

SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SUBSTITUTED PHENYL THIAZOLE DERIVATIVESPrateek Porwal^{*1}, Lavkush Tiwari², Sonali Paliwal¹, Harsh Sharma¹, Harendra Kushwah¹ and Komal Pal¹¹SRAM College of Pharmacy, Tundla, Firozabad.²Nalanda College of Pharmacy, Cherlapally, Nalgonda, T. S.

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ABSTRACT

The derivatives of substituted phenyl thiazoles are synthesized from acetophenones and thiourea. The synthesized compounds have been characterized by TLC, elemental analysis, IR,^[1] H.NMR spectroscopy. All the compounds were evaluated for anti-inflammatory activity by formalin and carrageenan induced rat hind paw edema method by using nimesulide drug as standard. Nitro substituted thiazole derivatives shows better anti-inflammatory activity when compared to standard drug.

KEYWORDS: Thiazole, anti-inflammatory, carrageenan, formalin.

INTRODUCTION

Inflammation is a local response to living mammalian tissues to injury due to any agent. Acute inflammation is a rapid response to an injurious agent that serves to deliver mediators of host defense-leukocytes and plasma proteins to the site of injury.^[1] Chronic inflammation can be considered to be inflammation of prolonged duration in which active inflammation; tissue injury and healing precede simultaneously.^[2] 2-substituted-N-(4-substituted-phenylthiazol-2yl) acetamides are synthesized from thiourea and substituted acetophenones.^[3] Phenyl thiazoles and their derivatives have possessed versatile biological activity. The new antioxidant and anti-inflammatory drugs lacking those effects are being searched all over the world as alternatives to synthetic drugs. On the other hand, the presence of polyphenolic compounds such as phenolic acids, vitamins (α -tocopherols, ascorbic acid) and other substances is widely used as safe natural non-nutritive chemicals have protected the humans from inflammation and oxidative stress related disorders.^[4] The synthesis of thiazole derivatives is important for their wide range of pharmaceutical and biological properties. There are widespread therapeutic uses of synthetic heterocycles such as antibacterial, antimycobacterial, trypanocidal, anti-HIV activity, genotoxic, herbicidal, analgesic, anti-inflammatory, muscle relaxants, antileishmanial agents, anticonvulsant, anticancer, antimalarial, antifungal and lipid peroxidation inhibitor, antitubercular, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents.^[5,6,7,8,9,10] Thiazole derivatives display a wide range of biological activities such as cardiotoxic, fungicidal, sedative, anaesthetic,

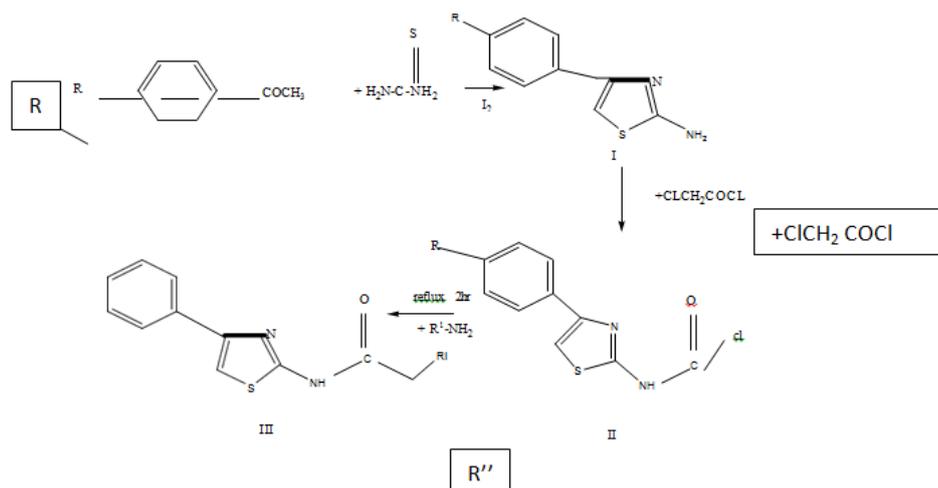
bactericidal and anti-inflammatory activity.^[11]**Experimental Work**

STEP 1: A mixture of Substituted acetophenones, thiourea and iodine to be heated overnight and cooled and extracted with ether. The solutions are dissolved in boiling water and add ammonium hydroxide. Finally amino thiazole is obtained and recrystallized from water, alcohol. M.P 125-135^oc.

