mixture of 2-amino benzimidazole derivative (Comp. 56a-56l) (2mmol) in dimethyl formamide (10 mL) and sodium hydride (60%, 2.4 mmol) was added at 0°C. After completion of addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred at this temperature for 1h. The reaction mixture was again cooled to 0°C and the respective ethyl iodide (2.4 mmol) was added. The temperature of the reaction mixture was then allowed to warm to room temperature and stirred for 2h and water (50 mL) was slowly added to reaction mixture and extracted with ethyl acetate (2×25 mL). The organic layer was washed with water (2×25 mL), brine and dried over anhydrous magnesium sulfate and concentrated under vacuum to yield the corresponding N-substituted derivative. The crude compounds were recrystallized from ethanol to obtain pure products. Using same procedure twelve derivatives (Comp. 57a-57l) were synthesized by using ethyl iodide. 2-amino benzimidazole derivative was obtained in 88% yield. The structure of final compounds was characterized by, IR, NMR techniques.

Scheme 1

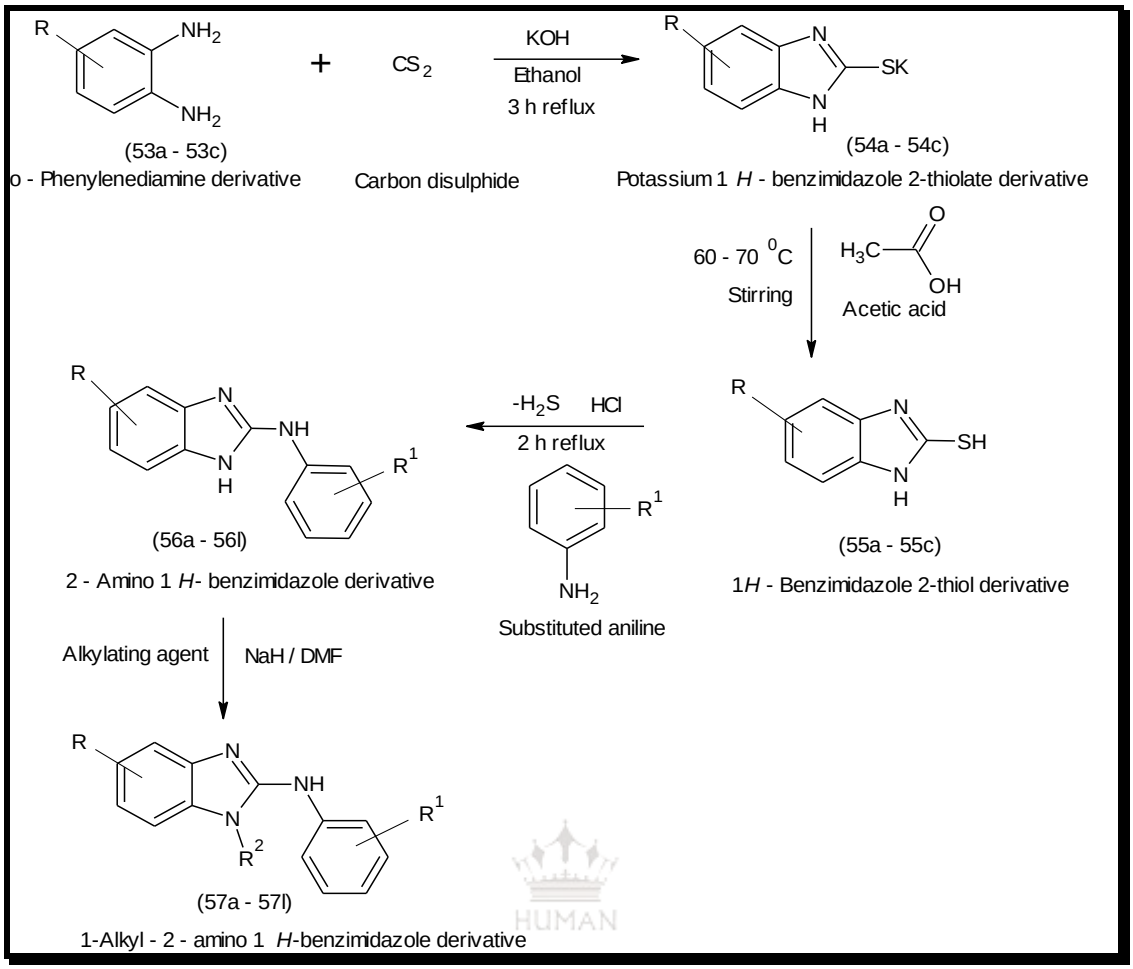

Table No. 1: Physicochemical properties of synthesized compound

Comp. code	Mol. Formula	Mol. Wt. (g)	% yield	R_f value	M.P. (°C)
57a	$C_{15}H_{14}ClN_3$	271.74	58.82	0.80	290-292
57b	$C_{15}H_{14}ClN_3$	271.74	56.78	0.71	214-216
57c	$C_{15}H_{14}N_4O_2$	282.29	56.67	0.81	227-229
57d	$C_{15}H_{14}N_3Br$	316.19	59.60	0.68	156-158
57e	$C_{15}H_{13}N_4O_2Cl$	316.74	44.23	0.75	205-207
57f	$C_{15}H_{13}N_4O_2Cl$	316.74	51.34	0.73	176-178
57g	$C_{15}H_{13}N_5O_4$	327.29	55.23	0.82	225-227
57h	$C_{15}H_{13}N_4O_2Br$	361.19	58.12	0.78	236-238
57i	$C_{15}H_{13}N_3Cl_2$	306.18	42.12	0.83	235-237
57j	$C_{15}H_{13}N_3Cl_2$	306.18	49.55	0.89	222-224
57k	$C_{15}H_{13}N_4O_2Cl$	316.74	51.45	0.87	186-188
57l	$C_{15}H_{13}ClBrN_3$	350.64	54.18	0.74	234-236

