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SYNTHESIS OF NOVEL 2-BENZYLBENZO[d] THIAZOLE-6-SULFONAMIDE DERIVATIVES AS POTENTIAL ANTI INFLAMMATORY AGENT

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ABSTRACT

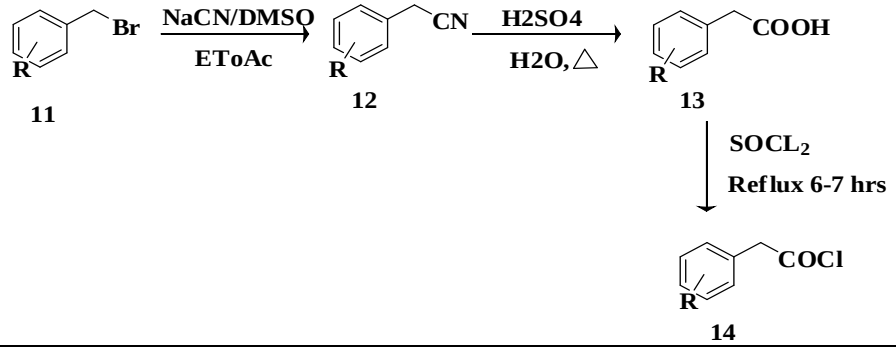
All the newly synthesized benzothiazole derivatives have shown considerable anti-inflammatory activity. In the present research work, we were synthesized a series of novel Benzothiazole derivatives and by using sulfa drugs. The Benzothiazole derivatives such as substituted 2-benzylbenzo[d]thiazole-6-sulfonamide were synthesized from substituted benzyl bromide by scheme 1 & 2. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, Mass spectral and elemental analysis. These compounds were screened for anti-inflammatory activity by carrageenan induced paw oedema method in rats at a dose of 100 mg/kg body weight. Among the tested compounds of benzothiazole derivatives, compounds Rm_2, Rm_3, Rm_5, Rm_8 & Rm_9 exhibited some anti-inflammatory activity but compounds Rm_1, Rm_4, Rm_6, Rm_7 & Rm_{10} were more potent when compared to standard drug celecoxib.

KEY WORDS: - Benzothiazoles, sulfanilamide, Antiinflammatory activity (carrageenan induced paw oedema model), celecoxib.

1. INTRODUCTION

Cyclooxygenase(COX) is the key enzyme which catalyses the conversion of arachidonic acid to prostaglandins and thromboxanes. There are two types of cyclooxygenase enzymes,COX-1 & COX-2.COX-1 is a constitutive enzyme, produced in many tissues such as the kidney and the gastrointestinal tract, and responsible for the normal functioning of kidney and GIT, while COX-2 is inducible and is expressed during inflammation at a site of injury. Currently available NSAIDs inhibit both COX-1 and COX-2 enzymes. Inhibition of COX-1 reduces the basal production of cytoprotective PGE2 and PGI2 and hence causes ulceration. Therefore complete inhibition of COX-1 is not preferred and drugs that inhibit the COX-2 enzyme are better anti-inflammatory agents. This discovery made us to turn our interest towards synthesis of new class of cyclooxygenase inhibitors. This discovery made us to turn our interest towards synthesis of new class of cyclooxygenase inhibitors. Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole which is fused with benzene ring to form benzothiazole moiety which possess interesting biological activities like antimicrobial, anticancer, anthelmintic, anti-diabetic, anti-inflammatory, anticonvulsant, antioxidant, anti-viral, anti-malarial. In present work, it was tried to synthesis compound containing the features namely sulfonamide bearing benzothiazole moiety fused with substituted benzyl moiety to study anti-inflammatory activity.

