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SYNTHESIS AND EVALUATION OF SOME NEW PHENYL THIAZOLE DERIVATIVES FOR THEIR ANTI-INFLAMMATORY ACTIVITES

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ABSTRACT:

The present research work is aimed to synthesize some novel substituted phenyl thiazole. The fifteen new derivatives of phenyl thiazole (Scheme) were synthesized during the course of research work. The structures of compounds have been established by means of FT IR, ^{1}H-NMR and CHN elemental analysis. All the compounds were evaluated for anti-inflammatory activity by Carrageenan Induced Rat hind paw method. Out of fifteen compounds **T_1 T_4**, **T_6**, **T_{11}**, **T_{13}**, and **T_{14}** show maximum anti-inflammatory activity.

Key words: Phenyl thiazole**,** anti-inflammatory; CHN analysis

INTRODUCTION:

Phenyl thiazole and their derivatives have possessed versatile biological activity. [1,2,3]. Inflammation is defined as the local response to living mammalian tissues to injury due to any agent. Specifically it is a series of molecular and cellular responses acquired during evolution designed to eliminate foreign agents and promote repair of damaged tissues. There are two fundamental types of inflammation

1) Acute inflammation 2) Chronic inflammation 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. This process has two major components. Vascular changes: Increased blood flow (vasodilation) and structural changes that permit plasma proteins to leave the circulation (increased vascular permeability). Cellular events: Emigration of the leukocytes from the microcirculation and accumulation in the focus of injury. Chronic inflammation can be considered to be inflammation of prolonged duration (weeks to months to years) in which active inflammation; tissue injury and healing proceed simultaneously. [2]

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MATERIAL AND METHODS

EXPERIMENTAL:

Synthesis of 2-amino-4-substituetedphenylthiazole (I): [5,6]

A mixture consisting of 0.1mole of ketone, 0.2mole of thiourea and 0.1 mole of Iodine were heated overnight on the steam bath. This crude reaction mixture was cooled and extracted with ether to remove unreacted ketone and iodine. This residue was then dissolved in boiling water and filtered to remove sulphur. Then the solution was cooled somewhat and made basic with ammonium hydroxide. The amino thiazole, which separated, was recrystallized from water alcohol. Melting point 125-135^{o}C.

Synthesis of (Z)-4-((2, 4-Dioxothiazolidin-5-ylidene) methyl)-*N*-(4-substituted phenylthiazol-2-yl) benzene sulfonamides (T_1-T_4)

0.1mole of substituted aryl thiazole and 0.1 mole of 4'-chlorosuplhonyl benzylidine-2, 4-thiazolidinedione were added to a mixture of 4 ml of dry pyridine and 20 ml of acetic anhydride. The mixture was refluxed for 2 hour. The reaction mixture was then poured into 20 ml of ice water and solid obtained was filtered and purified by recrystallization from ethanol. **(**Yadhav,L, et al.**)**

Synthesis of 2-chloro-N-(4-phenylthiazol-2-yl)-acetamide (II):

An exact quantity of 0.01 moles of substituted thiazole was dissolved in 25 ml of Glacial acetic acid and 25 ml of saturated solution of Sodium acetate. In case the substance did not dissolve completely, the mixture was slightly warmed. The solution was cooled in ice bath with stirring. To this stirred solution, chloroacetyl chloride (0.12 mole) solution added drop wise. To prevent the occurrence of vigorous reaction the temp was maintained at 0^{o}C then reaction was heated for 30 mins after this cool the mixture and pour over crushed ice white product was separated by filtration. The product was washed with 50% aqueous acetic acid and finally with water. It was recrystallized from ethanol. M.P. – 226-28°C. **(**Korekar, H.A *et al.,* 1978**)**

Synthesis of 2-substituted-N-(4-Substituted-phenylthiazol-2yl) Acetamides (T_5-T_{15}):

A mixture of 0.01 mole of each 2-chloro-N-(4-substituted phenylthiazol-2-yl)acetamides (II) were taken in dry 250 ml round bottom flask separately to this distilled alcohol is added as solvent and to this different secondary amines were added in 0.01 mole concentrations and refluxed for 2 hour after reflux add reaction mixture to crushed ice precipitation formed is filtered and recrystallized by distilled alcohol and product was dried in vacuum dessicator, melting points and percentage yields were reported in Table. (Xiao, H *et al.,* 1999).

