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Synthesis and anti-inflammatory activity of *N*-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl)acetamide derivatives.

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ABSTRACT

A variety of N-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl)acetamide derivatives (BA1-10) have been synthesized by nucleophilic displacement reaction of 1*H*-1,2,3-Benzotriazole with appropriate 2-Chloro-N-(Alkyl or Aryl)acetamide.. The starting material 2-Chloro-N-Alkyl or Arylacetamide was synthesized from Chloroacetylchloride with various amines. The title compounds obtained were characterized by IR, ^{1}HNMR and Mass spectral data. The prepared compounds were screened for their anti-inflammatory activity by carrageenan induced paw odema method in rats. The *N*-(2-CarboxyPhenyl)-2-(1*H*-benzotriazol-1-yl)-acetamide in dose of 25mg/kg showed 64.88% inhibition of paw edema.

Key word: Antiinflammatory activity; Benzotriazole,

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INTRODUCTION

Inflammation is typically thought of as a swelling, painful or otherwise uncomfortable situation – perhaps in your joints, sinus or intestine. But for most people, inflammation occurs without any symptoms. Inflammation is defined classically as a protective reaction by the body, in response to some physical or chemical injury; acute inflammatory response begins immediately after cellular injury [1]. Heterocyclic play a vital role in pharmacological, agricultural and synthetic fields [2]. Benzotrizole is very stable material readily prepared by the diazoation of 1,2 phenylenediamine [3]. 1,2,3-Benzotriazoles are pharmaceutically interesting as they show various biological activities such as anticonvulsant, analgesic, anti-inflammatory [4], antibacterial [5], antiemetic [6] and antifungal[7] activities.

The objective of the present investigation was to study the anti-inflammatory activity of ***N***-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl)acetamide derivatives in experimental animal models. The results indicated that the *N*-(Alkyl or Aryl)- 2-(1*H*-benzotriazol-1-yl)-acetamide derivatives was active against all the experimentally induced laboratory models of inflammation.

MATERIAL AND METHODS

All chemicals used are LR grade and were purchased from Research laboratory Pvt. Ltd. All solvents used for chromatography are AR grade and were purchased from Rankem Ltd. Melting points of all the synthesized compounds are uncorrected. The progress of reaction was monitored by TLC silica gel adsorbent on coated aluminium plates (Merck) and UV light as a visualiazing agent. The purity of synthesized compounds was checked by thin-layer chromatography. The IR spectra were recorded on Bruker FTIR spectrophotometer in the range of 4000-400 cm^{-1}. ^{1}HNMR spectra were scanned at 300 MHz on Varian-NMR-Mercury 300 FT NMR spectrophotometer using $CDCl_3$ as solvent and TMS as an internal standard and GC-MS spectra & chromatogram were recorded on GCMS-QP 2010 SHIMADZU instrument using electron impact ionization mode.

1*H*-1,2,3-Benzotriazole: OPD**(1)** (0.1mole) was dissolved in a mixture of glacial acetic acid (0.2mole) and 30ml of water contained in a 250ml of beaker, it was warmed slightly. Clear solution was cooled to 15^0C, and then it was stirred magnetically and added to a solution of sodium nitrate (0.11mole) in 15 ml of water. Reaction mixture became warmed and within 2-3 min reached a temperature of about 85°C, cooling was started with the change of colour from deep red to pale brown. Stirring was continued for 15min and then it was chilled in ice bath for 30 min. Pale brown precipitate of benzotriazole **(2)** separates out which was washed with ice cold water. Crude product was recrystalised using boiling water [8]
Yield: 67.90 %, Melting point: 96-99°C

General procedure for synthesis of 2-chloro-*N*-Alkyl/Arylacetamide: Chloroacetyl-chloride (0.1 mole) **(3)** was added drop wise over one hour to the amine **(4)** (0.1 mole) solution in THF(30 ml). Then the solution was left to stir overnight. The desired product was isolated as precipitate after pouring reaction mixture to an ice-cold water. Precipitate was filtered, washed with cold

