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Synthesis, characterization and *in vivo* anti inflammatory activity of some novel 6-fluorobenzothiazole substituted pyarzole analogues

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ABSTRACT

Benzothiazoles and pyrazoles moieties structurally have better pharmacological activity. A Series of 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-3-methyl-1H-pyrazol-5-ol derivatives were synthesized in four phases containing different functional groups have been synthesized by condensing 7- Chloro-6-Fluoro-2-amino-Benzothiazole with hydrazine hydrate in the presence of ethylene glycol and conc. HCl. Then it was treated with ethylacetoacetate in presence of ethanol. In fourth phase 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1H-pyrazol-5-ol was treated with equimolar quantities of various substituted anilines like morph line, piperazine aniline presence of 30ml N,N- dimethyl formamide (DMF). The characterization of the compounds were confirmed on the basis of their spectral (IR, ^{1}H-NMR and MASS) data. Further, they have been screened for their anti-microbial and anti-oxidant activities. Among the synthesized compounds. β-phenyl ethyl amine, m,o-toulidines and shows potent activity against the standard drug.

Key words: HCl, IR, ^{1}H-NMR, MASS, *β*-phenyl ethyl amine, *o*-toulidine,

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INTRODUCTION

Heterocyclic compounds containing nitrogen and sulphur possess potential pharmacological activities. Benzothiazoles are bicyclic ring systems which have been the subject of great interest because of their biological activities[1]. Benzothiazole is a heterocyclic bicyclic ring system with multiple applications, weak base, having varied biological activities and still of great scientific interest in now a days. Benzothiazole moeites are part of compounds showing numerous biological activities such as antimicrobial [2], anti-inflammatory [3], antiallergic [4], antitubercular [5], anticancer [6], fungicidal [7], anti-histamines [8], schistosomicidal [9] etc. Looking at the importance of these moieties, it was thought that the derivatives containing both the nuclei in the same compound are expected to show improved biological activities [10]. They have also found application in industry as anti-oxidants, vulcanization accelerators. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agent [11], and anticancer agents [12].

In the 1950's, a number of 2-aminobenzothiazoles were intensively studied, as the 2-amino benzothiazole scaffold is one of privileged structure in medicinal chemistry [13, 14] and reported cytotoxic on cancer cells [6]. It must be emphasized that combination of 2-aminobenzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering. In

addition, benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties.

The biological and pharmacological importance of various fluorobenzothiazoles and bearing in the importance of fluorine substitution is imparting enhanced activity. Therefore in continuation, it has been felt worthwhile to synthesis some new chloro-fluorobenzothiazoles in association with pyrazoles with hope of that possess anti-inflammatory, analgesic and antibacterial activities [15].

The chemistry and pharmacology of Pyarzole have been of great interest because of its various biological activities, so that the biological and pharmacological activity of pyrazoles with fluoro Benzothiazoles may be taken into account for synergism. It is well known that the introduction of fluorine atom into an organic molecule causes dramatic changes in its biological profile, mainly due to high electro negativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids. Therefore it was thought worthwhile to synthesize better kinds of drugs by incorporating pyrazoles and fluorine atom in Benzothiazole moiety [16-18].

In search for new bioactive potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the pyrazole nucleus and study their biological and pharmacological activity, the review of literature reveal prompted us to synthesis of substituted Fluoro Benzothiazole pyrazole compounds and those will be screened for antimicrobial [6-8], anti-inflammatory and anthelmintic activity to get potent bioactive molecule

MATERIALS AND METHODS

SYNTHETIC METHODS, ANALYTICAL AND SPECTRAL DATA

^{1}H NMR spectra were recorded on BRUKER 300 MHz spectrometer. Solvent is deuterio chloroform. IR Spectra were recorded on ELICO FTIR-8400 spectrophotometer shows different vibration levels of molecules by using KBr pellet technique. Mass spectra were recorded under electron impact at 70 eV on a 70EV Micromass70E instrument. Melting point was recorded on Thiele's apparatus. Thin layer chromatography was performed using precoated aluminium plates coated with silica gel GF_{254} [E.Merck]. N-hexane: ethyl acetate was used as the eluent. The spots were visualized in the ultraviolet light chamber. Mass spectrum was recorded on GCMS QP 5000 shimadzu.