ANTI-INFLAMMATORY ACTIVITY:

Materials: Edema was produced by using type IV lambada Carrageenan from sigma laboratories. Foot volumes were measured in Plethysmometer by water displacement.

The instrument was calibrated before performing the experiment using standard calibrated probe number and standard drug used Nimesulide was obtained from Lincoln Pharmaceuticals ltd. Ahmedabad.

Method:

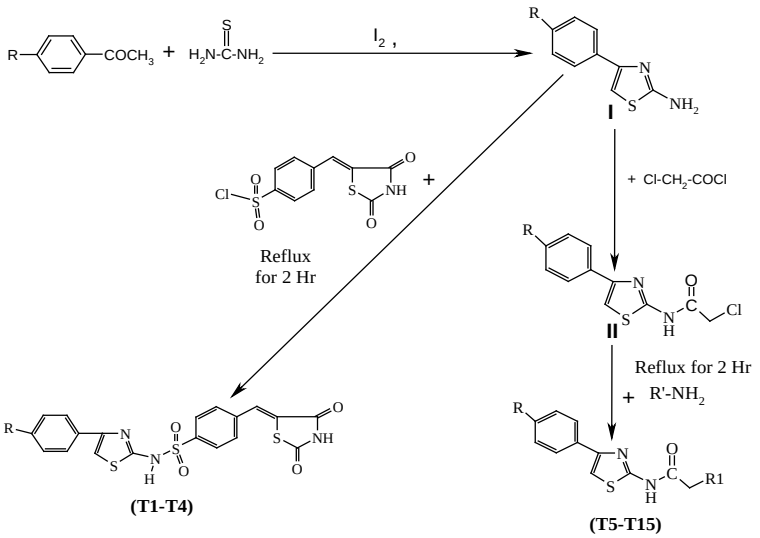
Carrageenan Induced Rat hind Paw Edema:

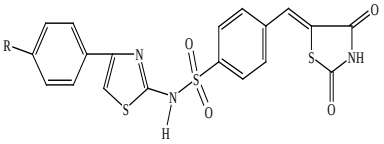
Anti-inflammatory activity was determined by Carrageenan Induced Rat hind Paw method of winter et al. wistar rats (120-150 g) was used for the experiment. The drugs were prepared as a suspension by triturating with water and 0.5% sodium CMC. The standard group received 50mg/kg body weight of Nimesulide, test group received 200mg/kg body weight of synthesized compounds and the control group received 1% w/v of CMC. The difference between 0hour reading and one of the subsequent readings provides the actual edema volume at that time. The mean paw volume at different times was calculated and compared with the control. The percentage inhibition of inflammation after 4 hour was then calculated by using the formula. **(**Salvemini, D *et al.,* 1995).

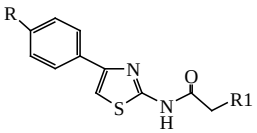
RESULT AND DISCUSSION

A new series of phenyl thiazole derivatives were synthesized. The structures of the synthesized compounds were confirmed by IR, NMR and CHN analysis. ClogP and CMR were also calculated. The compounds were subjected to anti-inflammatory activities by Paw Edema method using Nimesulide drug as standard. All the compounds have shown promising anti-inflammatory activities. Compounds T_1-T_{15} has shown excellent anti-inflammatory activities with molecular modification and manipulation these agents can be explored as promising anti-inflammatory agents in future.