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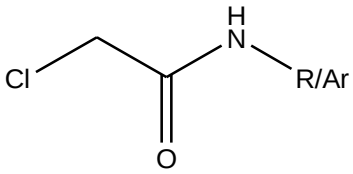
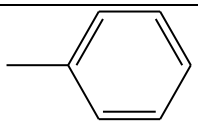
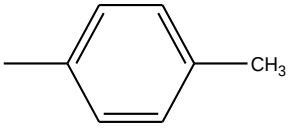
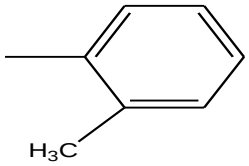
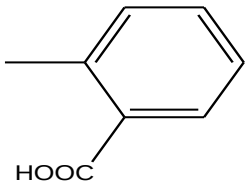
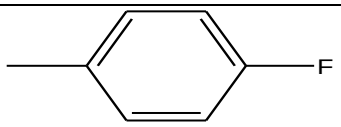
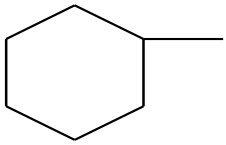
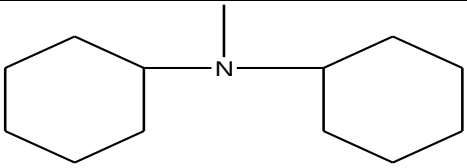
water and dried. Product recrystalised using 95% ethanol [9]. Melting point and percentage yield was reported in table no.1

Table No.1: Melting point, % yield and R_f Value 2-chloro-*N*- Alkyl/Aryl acetamides compounds



Sr. No.	R/Ar	Code	Melting point (^{0}C)	Yield (%)	R_f value
1		A1	135-138	42.70%	0.67
2		A2	148-150	56.69%	0.65
3		A3	170-172	89.40%	0.64
4		A4	190-192	50.28%	0.73
5		A5	90-92	54.59%	0.66
6		A6	208-210	32.49%	0.59
7		A7	240-242	38.10%	0.56

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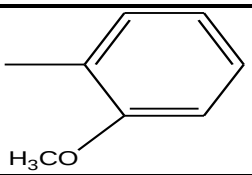
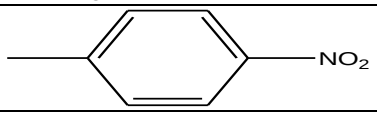
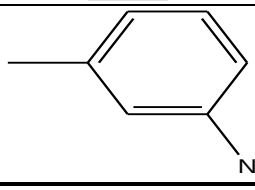
8		A8	118-120	85.6%	0.67
9		A9	180-183	86.96%	0.57
10		A10	174-176	75.38%	0.72

2-Chloro-N-Phenylacetamide(A1): IR 3364.03 (N-H), 3045.24 (C=C-H), 1666.77 (C=O bend), 745.97 (C-Cl); ^{1}HNMR: δ 2.305 (s, CH_3), 4.1 (s, CH_2), 7.35 (m, Aromatic), 6.9 (s, N-H).

2-Chloro-N-(4-methylPhenyl)acetamide(A2): IR: 3269.53 (N-H), 3066.57 (C=C-H), 2915 (C-H), 1671 (C=O), 745.18 (C-Cl).

2-Chloro-N-(2-methylPhenyl)acetamide (A3): IR:3269.83 (N-H), 3088.06 (C=C-H), 1671 (C=O), 1446.55 (C-H bend), 745.39 (C-Cl).

2-Chloro-N-(2-CarboxylPhenyl)acetamide(A4): IR: 2972.17 (C-H), 2622.21 (COOH broad), 1690.07 (C=O), 1407.02 (C-H bend), 752.19 (C-Cl).

2-Chloro-N-(4-FluroPhenyl)acetamide(A5): IR 3271.20 (N-H), 3094.92 (C=C-H), 2947.93 (C-H Bend), 732.67 (C-Cl).

2-Chloro-N-Cyclohexyl acetamide(A6): IR :3360.43 (N-H), 3055.88 (C=C-H), 2910.13 (C-H), 1705.77 (C=O bend), 735.07 C-Cl).

2-Chloro-N-Dicyclohexyl acetamide(A7): IR:3280.83 (N-H), 3058.06 (C=C-H), 1691 (C=O), 1436.45 (C-H bend), 735.29 (C-Cl).

2-Chloro-N-(2-methoxyPhenyl)acetamide(A8): IR: 3287.53 (N-H), 3045.50 (C=C-H), 2925.66 (C-H), 1682.45 (C=O), 746.38 (C-Cl).

2-Chloro-N-(2-NitroPhenyl)acetamide (A9): IR: 3245.33 (N-H), 3022.20 (C=C-H), 2900.26 (C-H), 1672.45 (C=O), 1510.87 (NO_2),733.36 (C-Cl).
2-Chloro-N-(3-NitroPhenyl)acetamide(A10): IR: 3315.13 (N-H), 3011.67 (C=C-H), 2943.26 (C-H), 1678.95 (C=O), 1515.77 (NO_2), 732.78 (C-Cl).