Scheme.1



11 12 13 14

Scheme.2

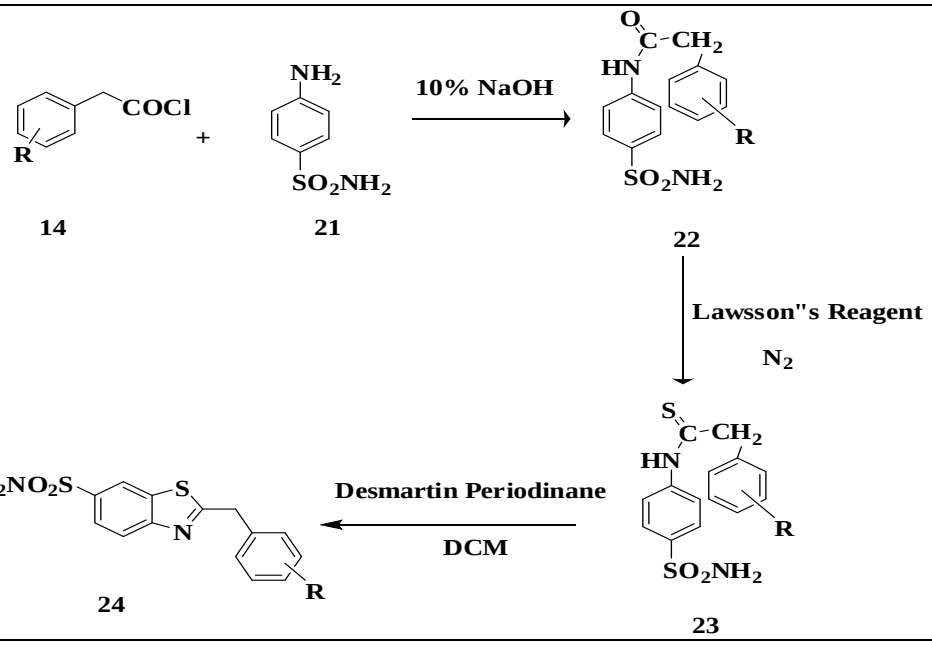


Table.1.Physicochemical properties of compounds (Rm_1-Rm_{10})

Code	-R	Mol. Wt.	M.P	%Yield	Elemental analysis calculated		
					C	N	S
Rm_1	-H	305	172-175^{0}C	77%	55.24	9.20	21.07
Rm_2	2-OH	321	190 ^{0}C	80%	52.48	8.74	20.02
Rm_3	2-oCH_3	334	195-200 ^{0}C	78%	53.87	8.38	19.18
Rm_4	3-Br	382	130 ^{0}C	81%	43.87	7.31	16.73
Rm_5	4-Br	382	185 ^{0}C	84%	43.87	7.31	16.73
Rm_6	2-F	322	150 ^{0}C	79%	52.16	8.69	19.89
Rm_7	4-F	322	155 ^{0}C	82%	52.16	8.69	19.89
Rm_8	2,5-F	331	145 ^{0}C	77%	49.40	8.23	18.84
Rm_9	-NO_2	349	175-180 ^{0}C	80%	48.13	12.03	18.36
Rm_{10}	-Cl	338	180-185 ^{0}C	81%	49.63	8.27	18.93

2. MATERIALS AND METHODS

Melting points of synthesized compounds were determined by open Capillary and are uncorrected. The IR spectra of synthesized compounds were obtained from PERKIN ELMER FTIR-spectrum spectrophotometer. ^{1}H NMR spectra were recorded on Brucker ultraspec 300MHZ using TMS as internal standard and d_6 DMSO as solvent. Mass spectra were recorded on WATERS-Q-T of Premier-HAB213 by ESI method.

General procedure for preparation of following:

Step 1: Synthesis of benzyl cyanide derivatives: A solution of compound 11 (5.26 gm; 20 mmol) in dry DMSO (5ml) was added dropwise to a rapid stirred mixture of NaCN (1.06 gm; 21.6 mmol) in 10 ml DMSO and the reaction mixture was stirried for 5 hrs at room temperature. Water (50 ml) was added and the solution was extracted with ethyl acetate (3x85 ml). The combined organic layer were washed with 30 ml brine and dried over anhydrous Na2SO4. The solution was filtered and the solvent was evaporated to yield compound 12.

Step 2: Synthesis of benzyl acetic acid derivatives: To a stirred suspension of compound 12 (3.4 mmol) in water (2.5 ml) conc. H_2SO_4 (2.5 ml) was added after stirring for 1.5 hr under reflux. The reaction mixture was cooled to room temperature. The combined organic layer was washed with brine water, dried over Na_2SO_4 and concentrated in vacuo to yield compound 13 as a pale orange solid, which was used for the next reaction without purification.

Step 3: Synthesis of benzyl acetyl chloride derivatives: It is prepared by the reaction of compound13 (1 mole) compounds with thionyl chloride (1 mole). The reaction release HCl and SO_2 gas at room temperature. When reaction is complete then benzene is added and the reaction mixture is refluxed for 6-7 hrs at 30˚-40˚C

Step 4: Synthesis of 2-Phenyl-N-(4-Sulfamoyl Phenyl)acetamide derivatives: 1.04 gm of sulphanilamide was added to 15ml of 10% NaOH solution and then 1.7 gm of compound 14 was added and shakes virgously for 20-30 min. The reaction was monitored by TLC. The reaction mixture was warmed on water bath to give compound 22.