SCHEME:







Compounds	R
T_1	-H
T_2	-OH
T_3	-Cl
T_4	-OCH_3

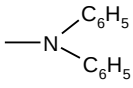
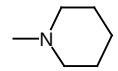
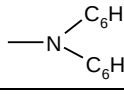
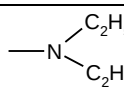
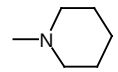
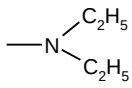
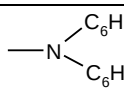
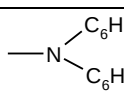
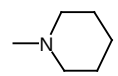
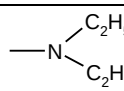
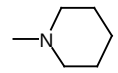
COMPOUNDS	R	R_1
T_5	-H	
T_6	-H	
T_7	-OH	
T_8	-OH	
T_9	-CH_3O	
T_{10}	-CH_3O	
T_{11}	-CH_3O	
T_{12}	-Cl	
T_{13}	-Cl	
T_{14}	H	
T_{15}	-OH	

Table No: 1 Anti-inflammatory activity of 2-substitutedamino-4-(4-substitueted) phenyl thiazole compounds (T_1-T_{15})

Compound code	Mean paw oedema volume ± SE					% Inhibition at 3rd hr
	0 hour	1/2 hour	1 hour	2hour	3hour	
Control.	1.20±0.03	1.44±0.05	1.58±0.02	1.76±0.02	1.82±0.02	
Std. (Nimesulide)	1.12±0.03	1.14±0.02**	1.22±0.02**	1.36±0.02**	1.24±0.02**	31.86
T_1	1.14±0.04	1.24±0.02*	1.30±0.04**	1.44±0.04**	1.36±0.02**	25.27
T_2	1.18±0.02	1.24±0.02*	1.32±0.04**	1.52±0.03**	1.50±0.00**	17.58
T_3	1.08±0.02	1.24±0.02*	1.32±0.02**	1.54±0.04**	1.42±0.02**	21.97
T_4	1.08±0.03	1.26±0.02*	1.34±0.02**	1.48±0.03**	1.36±0.04**	25.27
T_5	1.18±0.03	1.24±0.02*	1.34±0.02**	1.46±0.04**	1.38±0.02**	24.17
T_6	1.18±0.03	1.26±0.02*	1.32±0.02**	1.54±0.02**	1.34±0.02**	26.37
T_7	1.20±0.03	1.30±0.03*	1.36±0.02**	1.48±0.03**	1.42±0.02**	21.97
T_8	1.14±0.04	1.26±0.04*	1.30±0.02**	1.48±0.02**	1.44±0.02**	20.87
T_9	1.20±0.05	1.30±0.08*	1.40±0.03**	1.50±0.03**	1.42±0.02*	21.97
T_{10}	1.12±0.03	1.28±0.03*	1.38±0.03**	1.42±0.03**	1.38±0.03**	24.17
T_{11}	1.16±0.02	1.20±0.03*	1.36±0.02**	1.46±0.05**	1.34±0.02**	26.37
T_{12}	1.16±0.02	1.24±0.02*	1.32±0.03**	1.46±0.02**	1.40±0.03**	23.07
T_{13}	1.16±0.02	1.20±0.04*	1.26±0.04**	1.38±0.03**	1.34±0.02**	26.37
T_{14}	1.20±0.05	1.24±0.03*	1.30±0.04**	1.40±0.03**	1.28±0.03**	29.67
T_{15}	1.14±0.05	1.28±0.04*	1.36±0.02**	1.48±0.03**	1.38±0.02**	24.17

One way ANOVA followed by Dunnett's't' test
*P<0.05, **P<0.01-Significant.
Compounds **T_1** **T_4**, **T_6**, **T_{11}**, **T_{13}**, and **T_{14}** have shown significant anti-inflammatory activity. Nimesulide was used as a standard drug.