Table No. 2: Physicochemical properties of synthesized compound

Code	Compound Name	IR (KBr)cm^{-1}/1H NMR (CDCl3, δ)
57a	*2*(4-chlorophenyl) amino 1-ethyl-1*H*-benzimidazole	IR (KBr, v, cm^{-1}):1590 (NH),1438(C-C),1213(CN), 1600(CN),750 (CCl), ^{1}H-NMR (500 MHz, $CDCl_3$):δ 9.15 - 9.10 (m, 1H), H4-Fu),8.46 (ddd, *J*=24.1,1.72,1.8 Hz , 1H, HB), 8.25-8.21 (m, 2H,), 4.91 (dq, *J*=23.4, 6.1 Hz, 1H), (d, *J*=12.3 Hz, 1H)
57b	*2*(2-chlorophenyl) amino 1-ethyl-1*H*-benzimidazole	IR (KBr, v, cm^{-1}):1622 (NH),1504(C-C),1670(CN), 1261(CN),738 (CCl),3010(CH) ^{1}H-NMR (500 MHz, $CDCl_3$):δ 9.15 - 9.10 (m, 1H), H4-Fu),8.46 (ddd, *J*=24.1,1.72,1.8 Hz , 1H, HB), 8.25-8.21 (m, 2H,), 4.91 (dq, *J*=23.4, 6.1 Hz, 1H), (d, *J*=12.3 Hz, 1H)
57c	2(4-nitrophenyl) amino 1-ethyl 1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 3030 cm-1(CH); 1519 (NH), 1635(C-C),1635(CN), 12653(CN),3030(CH) ^{1}H-NMR (500 MHz, $CDCl_3$):δ 9.20 - 9.14 (m, 1H), H4-Fu),8.59 (ddd, *J*=25.1,1.74,1.7 Hz , 1H, HB), 8.35-8.22 (m, 2H,), 5.41 (dq, *J*=23.8, 6.3 Hz, 1H), (d, *J*=12.5 Hz, 1H)
57d	*2*(4-bromophenyl) amino 1-ethyl-1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 3050 (CH); 1623 (NH), 1500(C-C),1676(CN), 1253(CN),740(CBr) ^{1}H-NMR (500 MHz, $CDCl_3$):δ 9.34 - 9.44 (m, 1H), H4-Fu),8.44 (ddd, *J*=24.8,1.763,1.8 Hz , 1H, HB), 8.30-8.22 (m, 2H,), 5.43 (dq, *J*=24.1, 6.4 Hz, 1H), (d, *J*=12.8 Hz, 1H)
57e	*2*(4-chlorophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 3020 (CH); 1635 (NH), 1488(C-C),1656(CN), 1242(CN),820(CCl) ^{1}H-NMR (500 MHz, $CDCl_3$):δ 9.22 - 9.18 (m, 1H), H4-Fu),7.85 (ddd, *J*=23.9,1.76,1.5 Hz , 1H, HB), 7.40-7.52 (m, 2H,), 5.23 (dq, *J*=25.1, 6.8 Hz, 1H), (d, *J*=12.9Hz, 1H)
57f	*2*(2-chlorophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 3055 (CH); 1678 (NH), 1480(C-C),1670(CN), 1268(CN),933(CCl) ^{1}H-NMR (500 MHz, $CDCl_3$):δ 9.21 - 9.17(m, 1H), H4-Fu),7.80 (ddd, *J*=24.3,1.88,1.8 Hz , 1H, HB), 7.65-7.72 (m, 2H,), 5.42 (dq, *J*=25.5, 6.9 Hz, 1H), (d, *J*=13.1Hz, 1H)