General Procedure for Synthesis of 7-Chloro-6-fluorobenzo[*d*]thiazol-2-amine(1)

To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was placed in a water bath and stirred with magnetic stirrer while 1.6ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rises beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0C and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85^0C and filtered hot. The combined filtrate was cooled and neutralized with ammonia solution to the pH range 6.0 A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow crystals of 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole. After drying in a oven at 80^0C, the dry material (1gm 51.02%) melted at 210-212^{0}C. spectral data: Yellow solid; m.p. 210-211°C, ; R_f = 0.87 (n-hexane : EtOAc); MS *m/z*: 189 , (100%), 203(M^{+1}) ; (KBr) V_{max} (cm^{-1}) 678.12,848.02,1067, 1336.58, 1541.38, 1642.89; ^{1}HNMR(400MHz DMSO d_6 (δppm); 7.22 (s, 2H, NH_2), 7.53(m, 4H, aromatic).

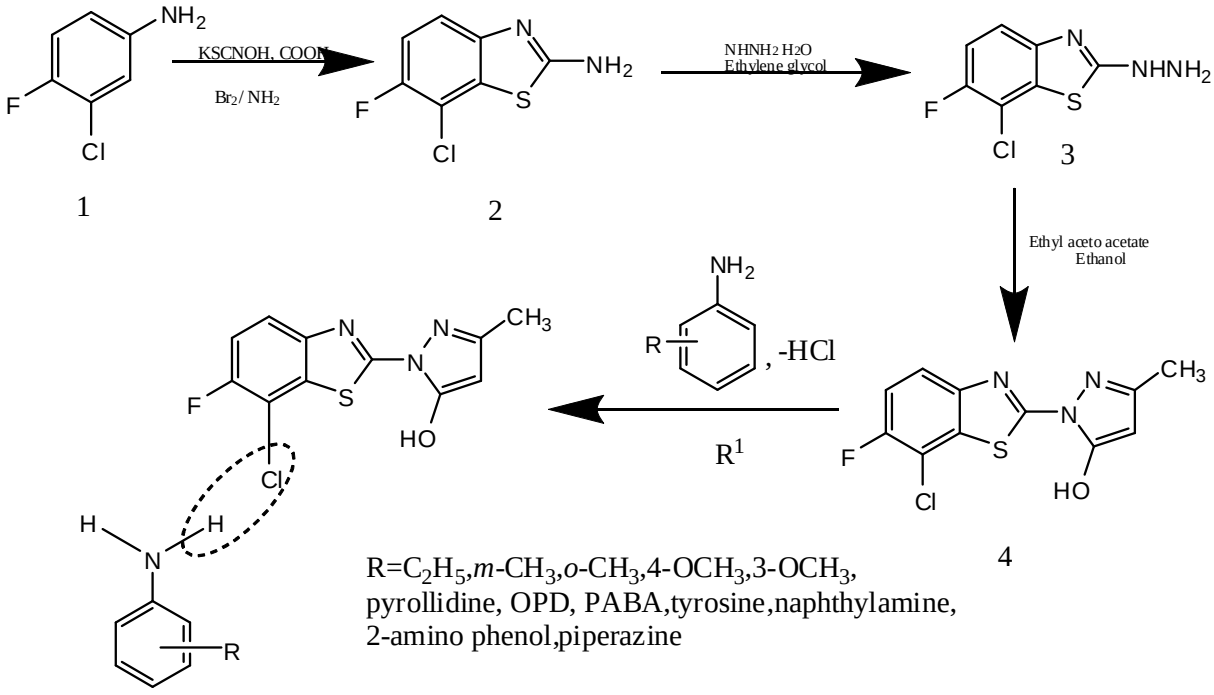
7-Chloro-6-fluoro-2-hydrazinylbenzo[*d*] thiazole (2)