Table No-2: Analytical & Physicochemical data of the synthesized compounds (T_1-T_{15})

Comp.	Mol. Formula	Mol. Wt.	m.p. ° C	Yield %	Elemental analyses Calcd. (Found)			LogP	CLogP	CMR
					C	H	N			
T_1	$C_{19}H_{13}N_3O_4S_3$	443.51	185-88	78	51.47 (51.45)	2.97 (2.95)	9.50 (9.47)	3.7	2.37	11.7
T_2	$C_{19}H_{13}N_3O_5S_3$	459.59	234-36	81	49.70	2.88	9.17	5.7	1.9	11.9
T_3	$C_{19}H_{12}ClN_3O_4S_3$	477.96	260-63	66	47.80	2.55	8..81	4.2	3.09	12.2
T_4	$C_{20}H_{15}N_3O_5S3$	473.54	241-43	55	50.75 (50.73)	3.21 (3.19)	8.90 (8.87)	3.1	1.3	12.3
T_5	$C_{35}H_{35}N_3OS$	387.14	90-94	84	71.31 (71.29)	5.48 (5.46)	10.87 (10.84)	6.0	5.9	11.5
T_6	$C_{16}H_{19}N_3OS$	301.40	153-55	71	63.80	6.38	13.97	3.3	3.8	8.6
T_7	$C_{23}H_{19}N_3O_2S$	401.80	74-76	67	68.84 (68.81)	4.80 (4.77)	10.50 (10.47)	5.6	5.4	11.6
T_8	$C_{15}H_{19}N_3O_2S$	305.39	105-107	80	59.22	5.98	13.83	-	1.54	8.1
T_9	$C_{17}H_{21}N_3O_2S$	331.43	225-227	83	61.65 (61.61)	6.42 (6.39)	12.70 (12.68)	2.7	2.8	9.2
T_{10}	$C_{16}H_{21}N_3O_2S$	319.42	233-35	75	60.19	6.65	13.19	-	0.48	8.56
T_{11}	$C_{24}H_{18}N_3O_2S$	415.50	140-42	73	69.39	5.12	10.14	-	1.9	12.0
T_{12}	$C_{23}H_{18}ClN_3OS$	419.92	95-97	68	65.80 (65.78)	4.35 (4.32)	10.06 (10.01)	-	3.7	11.94
T_{13}	$C_{16}H_{18}ClN_3OS$	335.85	104-06	72	57.25	5.44	12.54	3.8	4.5	9.1
T_{14}	$C_{15}H_{19}N_3OS$	289.39	128-130	86	62.50	6.32	14.60	-	2.0	8.0
T_{15}	$C_{16}H_{19}N_3O_2S$	377.40	83-86	54	60.58	6.05	13.28	2.9	3.37	8.7

The combustion analysis of compounds synthesized is within the limits of permissible errors.

SPECTRAL DATA:Infra Red / ^{1}H-NMR spectral study of the synthesized compounds. (T_1-T_{15})

Compound T_1: IR Bands (cm^{-1}): 3167(-N-H str), 3023(-C-H Ar. str) 1697(-C=O str.), 3065(-C=Cstr), 1580(-C=N str), 716(C-S str-) 820(-C-H def.).

^{1}H-NMR (δ Values in ppm): 11.96(2H of NH), 7.98(1H of HC=C), 7.41-7.79(9 H m Ar CH), and 7.28(1H Ar of thiazole).

Compound T_2: IR Bands (cm^{-1}): 3166(-N-H str), 2995(C-H Ar. str) 1697(-C=O str.), 3062(-C=Cstr) 1580(-C=N str), 693(-C-S str.), 799(-C-H def.).