57g	2(4-nitrophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 1590 (NH), 1500(C-C),1600(CN), 1260(CN),1480(C-NO_2) ^{1}H-NMR (500 MHz, $CDCl_3$):δ 9.38 - 9.42 (m, 1H), H4-Fu),8.42 (ddd, *J*=24.6,1.73,1.9 Hz , 1H, HB), 8.32-8.28 (m, 2H,), 5.48 (dq, *J*=24.2, 6.7 Hz, 1H), (d, *J*=12.5 Hz, 1H)
57h	*2*(4-bromophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 3040 (CH); 1642 (NH), 1550(C-C),1688(CN), 1265(CN),1490(C-NO_2) ^{1}H--NMR (500 MHz, $CDCl_3$):δ 9.34 - 9.44 (m, 1H), H4-Fu),9.14 (ddd, *J*=24.3,1.63,1.6 Hz , 1H, HB), 8.20-8.24 (m, 2H,), 5.48 (dq, J=24.2, 6.5 Hz, 1H), (d, *J*=12.7 Hz, 1H)
	2(4-chlorophenyl) amino 1-	IR (KBr, v, cm^{-1}): 1660 (CN); 1570 (NH), 1514(C-C),1688(CN),

57i	ethyl-5-chloro-1*H*-benzimidazole	1365(CN),740(CCl) ^{1}H--NMR (500 MHz, $CDCl_3$):δ 9.02 - 9.08 (m, 1H), H4-Fu),7.95(ddd, *J*=24.7,1.80,1.85 Hz , 1H, HB), 7.90-7.95 (m, 2H,), 5.92 (dq, J=25.7, 6.6 Hz, 1H), (d, *J*=12.9Hz, 1H)
57j	2(2-chlorophenyl)amino 1-ethyl-5-chloro-1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 1690 (CN); 1590 (NH), 1490(C-C),1656(CN), 1330(CN),650(CCl) ^{1}H--NMR (500 MHz, $CDCl_3$):δ 8.92 - 8.88 (m, 1H), H4-Fu),7.75(ddd, *J*=24.6,1.90,1.9 Hz , 1H, HB), 7.80-7.95 (m, 2H,), 5.85 (dq, *J*=25.8, 6.5 Hz, 1H), (d, *J*=12.8Hz, 1H)
57k	2(4-nitrophenyl) amino 1-ethyl-5-chloro-1*H*-benzimidazol	IR (KBr, v, cm^{-1}): 1620 (NH), 1512(C-C),1615(CN), 1275(CN),1490(C-NO_2) ^{1}H--NMR (500 MHz, $CDCl_3$):δ 9.58 - 9.62 (m, 1H), H4-Fu),9.22 (ddd, *J*=24.3,1.65,2.1 Hz , 1H, HB), 8.42-8.38 (m, 2H,), 5.38 (dq, *J*=24.4, 6.8 Hz, 1H), (d, *J*=12.8 Hz, 1H)
57l	*2*(4-bromophenyl) amino 1-ethyl-5-chloro-1*H*-benzimidazole	IR (KBr, v, cm^{-1}): 1660 (CN); 1537 (NH), 1490(C-C),1656(CN), 1330(CN),730(CCl),613(CBr) ^{1}H-NMR (500 MHz, $CDCl_3$):δ 8.80 - 8.75(m, 1H), H4-Fu),7.85(ddd, *J*=25.6,1.90,1.9 Hz , 1H, HB), 7.80-7.95 (m, 2H,), 5.65 (dq, *J*=24.8, 6.5 Hz, 1H), (d, *J*=11.8Hz, 1H)