General procedure for Synthesis of *N*-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl)acetamide derivatives: Synthesized 2-chloro-*N*-Alkyl/Arylacetamide derivative **(5)** (0.02mole) was

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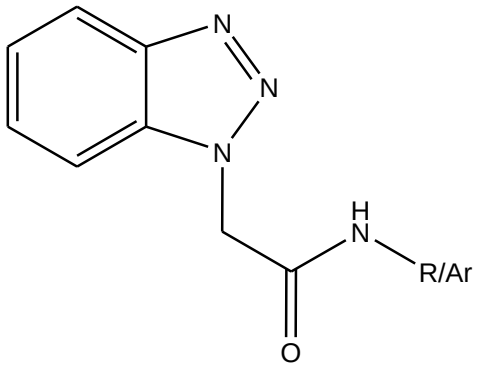
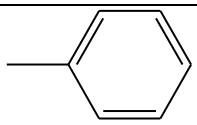
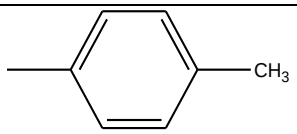
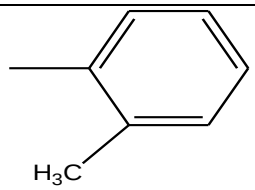
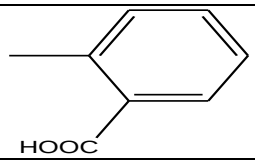
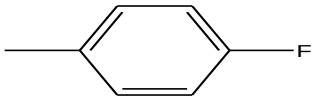
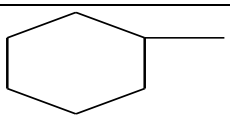
dissolved in DMF. To it benzotriazole **(2)** (0.02mole) in DMF was added. Anhydrous Potassium Carbonate (3g) was added to above reaction mixture. Was heated on heating metal for completion of reaction was monitored using TLC after every 10 min. After completion of reaction, mixture was poured into ice-cold water; precipitate obtained was filtered, dried and recrystalised using 95% ethanol. Melting point and percentage yield was reported in table no.2

Table No.2: Melting point, % yield and R_f Value of *N*-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl)-acetamide derivatives



Sr. No.	R	Code	Melting point (^{0}C)	Yield (%)	R_f value
1		BA1	215-216	28.35%	0.31
2		BA2	215-217	59.76%	0.69
3		BA3	198-200	90.09%	0.48
4		BA4	174-177	91.2%	0.53
5		BA5	204-206	82.14%	0.69
6		BA6	178-180	70.12%	0.69

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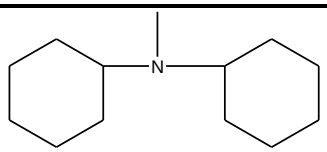
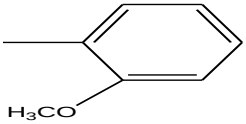
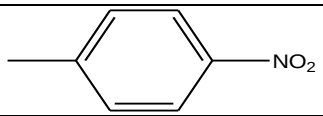
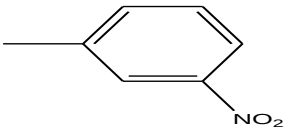
7		BA7	167-169	85.60%	0.66
8		BA8	190-192	79.50%	0.75
9		BA9	132-134	58.13%	0.67
10		B10	206-208	85.96%	0.62

***N*-(Phenyl)-2-(1*H*-benzotriazol-1-yl)-acetamide(BA1):** IR: 3267.47 (N-H), 2954.43 (C-H), 1718.35 (C=O); m/e: 252, 133, 104, 105, 65, 51.

***N*-(4-MethylPhenyl)-2-(1*H*-benzotriazol-1-yl)acetamide (BA2)**: IR: 3200 (N-H), 3074.89 (C=C-H), 1662.87 (C=O); HNMR: δ 1.22 (s, CH_2), 2.305 (s, 2.305); 7.115-7.615 (m, aromatic), 8.225 (s, N-H); m/e : 266, 147, 134, 91.
***N*-(2-MethylPhenyl)-2-(1*H*-benzotriazol-1-yl)acetamide (BA3)**: IR 3221 (N-H), 3078.22 (C=C-H), 1694.27 (C=O); m/e : 266, 134, 91, 77, 65.

