International Journal of Drug Development & Research | January-March 2012 | Vol. 4 | Issue 1 | ISSN 0975-9344 | Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03,& H index 2

Synthesis and Biological evaluation of substituted 4-Phenyl -1,3-Thiazole derivatives as potential Anti-Inflammatory agents

Apexa D Patel, Dr. C. N. Patel
Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India

Abstract
Thiazole derivatives are the heterocyclic compounds with very important biological activities such as anti inflammatory, antibacterial, antiviral, It K inhibiting, PI_3K inhibiting, NF-kb inhibiting activities etc. substituted 4-phenyl -1, 3-thiazole moiety was synthesised by cyclo condensation reaction between substituted benzoyl thiourea derivatives and ethylchloro acetate. These derivatives on hydrolysis produced the desired final compounds. Also energy minimization of proposed structure was done which gives the distance between different functional groups of basic moiety, which is identical to the reference compound. These compounds were screened for in vivo anti-inflammatory activity by carrageen induced rat paw edema method.

*Corresponding author, Mailing address:
Apexa D. Patel
E-mail: apexa178@gmail.com
Ph: 9723820259

Key words:
Thiazole, energy minimization, anti-inflammatory activity

How to Cite this Paper:
Apexa D Patel, Dr. C. N. Patel "Synthesis and Biological evaluation of substituted 4-Phenyl -1,3-Thiazole derivatives as potential Anti-Inflammatory agents", Int. J. Drug Dev. & Res., Jan-March 2012, 4(1): 106-111

Article History:----------
Date of Submission: 06-11-2011
Date of Acceptance: 14-12-2011
Conflict of Interest: NIL
Source of Support: NONE

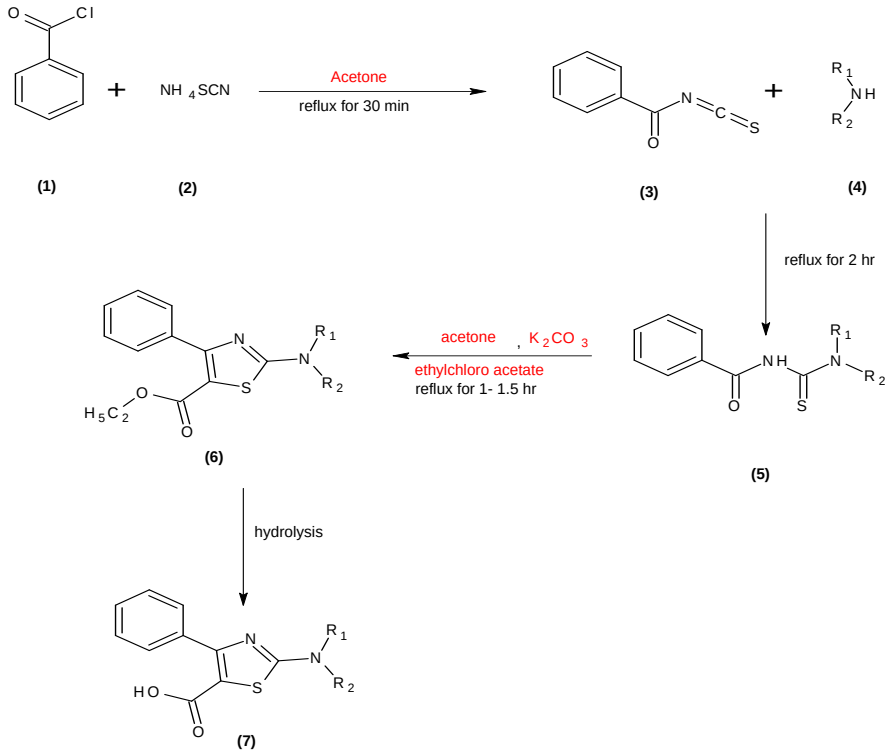
Introduction:
Inflammation remains a common and, all too often poorly controlled clinical problem which can be life threatening in extreme form of allergy, autoimmune diseases and rejection of transplanted organs. The major drawback of current treatment with anti-inflammatory agents are their GI side effects like GI irritation, ulceration etc. Also on long term usage they cause severe CVS & thrombotic side effect. To overcome this effect it is need to find out new drug which shows better anti-inflammatory activity with minimum side effect. From the