PHARMACOLOGICAL EVALUATION

All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of College, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA), Government of India.

Preliminary pharmacological screening was performed, which includes approximate toxicity testing (LD50) and anti-ulcer activity. The LD50 of the test compounds performed on the rats as per the OECD guidelines for selecting the dose. The LD50 of all the derivatives was found >75mg/kg.

1. Analgesic Activity:

1.1 Principle

Pain awareness is measured by nerve ending receptors in peripheral tissues and transmitted to the central nervous system (CNS) by primary afferent fibers to the brain. Transmission can be reduced by drug acting on several different neurotransmitters receptors or completely prevented by blocking the sodium channels required for conduction in the afferent neuron axon outside or inside spinal column.

1.2 Procedure

Swiss albino mice of either sex were divided into fourteen different groups each containing six animals, the animals were marked on tail individually. Food was withdrawn 12 h prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. To control group (0.3 mL) 1% v/v solution of tween 80, standard group (Tramadol, dose: 20mg/kg), and test groups (Comp. 57a-57l, dose: 20mg/kg) were given by oral route and after 0 min and 90 min behavioral changes count. The jumping and paw licking was noted 0 min, 90 min. The percentage inhibition of analgesic activity was evaluated using the following formula.

Percentage inhibition = [1-(before treatment /after treatment)] x 100

The analgesic activity was performed by hot plate method on Swiss albino mice by giving dose 20mg/kg of synthesized derivative. The % inhibitions in analgesic activity of synthesized compounds were calculated and given in Table No.3.

2. Anti-inflammatory activity:

2.1 Principle

The inflammatory reaction is readily produced in rats in the form of paw edema with the help of irritants or inflammagen. Carrageenan induced paw edema is the most commonly used experimental method. Carrageenan is a sulphated polysaccharide obtained from seaweed (Rhodophyceae) causing the release of histamine, 5-HT, bradykinin, and prostaglandins. It produces inflammation and edema.

Carrageenan induced rat paw edema method of winter *et.al* was used for evaluation of anti-inflammatory activity.

2.2 Procedure

Wistar albino rats of either sex were divided into fourteen different groups each containing six animals, the animals were marked on tail individually. Food was withdrawn 12 h prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. To control group (0.3 mL) 1% w/v solution of tween 80, standard group (Diclofenac sodium, dose: 10mg/kg), and test groups (Comp. 57a-57l, dose: 10mg/kg) were

given by oral route. After 1h, 0.3mL of 1% w/v carrageenan was injected in the sub plantar region of the left paw of control and test drug treated groups. The thickness of paw of all the groups of rats was noted at 0 h, 1 h, 2 h, and 3 h after carrageenan challenge. The percentage inhibition of inflammation in the standard or test drugs treated animals were recorded and calculated using the given formula.

Percentage inhibition = 1-[a-x / b-y] × 100

The anti-inflammatory activity was performed by carrageenan-induced paw edema method on wistar albino rats by giving dose 10mg/kg of synthesized derivative. The % inhibition in anti-inflammatory activity of synthesized compounds was calculated and results were given in Table No. 4.