***N*-(2-CarboxyPhenyl)-2-(1*H*-benzotriazol-1-yl)acetamide (BA4)**: IR: 2946.87 (C-H), 2730.61 (COOH broad), 1699.57 (C=O), 1420.06 (C-H bend).

***N*-(4-FluroPhenyl)-2-(1*H*-benzotriazol-1-yl)acetamide (BA5)**: IR: 3288.27 (N-H), 2900.13 (C-H), 1705.54 (C=O).

***N*-(Cyclohexyl)-2-(1*H*-benzotriazol-1-yl)acetamide (BA6)**: IR: 3274.98 (N-H), 2974.89 (C=C-H), 1649.80 (C=O).

***N*-(Dicyclohexyl)- 2-(1*H*-benzotriazol-1-yl)-acetamide(BA7)**: IR: 3314.18 (N-H), 2945.77 (C=C-H), 1710.83 (C=O).

***N*-(2-MethoxyPhenyl)-2-(1*H*-benzotriazol-1-yl)-acetamide(BA8)**: IR: 3269.55 (N-H), 2922.33 (C-H), 1720.67 (C=O); m/e: 266, 132,104.
***N*-(2-NitroPhenyl)-2-(1*H*-benzotriazol-1-yl)-acetamide(BA9)**: IR: 3248.13 (N-H), 2944.68 (C-H), 1731.14 (C=O).

***N*-(3-NitroPhenyl)-2-(1*H*-benzotriazol-1-yl)-acetamide(BA10)**: IR: 3310.53 (N-H), 2912.73 (C-H), 1718.60 (C=O)

Pharmacology Activity

Animals: Wister rats (150-200gms) were purchased from Serum lab ltd, Pune. The animals were maintained in the animal house of SND College of Pharmacy, Babhulgaon, Yeola for experimental purpose. Number of animals per group is six.

Acclimatization: One week in experimental room. All the protocols and the experiments were conducted in strict compliance according to ethical principles and guidelines provided by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Instrument: Plethysmometer from orchid scientific Pvt. Ltd. contain glass tube of 20 mm internal diameter and one end fabricated to a glass tube with 0.5 mm bore. This tube is fused to a flexible tube and a pump (glass syringe) and fixed to other end of the tube. This pump is used to adjust the level of mercury in both the flexible tube and graduated glass tube up to zero level.

Selection of animals: After acclimatization, the animals were subjected to a gross observation, to ensure that the selected animals were in a healthy condition. They were then randomly selected for final allotment of the study.

Environmental conditions: Room temperature of 25 ± 1^0C; relative humidity 45-55% and a 12 hr light/ 12 hr dark cycle.

Approval: Approval from the Institutional Animal Ethical Committee (IAEC) of SND College of Pharmacy, Babhulgaon, Yeola with vide letter no. SND/B-ph/2012-13/1156 dated 02/01/2013.

Carrageenan induced rat paw edema method:

sets of groups used for anti-inflammatory activity and contain six animals in each group. All groups were treated orally. Wistar rats (150-200g) of either sex, each group consists of 6 animals. The animals were starved overnight. To ensure uniform hydration, the rats received 5 ml of water by stomach tube (controls) or the test drug dissolved or suspended in the same volume. The animals received vehicle/drug/Diclofenac sodium orally. Sixty minutes later the rats are challenged by injection of 0.1 ml of 1% v/v carregeenan into the plantar region of the left hind paw. The paw was marked with ink at the level of the lateral malleolus and immersed in mercury up to this mark. The paw volume is measured plethysmographically immediately after injection, again at 1, 2, 3, 4 & 5 hrs after challenge. Compare the mean percent change in paw volume.[10]

For comparison purpose, the volume of edema at various prefixed time intervals was measured. The difference between paw volumes of the treated animals was measured and the mean oedema volume was calculated. Group classification and dose of compounds for anti-inflammatory activity are mention in table no. 3

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Table no.3 Group classification and dose of compounds for anti-inflammatory activity