Take 10 ml of concentrated hydrochloric acid in round bottom flask add 12 ml of hydrazine hydrate drop wise cool the mixture and add 20.2gm (0.1 mol) of 2-amino benzothiazole add 40ml of ethylene glycol refluxed for 8hrs, then in hot condition poured into crushed ice. Filter and dry the product and Recrystalised form alcohol. Off white solid; m.p. 233-234°C; R_f =0.89(n--hexane: EtOAc);MS *m/z*:172(100%), 219(M^{+2}).; (KBr)712.96, 802.80,1072.81, 1246.14,1313.91,1547.30,1640.79;^{1}HNMR(400MHz DMSO d_6 (δppm); 4.0(s, 1H, NH),4.59(s,2H, NH_2), 7.53-8.18(M, 4H, aromatic).

1-(7-Chloro-6-fluorobenzo[*d*]thiazol-2-yl)-4-methyl-1*H*-pyrrol-2-ol (3)
21.7gm (0.1mol) of hydrazine Benzothiazole mix with 13.6 ml (0.1mol) of ethyl aceto acetate in a round bottom flask into the 40ml ethanol reflux for 2hrs and later excess of ethanol was distilled of and poured onto the crushed ice. The product obtained was filter and recrystallised form ethanol.Orange white solid; m.p. 233-234°C, R_f= 0.89 (n-hexane: EtOAc); MS *m/z*: 246(100%), 282(M^{-1}). ; (KBr) V_{max} (cm^{-1}) 678.12, 848.56, 1067.01,1200, 1335.78, 1449.02, 1541.59, 1649.59; ^{1}HNMR (400MHz DMSO d_6 (δppm); 2.04(S, 3H, CH_3), 7.53(M, 6H, aromatic), 11.40(s, 1H, OH).

Synthesis of 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1H-pyrazol- 5-ol derivatives(4a-l) To 0.01 mol of 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1H-pyrazol-5-ol was treated with equimolar quantities of various substituted aniline, morph line, piperazine and diphenylamine refluxed for 2 hours in oil bath in presence of 30ml N,N- dimethyl formamide (DMF). The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and crystallized from alcohol and benzene.

SCHEME



1 2 3 4 4a-l

STATISTICAL ANALYSIS

1-(7-(4-ethylphenylamino)-6-fluorobenzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol (4a)

Pale yellow solid; m.p. 140°C; R_f = 0.93 ($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 254, 289,316(100%), 367(M^{-1}) ; IR (KBr) V_{max} (cm^{-1}) 860.16, 1677.2, 1542.14, 1076.14, 1449.01, 1200.94; ^{1}HNMR(400MHz DMSO d_6 (δppm); 2.3-2.4(d,6H,2CH_3, j =4.0), 2.7 (S,2H,CH_2), 7.2-8.7(m,7H,aromatic), 9.77(s,1H,NH), 11.78 (S, 1H, OH).

1-(6-fluoro-7-(m-tolylamino)benzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4b)

Brick red solid; m.p.135°C; R_f=0.84($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* : 286, 301,314(100%), 356(M^{+2}) ; IR (KBr) V_{max} (cm^{-1}) 843.01, 1642.87, 1541.21, 1068.70, 296.90, -1192.12 ; ^{1}HNMR (400MHz,DMSO D_6) (δppm) ;2.30-2.34(d,6H, 2CH_3, j =1.6),7.08-7.30(m,7H,aromatic), 9.77(s,1H,NH) , 11.78 (S, 1H, OH).

1-(6-fluoro-7-(o-tolylamino)benzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol (4c)
Brick red solid; m.p. 137°C; R_f =0.83($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 234,267, 301,323(100%), 355(M^{+1}) ; IR (KBr) V_{max} (cm^{-1}) 843.01, 1642.87, 1541.21, 1068.70, 296.90, -1192.12 ; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm); 2.30-2.34(d,6H, $2CH_3$, *j* =1.6),7.08-7.30(m,7H,aromatic), 9.77(s,1H,NH) , 11.78 (S, 1H, OH).