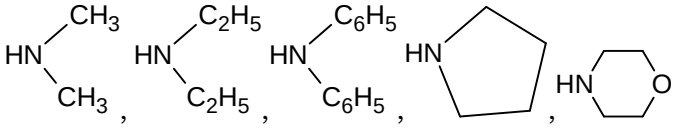
Literature survey thiazole was found to be having diverse activity like anti-inflammatory, antimicrobial, antifungal, antiviral, analgesic, anti-mycobacterial etc. So it was planned to design a novel series of substituted 4-phenyl -1, 3-thiazole derivatives & to check their anti-inflammatory activity. Energy minimization of the refence molecule and target molecule was done by using chem. Draw software and distance between functional groups of the pharmacophore was measured. those distance of targeted molecues were identical to the distance of the reference molecule. On the basis of these one can thought that targeted molecule may also give anti-inflammatory activity. On these basis, by using different amines different five molecule were synthesised and after hydrolysis of those molecule more five compounds were obtained. Then all the compounds were screened for in vivo anti-inflammatory activity by carrageen induced rat paw edema method.[1-7]

Materials and method:

- The entire chemicals were supplied by S. D. Fine Chem. (Mumbai), Finar Chem. Ltd (Ahmedabad) and Loba Chemie. Pvt. Ltd. (Mumbai).
- Melting points were determined by open tube capillary method and were uncorrected.
- Purity of compounds were checked by thin layer chromatography (TLC) on silicagel-G in solvent system hexane-ethyl acetate (1:1) and the spots were located under iodine vapours and UV light.
- IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr.
- Mass spectra were obtained using 2010EV LCMS Shimadzu instrument.

SYNTHETIC PATHWAY



Amines are 4(a to e): 

Synthetic procedure of benzoyl isothiocyanate[8]

In 250 ml three necked flask fitted with a reflux condenser, a mechanical stirrer & a 100 ml dropping funnel are placed .In to this ammonium thiocyanate(0.1 M) was dissolved in about 50 ml of Acetone. To this solution Benzoyl chloride (0.1 M) was added through dropping funnel with stirring. After the addition was complete, the mixture was refluxed around 25-30 minutes with stirring. So yellow colored benzoyl isothiocyanate is obtained. After that cool the reaction mixture at room temperature.

Synthetic procedure of (N-substituted) benzoyl thioureas

In 250 ml three necked round bottom flask containing benzoyl isothiocyanate, substituted amine (0.1 M) was added dropwise. This reaction mixture was refluxed for about 4 hr with stirring. After that reaction mixture was cooled to room temperature & then this solution was added in the crushed ice to get the solid, dried & recrystallize from ethanol.

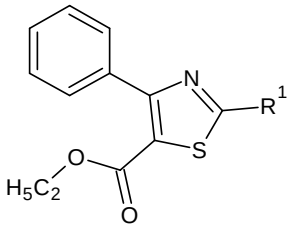
Synthetic procedure of ethyl-(N-substituted)-4- phenyl-1, 3-thiazole -5-carboxylate:

In 250 ml round bottom flask (N-substituted) benzoyl thioureas (0.01M) was dissolved in 30 ml of acetone. To this solution anhydrous potassium carbonate was added as catalyst, after that ethyl chloroacetate (0.01 M) was mixed in above solution & stirred well, this reaction mixture was refluxed for about 3 hr. After that reaction mixture was cooled to room temperature. & then this solution was poured in the crushed ice to get the solid. dried under IR lamp & recrystallize from ethanol.

Synthetic procedure of 2-(N-substituted)-4-phenyl-1, 3-thiazole-5-carboxylic acids.

In 100 ml round bottom flask ethyl-(N-substituted)-4- phenyl-1, 3-thiazole -5-carboxylate (0.005 M) was dissolved in about 30 ml of ethanol. To that potassium hydroxide solution (1N) was added. This reaction mixture was refluxed for about 1 hr. After that cool the reaction mixture at room temperature. Then in this solution dil HCl was added dropwise with stirring still precipitates persist. That precipitates was filtered and washed with cold water, dry it. It was recrystallised by using ethanol.