STEP 2: To substituted amino thiazole add 25ml glacial acetic acid and 25ml sodium acetate, stir the solution. To this add chloro acetyl chloride and heated for 30min and pour over crushed ice and finally washed with 50% aqueous acetic acid and with water. Finally recrystallized from ethanol. M.P 226-228^oc.

STEP 3: To the compound2 add alcohol and different secondary amines and refluxed for 2hour and add crushed ice. Finally recrystallized by distilled alcohol and dried in vacuum desiccators.

Scheme



List of Substituents

Compounds	R	R'' -	
3a	NH ₂	C ₆ H ₅ C ₆ H ₅	N
3b	NH ₂	CH ₃ CH ₂ CH ₂ CH ₃ CH ₂ CH ₂	N
3c	NO ₂	C ₆ H ₅ C ₆ H ₅	N
3d	NO ₂	CH ₃ CH ₂ CH ₂ CH ₃ CH ₂ CH ₂	N
3e	Br ₂	C ₆ H ₅ C ₆ H ₅	N

Anti-inflammatory activity**Carrageenan induced rat hind paw edema method**

Anti inflammatory activity to be evaluated using carrageenan induced rat hind paw edema method. Wister rats of either sex weighing between 150-200 g were divided into five groups of six animals in each group. The I group served as a control and received the vehicle (saline) only. II group of animals were treated with standard drug Nimesulide (20mg/kg). Nimesulide it's used as selective COX-2 inhibitors compare with indomethacin and naproxen.

The animals of the other groups (3, 4 and 5) to be treat with calculated doses of synthesized thiazoles. The mark to be made on both hind paws just below the tibio-tarsal joint. So that always the paw could maintain constant paw volume. After 30 minutes of drug treatment and inflammation of induced in the left hind paw by injecting 0.1 ml of carrageen 1% solution in the sub planter region of all the animals. The paw volume is to be measured at 15, 30, 60,120,150,180,210,240 minutes after the carrageen challenging.

The mean difference in initial paw volume and subsequent reading was noted and percentage inhibition of edema to be calculated using the formula.

- Percentage inhibition = $100(1-V_t/V_c)$

- Where V_t = represent edema volume in test
- V_c = represent edema volume in control.

Formalin Induced Acute Paw Edema Method

Overnight-fasted Wister rats were randomly assigned to 5 groups of 6 rats in each group. Such animals received intra peritoneally solvent, or test drugs or Diclofenac sodium (45mg/kg). Inflammation was produced in all the animals by injection of 0.1 ml of 1% w/v formalin into the subplantar region of left hind paw. The paw volume was measured using mercury displacement technique, with the help of plethysmograph at 0 to 3 hour after formalin injection. The difference between 0 and 3hour reading were taken as the volume of edema and percentage reduction of edema was calculated for each group.

RESULTS AND DISCUSSION

A new series of phenyl thiazole derivatives were synthesized. The structures of the synthesized compounds were confirmed by IR, NMR and C, H, N analysis. The compounds were subjected to anti-inflammatory activity by carrageenan induced rat hind paw edema method using Nimesulide drug as a standard. Melting points were determined in open capillary tubes and were found uncorrected. IR spectra were recorded on FT-IR spectrometer using KBr pellet method. ¹HNMR

spectra were recorded on ¹H FT-NMR spectrometer in DMSO. The compounds were analyzed for elemental analysis and the percentage of elements was found to be

very near that of the calculated values. Physical data were recorded in table-1 and spectral data in table-2.

Table 1: Physical Parameters and Elemental Analysis of Synthesized Compounds.