1-(6-fluoro-7-(4-methoxyphenylamino)benzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4d) Yash color solid; m.p. 157 °C; R_f =0.86($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z*256, 284,,319(100%), 370(M^+) ; IR (KBr) V_{max} (cm^{-1}) 840.151, 1640.56, 1538.45, 1067.02, 1448.58, 1192.01, 2831.90 12 ; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm) ; 2.30-3.83(d,6H, $2CH_3$, *j* =6.0),7.02-7.55(m,7H,aromatic), 9.77(s,1H,NH) , 11.78 (S, 1H, OH).

1-(6-fluoro-7-(3-methoxyphenylamino)benzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4e)Yash color solid; m.p. 160 °C; R_f =0.83($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z*256, 284,319(100%), 370(M^+) ; IR (KBr) V_{max} (cm^{-1}) 840.151, 1640.56, 1538.45, 1067.02, 1448.58, 1192.01, 2831.90 ; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm); 2.30-3.83(d,6H, $2CH_3$, *j* =6.12),7.02-7.55(m,7H,aromatic), 9.77(s,1H,NH) , 11.78 (S, 1H, OH).

1-(6-fluoro-7-(piperizn-1-yl)benzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4f) Light brown solid; m.p148 °C; R_f =0.62($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 268, 298, 312(100%), 333(M^+).; IR (KBr) V_{max} (cm^{-1}) 854.87, 1633.12, 1545.25, 1076.12, 1453.86, 1200.84 ; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm) 2.0(s, 1H, NH), 2.30(S, 3h, CH_3), 2.78-3.46(m, 6H, $3CH_2$), 7.08 (m,11H, aromatic), 11.77 (S, 1H, OH).

1-(6-fluoro-7-amino benzo [d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4g) Off-white solid; m.p. 182°C; R_f =0.81 ($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 198, 209, 221(100%), 265(M^{+2}) ; IR (KBr) V_{max} (cm^{-1}) 848.65, 1646.25, 1545.01, 1069.41, 1449.15, 1193.47 ; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm) 2.30(s, 3H, CH_3),1.92-3.44(d, 8H, $4CH_2$, *j*=6.08),7.28(m, 3H, aromatic), 11.77 (S, 1H, OH).

(S)-2-(6-fluoro-2-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)benzo[d]thiazol-7-ylamino)-3-(4-hydroxy phenyl)propanoic acid (4h) Off-white solid; m.p. =176 °C; R_f =0.55 ($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 289, 346, 387, 401(100%), 430(M^{+2}) ; IR (KBr) V_{max} (cm^{-1}) 837.37, 1580.14, 1580.56, 1042.45, 1450.13, 1197.03; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm) 2.30 (s, 3H, CH_3),3.40(s, 2H, CH_2),6.70-7.05(m, 5H, aromatic), 9.13(s, 1H, NH), 11.78-12.58(m, 3H, 3 OH).

4-(6-fluoro-2-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)benzo[d]thiazol-7-ylamino)-benzoic acid(4i)Brown solid; m.p. =129°C; R_f =0.69 ($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* : 291, 325, 346(100%), 383(M^-) ; IR (KBr) V_{max} (cm^{-1}) 857.72, 1543.78, 1543.66, 1074.89, 1452.10, 1199.1; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm) 2.30 (s, 3H, CH_3), 7.73(m, 7H, aromatic), 9.77(s, 1H, NH), 11.78-12.74(d, 2H, 2 OH, *j*-1.08).

1-(7-(2-aminophenylamino)-6-fluorobenzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4j) Brown solid; m.p. =135°C; R_f =0.84 ($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 267, 319, 349(100%), 357(M^{+2}). ; IR (KBr) V_{max} (cm^{-1}) 846.05, 1544.19, 1644.12, 1068.13, 1450.89, 1193.7; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm); 2.30 (s, 3H, CH_3),6.38-7.02(m, 7H, aromatic),5.19(s, 2H, $1NH_2$) 9.77(s, 1H, NH), 11.78(d, 1H, 1 OH).