Step5: Synthesis of 2- Phenyl-N-(4-Sulfamoyl Phenyl)ethanethioamide derivatives: Lawesson's reagent (1.21gm; 1 mole) was added to a stirred solution of compound 22 (1 gm; 1 mole) in toluene. The mixture was stirred at 100˚C for 3 hrs under N_2. The reaction was monitored by TLC.

Step 6: Synthesis of 2-Benzylbenzo[d]thiazole-6-Sulfonamide derivatives: Dess-Martin priodinane (5.5 mmol) was added to a stirred solution of compound 23 (5.0 mmol) in CH_2Cl_2 at room temperature. The progress of reaction was monitered by TLC. After completion, it was quenched with water (2x5 ml) and the reaction mixture was extracted with CH_2Cl_2 (2x10 ml). The combined organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed in vacuo, to afford the crude product which was purified by the column chromatography on silica gel using petroleum ether/ethyl acetate (8:2) as eluent to give compound 24.

STATISTICS: The reading were calculated by one way ANOVA followed by Dunnet's test

Table-2: Spectral study of compounds (Rm_1-Rm_{10})

Compounds	FTIR (KBr, cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (ppm)	Mass (ESI) m/z
Rm_1	3370 (-NH_2), 1650 (C= N), 1294 (C-N), 795 (C-S-C)	δ 3.81 (s,2H,CH_2), 7.23-7.33 (s,5H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2)	304.03
Rm_2	3372 (-NH_2), 1655 (C= N), 1275(C-N), 756 (C-S-C), 3450 (-OH)	δ 3.81 (s,2H,CH_2), 6.83-7.07 (s,4H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2) 9.68 (s,1H,OH)	320.39
Rm_3	3392 (-NH_2), 1652 (C= N), 1280 (C-N), 795 (C-S-C), 1375 (-CH_3)	δ 3.81 (s,2H,CH_2), 3.83 (s,3H,CH_3), 6.87-7.12 (s,3H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2)	334.41
Rm_4	3376 (-NH_2), 1662 (C= N), 1291 (C-N), 795 (C-S-C), 650 (-Br)	δ 3.81 (s,2H,CH_2), 7.17-7.41 (s,4H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s, 2H, NH_2)	383.28
Rm_5	3375 (-NH_2), 1660 (C= N), 1255 (C-N), 795 (C-S-C), 650 (-Br)	δ 3.81 (s,2H,CH_2), 7.12-7.85 (s,4H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2)	383.28
Rm_6	3370 (-NH_2), 1676 (C= N), 1255 (C-N), 767 (C-S-C), 1029 (-F)	δ 3.81 (s,2H,CH_2), 7.10-7.56 (s,4H,Ar-H), 7.84-8.41 (s,5H,Ar-H), 7.39 (s,2H,NH_2)	322.38
Rm_7	3338 (-NH_2), 1660 (C= N), 1266 (C-N), 767 (C-S-C), 1029 (-F)	δ 3.81 (s,2H,CH_2), 7.12-7.21 (s,4H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2)	322.38
Rm_8	3348 (-NH_2), 1665 (C= N), 1265 (C-N), 765 (C-S-C), 1029 (-F)	δ 3.81 (s,2H,CH_2), 6.75-7.10 (s,3H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2)	340.37
Rm_9	3332 (-NH_2), 1644 (C= N), 1259 (C-N), 754 (C-S-C), 1512 (-NO_2).	δ 3.81 (s,2H,CH_2), 7.49-8.14 (s,4H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2)	349.38
Rm_{10}	3334 (-NH_2), 1650 (C= N), 1291 (C-N), 771 (C-S-C), 724 (-Cl)	δ 3.81 (s,2H,CH_2), 7.17-7.37 (s,5H,Ar-H), 7.84-8.41 (s,3H,Ar-H), 7.39 (s,2H,NH_2).	338.00

Anti-inflammatory activity: Edema was produced by using 1% carrageenan solution. Foot volume were measured in plethysmometer by mercury displacement. The instrument was calibrated before performing the experiment using standard calibrated probe number and standard drug used celecoxib.