Sr. No.	Group	Compound	Dose
1	I	vehicle	100 mL/Kg
2	II	Diclofenac sodium (std drug)	3 mg/Kg
3	III	BA1	25 mg/Kg
4	IV	BA1	50 mg/Kg
5	V	BA2	25 mg/Kg
6	VI	BA2	50 mg/Kg
7	VII	BA3	25 mg/Kg
8	VIII	BA3	50 mg/Kg
9	IX	BA4	25 mg/Kg
10	X	BA4	50 mg/Kg
11	XI	BA5	25 mg/Kg
12	XII	BA5	50 mg/Kg
13	XIII	BA6	25 mg/Kg
14	XIV	BA6	50 mg/Kg
15	XV	BA7	25 mg/Kg
16	XVI	BA7	50 mg/Kg
17	XVII	BA8	25 mg/Kg
18	XVIII	BA8	50 mg/Kg
19	XIX	BA9	25 mg/Kg
20	XX	BA9	50 mg/Kg
21	XXI	BA10	25 mg/Kg
22	XXII	BA10	50 mg/Kg

Percentage reduction in oedema volume was calculated by using the formula,

$$\text{Percentage reduction} = \frac{Vo - Vt}{Vo} \times 100$$

Where, Vo = Volume of the paw of control at time‘t’.
Vt = Volume of the paw of drug treated at time‘t’.

RESULT AND DISCUSSION

Target compounds were prepared by synthetic scheme described in fig no. 1. 1*H*-1,2,3-Benzotriazole synthesize by reaction of o-phenylenediamine with sodium nitrite in aqueous solution. 2-chloro-*N*- Alkyl or Aryl acetamides prepare by reaction between the different amines and chloroacetylchloride by simple mixing. N-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl) acetamide derivatives synthesize by nucleophilic displacement reaction of 1*H*-1,2,3-Benzotriazole with appropriate 2-Chloro-N- Alkyl or Aryl acetamide. All compounds were obtaining in good yield. All reactions were monitored by analytical thin-layer chromatography. The spectral data (IR and ^{1}HNMR, and Mass spectra) are consistent with assign structures of the compounds.

The anti inflammatory activities of *N*-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl)-acetamide derivatives were studied by Carragennan induced paw edema method. The *N*-(2-

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CarboxyPhenyl)-2-(1*H*-benzotriazol-1-yl)-acetamide in doses of 25mg/kg showed 64.88% inhibition of paw edema. The studies were conducted on Wistar rats of either sex (160-180 g). The change in oedema volume of the rat hind paw was measured using plethysmometer. The *N*-(Alkyl or Aryl)- 2-(1*H*-benzotriazol-1-yl)-acetamide derivatives revealed significant anti inflammatory activities. The anti-inflammatory activity result of 10 derivatives are shown in table no. 4.

Table no.4 Result of anti-inflammatory activity on rat using paw edema volume

S. N.	Treatment	Dose mg/kg	Difference in Paw edema volume (ml) and % of inhibition									
			After 1st hour		After 2nd hour		After 3rd hour		After 4th hour		After 5th hour	
			Edema Volume (ml)	% ROV	Edema Volume (ml)	% ROV	Edema Volume (ml)	% ROV	Edema volume (ml)	% ROV	Edema Volume (ml)	% ROV
1	VEHICLE	10 ml/kg	0.19 ±0.02	--	0.35 ± 0.05	--	0.45 ±0.03	--	0.48 ±.03	--	.44 ±.02	--
2	STD	3	0.13 ±0.01	31.57	0.33 ±0.04	57.41	0.41 ±0.03	88.88	0.20 ±.02***	58.33	0.09 ±.02***	0.795
3	BA1	25	0.18 ±0.1	5.26	0.2333 ±0.03	32.42	0.2352 ±0.02	51.39	0.300 ±.02**	31.25	0.205 ±0.02***	53.4
4	BA1	50	0.17 ±0.02	10.52	0.3350 ±0.04	42.85	0.20 ±0.02	55.55	0.1717 ±.01***	61.84	0.071 ±.04***	83.86
5	BA2	25	0.165 ±0.11	13.15	0.2033 ±0.03	41.91	0.1586 ±0.03	58.08	0.32 ±.03*	35.55	0.2333 ±.01	43.06
6	BA 2	50	0.17 ±0.01*	10.52	0.221 ±0.01**	36.85	0.15 ±0.04*	66.66	0.156 ±.03***	67.5	0.15 ±.02***	65.90
7	BA3	25	0.12 ±0.12	36.84	0.1812 ±0.02	48.22	0.152 ±0.02	66.22	0.145 ±.03***	69.79	0.071 ±.02***	83.86
8	BA3	50	0.166 ±0.01	12.63	0.245 ±0.03	30.0	0.225 ±0.03	50.00	0.175 ±.02***	63.54	0.081 ±.02***	81.59
9	BA4	25	0.14 ±0.01	26.31	0.14 ±0.01	60.0	0.158 ±0.02	64.88	0.18 ±0.01	62.56	0.10 ±0.01	77.27
10	BA4	50	0.145 ±0.01	23.68	0.195 ±0.03	44.28	0.189 ±0.03	58.00	0.169 ±.02***	64.79	.175 ±.02***	60.22
11	BA5	25	0.145 ±0.01	26.31	0.24 ±0.01	31.42	0.425 ±0.02	5.55	0.22 ±0.01	54.16	0.12 ±0.01	72.1