RESULT AND DISCUSSION

The 2-Amino Benzimidazole compounds were synthesized in good yield by mentioned synthetic procedure. The purity and homogeneity of compounds were ascertained by sharp melting points and thin layer chromatography

In IR spectra of all derivatives shows aromatic C-H stretching vibration 3010-3030cm-1 this indicated that the C-H bond present in aromatic ring. The characteristic absorbance at wavelength 1590-1630cm^{-1} for NH bond indicates presence of secondary nitrogen. All derivatives show absorbance at wavelength 1400-1450cm^{-1} for N-C_2H_5 deformation indicating presence of ethyl group and the absorption at wavelength 1600-1690cm^{-1} associated with stretching vibration of bonded –C=N- indicating presence of nitrogen in the ring. All derivatives showed absorbance at wavelength 1260 cm^{-1} for C-N stretching indicating presence of nitrogen in the ring. Comp. 57c, g, and k showed absorbance at wavelength 1480 cm^{-1} stretching vibration indicating presence of nitro group. Comp. 57a, b, e, f, i, and j showed absorbance at wavelength 750 cm^{-1} stretching vibration indicating presence of Cl group. Comp.57d, h, and l showed absorbance at wavelength 740cm-1 stretching vibration indicating presence of Br group.

The structures of synthesized derivative were further confirmed by NMR spectra. In ^{1}H-NMR spectra of Comp. 57c, g, and j show a sharp multiplet peak at 6.7-7.9ppm indicating hydrogen attached to an aromatic ring. The sharp multiplet peak at 2.5ppm indicates the presence of N-C_2H_5 group. A sharp singlet peak at 3.3ppm showed the presence of NH group.

Table No. 3: Analgesic activity of 2-Amino benzimidazole derivatives

Test compounds	Mean latency		% Inhibition
	0 min	After 90 min	
Ctrl	3.36±0.41	6.50±0.32	-
STD (Tramadol)	2.47±0.31	6.31±0.25	61.30±3.64
57a	2.16±0.35	4.81±0.55	5586±2.33
57b	1.64±0.21	3.43±0.33	52.46±1.34
57c	1.93±0.33	3.70±0.09	47.96±8.77
57d	1.71±0.23	2.92±0.22	42.36±3.96
57e	2.19±0.23	4.1±0.30	47.32±1.96
57f	1.78±0.28	2.82±0.27	37.60±5.10
57g	2.15±0.25	3.93±0.45	45.43±0.92
57h	2.10±0.37	4.38±0.47	53.30±3.70
57i	1.92±0.21	3.40±0.40	43.33±1.42
57j	1.66±0.19	2.75±0.15	40.03±3.47
57k	1.88±0.19	3.80±0.30	50.90±1.18
57l	1.94±0.33	3.26±0.42	41.50±2.43

Dose of STD and test group 20mg/kg body weight, No. of animal in group (n) = 6

Values are the mean ± SEM, table follows one way ANOVA

Table No. 4: Anti-inflammatory activity of 2-Amino benzimidazole derivatives

Test compounds	Paw thickness (mm)		% Inhibition
	Initial	After 3 hrs	
Ctrl	3.76±0.28	6.22±0.25	-
STD (Diclofenac)	3.72±0.28	4.35±0.30	74.40±4.72
57a	3.75±0.23	4.55±0.32	67.50±1.33
57b	3.54±0.19	4.45±0.29	61.40±3.51
57c	3.82±0.28	4.70±0.39	64.30±1.82
57d`	3.44±0.28	4.90±0.70	40.70±1.27
57e	3.41±0.24	4.27±0.32	65.10±1.89
57f	3.39±0.24	5.01±0.24	34.20±2.87
57g	3.86±0.21	4.81±0.16	61.40±2.58
57h	3.34±0.37	4.86±0.32	38.30±2.49
57i	4.20±0.27	5.10±0.19	63.50±2.28
57j	3.88±0.44	5.22±0.40	45.60±1.52
57k	4.10±0.29	4.98±0.27	64.30±2.98
57l	3.37±0.27	4.99±0.19	34.20±2.78