Carrageenane induced rat hind paw edema: Anti-inflammatory activity was determined by Carrageenane induced rat hind paw edema method. The tested compounds and reference drug (Celecoxib) were administered orally at a dose level of 100mg/kg and 25mg/kg respectively. After an hour of oral medication, all rats were injected with 1% carrageenan suspension (0.05 ml / animal) into the sub-planter surface of the right hind paw. The thickness of both paws was measured at different time intervals of zero, 1h, 2h and 3h, after carrageenan injection. The anti-inflammatory activity of the tested compounds and celecoxib were calculated as the percentage decrease in edema thickness induced by carrageenan and was determined with the following formula.

$$\text{Percentage inhibition} = \frac{V_c - V_t}{V_c} \times 100$$

Table.3.The anti inflammatory activity of compounds Rm_1-Rm_{10} at different time intervals using carrageenan induced paw edema in rats compared to Celecoxib.

Treatment	N	Paw volume (ml) at time after carrageenan (Mean ± S.E.M)				%I at 3hr
		Initial	1hr	2hr	3hr	
Control	4	0.122 ± 0.0041	0.140 ± 0.0035	0.152 ± 0.0021	0.195 ± 0.0025	-------
Standard	4	0.135 ± 0.0025	0.170 ± 0.0035	0.152 ± 0.0021	0.135 ± 0.0025	30.77 ***
Rm_1	4	0.140 ± 0.0035	0.180 ± 0.0035	0.152 ± 0.0021	0.145 ± 0.0025	25.65 ***
Rm_2	4	0.140 ± 0.0035	0.152 ± 0.0021	0.180 ± 0.0035	0.185 ± 0.0025	5.13
Rm_3	4	0.135 ± 0.0025	0.152 ± 0.0021	0.170 ± 0.0035	0.183 ± 0.0020	6.15
Rm_4	4	0.140 ± 0.0035	0.170 ± 0.0035	0.160 ± 0.0035	0.148 ± 0.0017	24.10 ***
Rm_5	4	0.135 ± 0.0025	0.152 ± 0.0021	0.180 ± 0.0035	0.180 ± 0.0025	7.69
Rm_6	4	0.145 ± 0.0025	0.170 ± 0.0035	0.152 ± 0.0021	0.150 ± 0.0035	23.08 ***
Rm_7	4	0.140 ± 0.0035	0.180 ± 0.0035	0.160 ± 0.0035	0.152 ± 0.0021	22.02 ***
Rm_8	4	0.140 ± 0.0035	0.152 ± 0.0021	0.170 ± 0.0035	0.182 ± 0.0035	6.67
Rm_9	4	0.135 ± 0.0025	0.160 ± 0.0035	0.180 ± 0.0035	0.181 ± 0.0036	7.18
Rm_{10}	4	0.145 ± 0.0025	0.180 ± 0.0035	0.160 ± 0.0035	0.144 ± 0.0048	26.15 ***

Data represent:Mean ± S.E.M = Standard Error Mean, N= numbers of animals, % I= Percentage reduction of oedema, * = significant (P < 0.05)**

3. RESULTS AND DISCUSSION

The anti-inflammatory activity of the synthesized benzothiazole derivatives of compounds were determined by the carrageenan induced paw edema methods in rats. The anti-inflammatory activity of the synthesized compounds was observed in respect to the standard anti-inflammatory drug Celecoxib. The all synthesized compounds Rm_1-Rm_{10} were selected for anti-inflammatory activity in a dose 100 mg/kg body weight. The compounds Rm_2, Rm_3, Rm_5, Rm_8 and Rm_9 were show very slightly effect of activity, which was shown in Table 3. So the compounds Rm_1, Rm_4, Rm_6, Rm_7 and Rm_{10} can be considered as potent anti inlammatory agents of benzothiazole derivatives.

4. CONCLUSION

From the data of the anti-inflammatory activity it is clearly concluded that the synthesized compounds are promisingly significant and good anti-inflammatory agents. From the results of screening it is clearly indicated that the compound Rm_1 i.e. benzyl bromide which is attached to benzothiazole molecule had shown the potent activity, and Rm_4, Rm_6, Rm_7 and Rm_{10}, i.e.-3-bromo benzyl, 2-flouro benzyl, 4-flouro benzyl, & p-chloro benzyl attached to benzothiazole molecule had shown the potent activity.

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