12	**BA5**	**50**	0.123 ±0.01*	35.26	0.177 ±0.01**	49.42	0.2967 ±0.04*	34.06	0.253 ±.03***	47.29	0.15 ±.02***	65.90
13	**BA6**	**25**	0.12 ±0.12	36.84	0.168 ±0.02	52.00	0.172 ±0.02	61.77	0.151 ±.03***	68.54	0.17 ±.02***	61.36
14	**BA6**	**50**	0.13 ±0.01	31.57	0.21 ±0.04	40.00	0.191 ±0.03	58.22	0.20 ±.02***	58.33	0.10 ±.02***	71.27
15	**BA7**	**25**	0.12 ±0.12	36.84	0.163 ±0.02	53.42	0.164 ±0.02	63.55	0.146 ±.03***	69.58	0.14 ±.02***	68.1
16	**BA7**	**50**	0.155 ±0.01	18.42	0.245 ±0.03	30.0	0.192 ±0.03	57.33	0.175 ±.02***	63.54	0.06 ±.02***	86.36
17	**BA8**	**25**	0.146 ±0.11	23.15	0.333 ±0.03	48.57	0.204 ±0.03	54.66	0.156 ±.03*	67.5	0.1333 ±.01	69.7
18	**BA8**	**50**	0.154 ±0.01*	18.94	0.145 ±0.01**	58.57	0.198 ±0.04*	56.00	0.21 ±.03***	56.25	0.15 ±.02***	65.9
19	**BA9**	**25**	0.148 ±0.1	22.10	0.257 ±0.03	26.57	0.174 ±0.02	61.33	0.138 ±.02**	71.25	0.185 ±0.02***	76.36
20	**BA9**	**50**	0.130 ±0.02	31.57	0.222 ±0.04	36.57	0.183 +-0.02	59.33	0.165 ±.01***	65.92	0.080 ±.04***	81.81
21	**BA10**	**25**	0.13 ±0.01	31.57	0.204 ±0.01	41.71	0.169 ±0.02	62.44	0.146 ±0.01	69.58	0.12 ±0.01	72.1
22	**BA10**	**50**	0.123 ±0.01*	35.26	0.175 ±0.01**	50.0	0.174 ±0.04*	61.33	0.155 ±.03***	67.3	0.085 ±.02***	80.68

Values are expressed as mean ± SEM; n=6

*P<0.05, ***P<0.001 compared with vehicle treated group using one way ANOVA.

In this above study with comparison of STD (Diclofinac sodium) the drug sample BA4 in dose 25 mg/kg show effective Anti-inflammatory activity at 3Hr also other sample of drug BA4, BA6, BA7, BA10 show anti-inflammatory activity. The *N*-(2-CarboxyPhenyl)-2-(1*H*-benzotriazol-1-yl)-acetamide (BA4) contain the free carboxyl group show good anti-inflammatory activity. The drug BA2 in dose 50 mg show effective Anti-inflammatory activity at 2Hr and also other sample of drug BA3, BA5, BA6, BA9, BA10 show anti-inflammatory activity. These results suggest that the *N*-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl)acetamide derivatives possesses anti inflammatory. The bar graph of Effect (% inhibition) of Benzotriazole derivatives in Carrageenan induced rat paw edema (Dose 25 & 50 mg/kg) present in fig no 2 & 3.

CONCLUSION

The *N*-(Alkyl or Aryl)-2-(1*H*-benzotriazol-1-yl) acetamide series exhibited anti inflammatory activity with different substituent in different percentages. Compound (BA4)

exhibited 64.88 % at 25 mg/kg dose anti inflammatory activity when compared to the standard drug Diclofenac sodium which showed 88.88% activity. The remaining compounds showed mild moderate (50.00-63.55%) activity. So it confirms that the above mentioned compound having excellent anti inflammatory activity. The carboxyl group is important for the anti-inflammatory activity.

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