1-(6-fluoro-7-(4-hydroxyphenylamino)benzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4k) Black solid; m.p. = 190 °C ;R_f =0.84 ($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 267, 319, 349(100%), 357(M^{+1}) ; IR (KBr) V_{max} (cm^{-1}) 845.59, 1544.45, 1644.86, 1067, 1448.5, 1191.92; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm) 2.30 (s, 3H, CH_3),6.38-7.02(m, 7H, aromatic), 9.77(s, 1H, NH), 9.43, 11.78(d, 2H, 2 OH *j*=8..48).

1-(6-fluoro-7-(naphthalene-1-ylamino)benzo[d]thiazol-2-yl)-3-methyl-1H-pyrazol-5-ol(4l) Brown solid; m.p. = 121°C; R_f =0.97 ($CHCl_3$:EtOAc: n-Bu 1:2:1); MS *m/z* 247, 299, 318,357(100%), 391(M^{+1}). ; IR (KBr) V_{max} (cm^{-1}) 848.19, 1544.85, 1644.86, 1069.58, 1450.1, 1193.4; ^{1}HNMR (400 MHz ,DMSO D_6) (δppm) 2.30 (s, 3H, CH_3),6.98-7.38(m, 10H, aromatic), 9.77(s, 1H, NH), 11.78(d, 1H, 1OH,).

Table-1: physical Parameters of the synthesized compounds (4a-l)

Compounds	Various Amines used	Mol. Formula	Mol. Weight	M.P°C	%Yield	R_f Value	Elemental analysis Calculated		
							C	H	N
4a	β-phenyl ethyl amine	$C_{19}H_{17}FN_4OS$	368.43	140	13.7%	0.93	58.98	5.22	18.17
4b	*m*-toulidine	$C_{18}H_{15}FN_4OS$	354.40	135	17%	0.84	58.37	4.08	18.17
4c	*o*-toulidine	$C_{18}H_{15}FN_4OS$	354.40	157	16%	0.83	58.37	4.08	18.17
4d	*m*-Anisidine	$C_{18}H_{15}FN_4O_2S$	370.40	160	14%	0.86	58.37	4.52	14.95
4e	*p*-Anisidine	$C_{18}H_{15}FN_4O_2S$	370.40	137	11%	0.83	58.37	4.27	14.95
4f	Piperazine	$C_{15}H_{16}FN_5OS$	333.38	148	28%	0.62	53.88	4.39	14.95
4g	pyrrolidine	$C_{15}H_{15}FN_4OS$	264.28	182	16%	0.81	53.88	4.34	16.46
4h	L-Tyrosine	$C_{20}H_{17}FN_4O_4S$	428.44	176	23%	0.55	5924	4.78	15.13
4i	*p*-Amino Benzoic Acid	$C_{18}H_{13}FN_4O_3S$	384.38	129	17%	0.69	58.37	4.48	15.13
4j	*o-phenylene diamine*	$C_{17}H_{14}FN_5OS$	355.39	135	20%	0.84	52.98	4.48	16.76
4k	4-amino phenol	$C_{17}H_{13}FN_4O_2S$	356.37	190	10%	0.75	52.98	3.23	20.16
4l	Naphthyl amine	$C_{21}H_{15}FN_4OS$	390.43	121	25%	0.97	59.74	4.24	16.23

PHARMACOLOGY, CHEMICALS AND REAGENTS

Nutrient agar medium, DMSO, Ciprofloxacin, potato dextrose medium, fluconazole, *p*- nitroso dimethyl aniline, ascorbic acid, hydrogen peroxide, phosphate buffer (pH 7.4), EDTA, wlister rats, tween 80, Diclofenac Sodium, Carrageenan solution.