Dose of STD and test group 10mg/kg body weight, No. of animal in group (n) = 6

Values are the mean ± SEM, table follows one way ANOVA

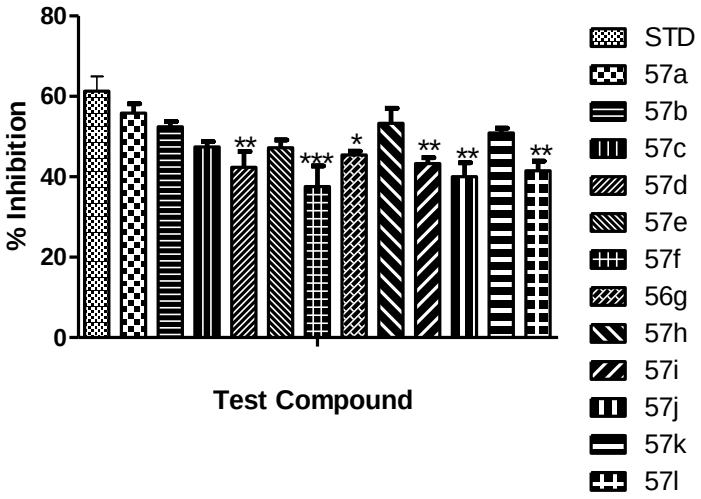

Figure No. 1: Analgesic activity of synthesized compounds

Note: Data are expressed as mean latency of before and after drug, one way ANOVA followed by Bonferroni test was applied to determine the significances of the difference between the control group and mice treated with the test compounds. The differences in results were considered significant when. $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$. Dose of test group 20mg/kg. All statistical calculations were carried out using Graph Pad® Prism 7.0 (USA) statistical software.

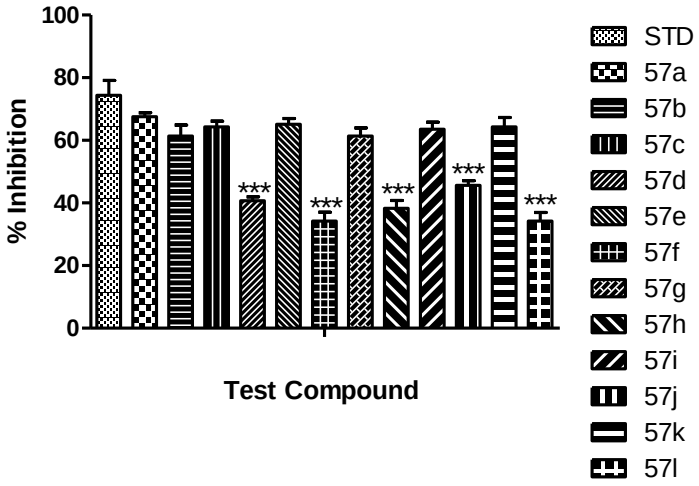

Figure No. 2: Anti-inflammatory activity of synthesized compounds

Note: Anti-inflammatory activity of the test compounds were compared w.r.t control. Data are expressed as % inhibition ± S.E.M. and analyzed by one way ANOVA followed by Bonferroni test was applied to determine the significances of the difference between the control group and mice treated with the test compounds. The differences in results were considered significant when. $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$ Vs STD. All statistical calculations were carried out using Graph Pad® Prism 7.0 (USA) statistical software.

CONCLUSION

All the synthesized 2-Amino benzimidazole derivatives compounds were screened their pharmacological activities such as analgesic & anti-inflammatory activities done by hot plate method, carrageenan induced rat paw edema and method respectively. It was observed that compounds 57a, b, c, e, g, h, i and k showed good analgesic activity where as other compounds possess significant analgesic activity with compared to standard drug Tramadol. While the compounds 57a, b, c, e, g, i, and k showed good anti-inflammatory activity where as other compounds possess significant activity with compared to standard drug diclofenac

sodium. All of the synthesized compounds showed good anti-inflammatory activity. However, the analgesic & anti-inflammatory activities of the synthesized compounds were found to be less than that of respective standard drug at tested dose level.

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