Compound T_3: IR Bands (cm^{-1}): 3173(-N-H str), 2998(-C-H Ar.str), 1700(-C=O str), 3069(-C=Cstr), 1581(-C=N str), 711(-C-S str), 733(-C-H def)

Compound T_4: IR Bands (cm^{-1}): 1177(-C-O-N-H str), 3169(-C-H Ar.str), 1696(-C=O str), 3034(-C=Cstr), 1581(-C=N str), 690(-C-S str)

^{1}H-NMR (δ Values in ppm): 12.0(2H of NH), 7.94(1H of HC=C), 7.01-7.69(8H m Ar CH), 7.35(1H of thiazole), and 3.82(3H of -OCH_3).

Compound T_5: IR Bands (cm^{-1}): 3159(-N-H str), 3114(-C-H Ar.str), 1597(-C=O str.), 3041(-C=Cstr), 1533(-C=N str), 1315(-C-N str) 716(C-S- str), 746(-C-H def).

^{1}H-NMR (δ Values in ppm): 6.68-7.34(15H m Ar CH), 7.25(1H of thiazole), and
3.2(3H of CH_2)

Compound T_6: IR Bands (cm^{-1}): 3255(-N-H str), 3114(-C-H Ar.str), 1599(-C=O str), 1533(-C=N str), 3072(-C-N str)

Compound T_7: IR Bands (cm^{-1}): 3381(O-H str), 3127(-N-H str), 3040(-C-H Ar. str.), 1736(C=O str), 3084(-C-N str.), 1596(-C=N str), 746(-C-S str).

^{1}H-NMR (δ Values in ppm): 9.23(1H of Ar-OH), 7.68(14 H m Ar CH), 6.42-7.59(1H of thiazole), 3.28(2H of CH2), 2.15(1H of NH).

Compound T_8: IR Bands (cm^{-1}): 3273(O-H str), 3135(-N-H str), 2861(-C-H Ar. str), 1589(-C=O str.), 1562(-C=Nstr), 1389(-C-N str), 732(-C-S str).

Compound T_9: IR Bands (cm^{-1}): 3117(-N-H str), 2962 (-C-H Ar. str), 1607(-C=O str), 2924(-C-H. str of Alkyl), 1179(-C-O str), 1537(-C=N str), 1246(-C-N str).

^{1}H-NMR (δ Values in ppm): 7.61(1H of thiazole), 7.05-7.55(4H of Ar CH), 3.80-3.86(3H ofCH_3), 3.34(2H of CH_2), 1.25-2.54(10H of piperidine).

Compound T_{10}: IR Bands (cm^{-1}): 1179(-C-O str), 3116(-N-H str), 2998(-C-H Ar.str.), 1606(-C=O str), 1534(-C=N str), 738(-C-S-str), 2838(-C-H Alk. str).

Compound T_{11}: IR Bands (cm^{-1}): 3118(-N-H str), 2994(-C-H Ar. str), 1598(-C=O str),
2839(-C-H Alk.str), 1179(-C-O str), 1537(-C=N str), 787(-C-H str).

Compound T_{12}: IR Bands (cm^{-1}): 827(-C-Cl str), 2972(-C-H Ar. str), 1595(-C=O str), 3113(-N-H str), 2852(-C-H Alk str), 1536(-C=N str), 1317(-C-N str).

Compound T_{13}: IR Bands (cm^{-1}): 827(-C-Cl), 2922(-C-H Ar. str), 1591(-C=O str),

2852(-C-H Alk.str), 3115(-N-H str), 1340(-C-N str).

Compound T_{14}: IR Bands (cm^{-1}): 3112(-N-H str), 2955(-C-H Ar. str), 1600(-C=O str),
2851(-C-H Alk.str), 1339(-C-N str), 716(-C-H def).

Compound T_{15}: IR Bands (cm^{-1}): 3378(-O-H str), 3126(-N-H str.), 2923(-C-H Ar. str), 1602(-C=O str), 2854(-C-H Alk.str), 1536(-C=N str), 1341) (.-C-N str).

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