Compound	Molecular Formula	Molecular weight	M.P(°C)	Yield (%)	Rf value
3a	C ₂₃ H ₂₀ N ₄ OS	400.5	175-177	72	0.7
3b	C ₁₄ H ₁₈ N ₄ OS	290.38	180-181	60	0.69
3c	C ₂₃ H ₁₈ N ₄ O ₃ S	430.48	172-174	70	0.8
3d	C ₁₄ H ₁₆ N ₄ O ₃ S	320.37	170-171	76	0.73
3e	C ₂₃ H ₁₈ BrN ₃ OS	464.38	178-181	58	0.61

Table 2: Spectral Analysis of Synthesized Compounds.

Compound	IR-KBr (cm ⁻¹)	¹ H NMR(DMSO)δ in ppm
3a	3637,3625,3605,3583,2941,2866,2690,1819,1804, 1757,1742,1725,1691,1582,1549,1368,1183,599, 568	8(s,H),7.2(s,H),6(s,H),6.6(s, H),6.5(s,H),4(s,H)3.9(s,H)
3c	3109,1961,1862,1822,1786,1692,1652,1523,1364, 1318,1262,962,900,855,707,618	8.2(s,H),4(s,2H),3.5(s,H),2.5 d,4H)
3d	2986,2176,1964,1861,1786,1513,1364,1134,803, 640,569	8(s,H),6.6(s,H),4(s,H),2(s,H), 1.1(t,6H)

Table 3: Carrageenan Induced Rat Paw Oedema Method For Synthesized Compounds.

S. No.	Compound	Mean Paw Oedema Volume(ml)± SD				Percentage inhibition
		0h	1h	2h	3h	
1	Control(2 % cmc)	0.68± 0.0041	0.703± 0.005**	0.72± 0.0089	0.7416± 0.0075	–
2	Standard (Nimesulide 20mg/kg)	0.678± 0.0075**	0.633± 0.010**	0.556± 0.005**	0.513± 0.008**	60%
3	Compound 3a	0.656± 0.01	0.626± 0.02**	0.556± 0.01**	0.571± 0.063*	23%
4	Compound 3c	0.654± 0.007**	0.607±0.0 1**	0.535±0.01 *	0.524± 0.009**	30%
5	Compound 3d	0.644± 0.025	0.6071± 0.017**	0.521± 0.613 ^{ns}	0.428± 0.015*	44%

All the values are expressed as mean ± SEM (n=6), *p <0.05, **p<0.01vs control. (One-way ANOVA followed by Dennett's test)

Table 4: Formalin Induced Rat Paw Oedema Method For Synthesized Compounds.

S. No.	Compound	MEAN ± SD				Percentage inhibition
		0h	1h	2h	3h	
1	Control (2 % cmc)	0.68± 0.0041	0.703± 0.005**	0.72± 0.0089	0.7416± 0.0075	–
2	Standard (Indomethac in 45mg/kg)	0.678± 0.0075**	0.633± 0.010**	0.556± 0.005**	0.513± 0.008**	60%
3	Compound 3a	0.58± 0.003	0.615± 0.01**	0.576± 0.016**	0.529± 0.013	29%
4	Compound 3c	0.650± 0.035	0.64± 0.012**	0.56± 0.69 ^{ns}	0.48± 0.03*	36%
5	Compound 3d	0.632± 0.005**	0.635± 0.03**	0.815± 0.02**	0.44± 0.006*	41%

All the values are expressed as mean ± SEM (n=6), *p <0.05, **p<0.01vs control. (One-way ANOVA followed by Dennett's test)

CONCLUSION

The anti-inflammatory activity may derive from a combination of inhibition of pro-inflammatory mediator

release, vascular permeability and neutrophil migration.^[18] Based on the literature review some of the thiazole derivatives were synthesized. The completions

of the reaction were confirmed by TLC and all the synthesized compounds were purified by recrystallization. These compounds were characterised by IR, ¹H NMR and evaluated for their anti-inflammatory activity. An IR and ¹H NMR study shows the structure of the synthesized compounds. In the sense, we found that all the synthesised thiazole derivatives possess appreciable anti-inflammatory activity. The anti-inflammatory activity of all the synthesized compounds were screened by Carrageenan and formalin induced rat paw edema method. The results were tabulated in table-3, 4 showed that the 3c compound better activity at 3rd hour and others 3a, 3d, showed appreciable anti-inflammatory activity.

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