Table-2: Anti inflammatory activity (*in-vivo*) of synthesized compounds (4a-4l)

S. No	Experimental groups	Mean±SEM (Paw Volume in ml) followed by % Inhibition				
		0hr	1hr	2hr	3hr	4hr
1	Control	1.48±0.03	1.82±0.04	2.19±0.12	2.28±0.32	2.26±0.26
2	4a	1.18±0.08 20.27	1.43±0.14 21.42	1.50±0.12 31.50	1.39±0.10 38.76	1.29±0.10 43.42
3	4b	1.23±0.13 16.89	1.42±0.16 16.89	1.82±0.11 21.97	1.28±0.24 43.61	1.27±0.14 42.29
4	4c	1.40±0.12 5.40	1.83±0.11 26.92	1.51±0.12 29.07	1.61±0.12 31.05	1.47±0.10 35.52
5	4d	1.30±0.13 12.16	1.46±0.11 14.03	1.79±0.10 18.06	1.86±0.09 18.26	1.96±0.04 19.78
6	4e	1.32± 0.14 8.24	1.67±0.16 10.81	1.86±0.13 11.45	2.01±0.13 20.16	2.02±0.16 23.74
7	4f	1.29±0.14 12.8	1.56±0.11 14.28	1.84±0.12 15.98	1.42±0.12 37.44	1.19±0.10 47.80
8	4g	1.32±0.10 16.0	1.49±0.07 18.13	1.68±0.11 23.28	1.69±0.18 25.55	1.58±0.09 30.70
9	4h	1.17±0.10 20.94	1.26±0.09 30.76	1.38±0.12 36.98	1.34±0.07 40.96	1.29±0.08 43.42
10	4i	1.21±0.13 18.24	1.35±0.16 25.82	1.43±0.11 22.63	1.62±0.24 28.41	1.48±0.14 35.08
11	4j	1.32±0.08 11.26	1.58±0.11 11.45	1.82±0.07 13.18	2.01±0.09 14.61	1.92±0.06 15.78
12	4k	1.09 ±0.08 10.50	1.28±0.08 26.35	1.96 ±0.21 29.67	1.47±0.12 35.24	1.30±0.11 42.98
13	4l	1.27±0.14 3.84	1.75±0.22 14.18	1.73±0.21 21.0	1.78±.0.22 21.54	1.56±0.1 29.38
14	Standard	1.37±0.14 7.43	1.47±0.16 19.23	1.51±0.13 31.05	1.47±0.13 35.24	1.40±0.16 38.59

Anti Inflammatory Activity (*In-Vivo*)

Anti-inflammatory activity of prepared compounds was evaluated using carrageenan induced rat hind paw method. The animals were divided into control, standard and test groups each consisting of 6 animals. The first group was treated with Tween80 1% suspension which served as a control. Second group was administered with a dose of 20mg/kg suspension of Diclofenac sodium intra-peritoneal which served as a standard and other groups were treated with 30mg/kg of suspension of test compounds in tween80 after 30min, the rats were injected with 0.1ml carrageenan (1%w/v) to the sub plantar region of left paw of the rats. The volume of paw was measured using potassium permanganate solution displacement technique with the help of plethysmograph both in control and

animals treated with standard and test compounds at 0, 1, 2 and 3hrs after injection of carrageenan. The percentage inhibition of edema was calculated by using the formula [20].

% inhibition = $(1-V_t/ V_C) *100$

Where V_T is the mean paw volume of the test drug, V_C is the mean paw volume of control.

RESULTS AND DISCUSSION

***In-Vivo* Anti Inflammatory Activity:**
Compounds synthesized are screened for *In-Vivo* Anti Inflammatory activity by using Carrageenan induced rat hind paw method at 0,1,2,3 and 4 hrs interval using Diclofenac sodium as standard. The % inhibitions of the synthesized compounds (4a-l) were calculated from mean and standard deviation values. Among the screened compounds **4f, 4b, 4c, 4j and 4k** shows potent activity against the standard. Compounds **4i, 4a, and 4j** shows moderate activity and compound **4l** shows less activity against the standard.

CONCLUSION

It can be concluded that the projected structures of the synthesized compounds are well supported by spectroscopic data and -*Vivo* Anti Inflammatory activity by using Carrageenan induced rat hind paw method. Benzothiazole substituted with **4f, 4b, 4c, 4j and 4k** compounds have significant activity.

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