Table-1: Physicochemical Parameters of ethyl-(N-substituted)-4- phenyl-1, 3-thiazole -5-carboxylate



(6)

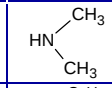
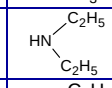
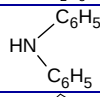
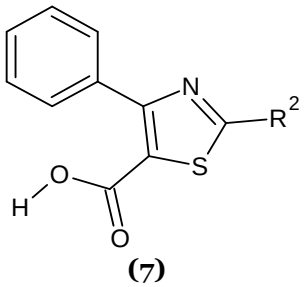
Compound Code	R^1	Molecular Formula	Molecular Weight	M.P (°C)	Yield (%)
6a		$C_{14}H_{16}N_2O_2S$	276.35	155-160	53
6b		$C_{16}H_{20}N_2O_2S$	304.4	85-89	74
6c		$C_{24}H_{20}N_2O_2S$	400.49	176-179	78
6d		$C_{16}H_{18}N_2O_2S$	302.39	114-115	45
6e		$C_{16}H_{18}N_2O_3S$	318.39	105-109	89

Table- 2: Physicochemical Parameters of 2-(N-substituted)-4-phenyl-1,3-thiazole-5-carboxylic acids



(7)

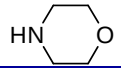
Compound Code	R^2	Molecular Formula	Molecular Weight	M.P (°C)	Yield (%)
7a		$C_{12}H_{12}N_2O_2S$	248.30	121-123	47
7b		$C_{14}H_{16}N_2O_2S$	276.35	111-114	61
7c		$C_{22}H_{16}N_2O_2S$	372.43	160-165	65
7d		$C_{14}N_{14}N_2O_2S$	274.33	131-133	41
7e		$C_{14}H_{14}N_2O_3S$	290.33	158-160	77

Table- 3: Spectral characteristics of ethyl-(N-substituted)-4- phenyl-1, 3-thiazole -5-carboxylate

Compound Code	λmax	Mass m/e	IR cm^{-1}	^1H NMR δ PPM
6a	247,322.5	277.2(M^+)	1737 (-C=O, ester)	
6b	249.5,330	304.2(M^+)	1697 (-C=O, ester)	1.23(t,3H,N-CH_2-CH_3) 1.31(t,3H,CH_3-CH_2-O) 3.54(q,2H, N-CH_2-CH_3) 4.2(q,2H, CH_3-CH_2-O) 7.2-7.7(m,5H,Ar-H)
6c	272,338	400.6(M^+)	1668 (-C=O, ester)	
6d	246,325	302.5(M^+)	1706 (-C=O, ester)	
6e	249.5,322	318.7(M^+)	1674 (-C=O, ester)	1.26(t,3H,CH_3-CH_2-O) 3.75(t,2H,N-CH_2-CH_2-O) 3.85(t,2H,N-CH_2-CH_2-O) 4.2(q,2H,CH_3-CH_2-O) 7.2-7.7(m,5H,Ar-H)

Table- 4: Spectral characteristics of 2-(N-substituted)-4-phenyl-1,3-thiazole-5-carboxylic acids

Compound Code	λmax	Mass m/e	IR cm^{-1}	^1H NMR δ PPM
7a	245,320	248.9(M^+)	1645(-C=O,acid)	
7b	251.5,329	276.8(M^+)	1680(-C=O,acid)	
7c	276.5,343	372.6(M^+)	1650(-C=O,acid)	
7d	249.3,332.5	274.6(M^+)	1700(-C=O,acid)	
7e	248,318	290.7(M^+)	1683(-C=O,acid)	3.5(t,2H,N-CH_2-CH_2) 3.72(t,2H,CH_2-CH_2-O) 7.3-1.7(m, Ar-H)

Pharmacological Screening:

Antiinflammatory activity (*in vivo*)

All the synthesized compounds were screened for the *in vivo* anti-inflammatory activity by carrageenan induced rat paw edema method.

- Method: Inhibition of carrageenan induced inflammation in rat paw
- Animals used: Albino wistar rats
- Number of animals used: 3
- Dose of test compounds: 50 mg/kg
- Dose of standard drug: 50 mg/kg (Diclofenac sodium)
- Route of administration: Oral (1% w/v Tween 80 suspension)
- carrageenan suspension : Sub planter (0.1 ml of 1% w/v suspension in 0.9% saline solution)

Method: The method developed by Winter et al.[9-10] was employed. Albino wistar rats of either sex (250-300 g) were divided into various groups of three animals each. Animals were deprived of food for 12 h prior to experiment and only water was given *ad libitum*. First group was used as a control group and received 1 ml of 1% w/v Tween 80 suspension in saline, the second group received Tween 80 suspension of diclofenac sodium (50 mg/kg) orally and the third group received Tween 80 suspension of test compounds at a dose of 50 mg/kg orally.

One hour after the administration of the compounds, carrageenan suspension (0.1 ml of 1% w/v suspension in 0.9% saline solution) was injected into the sub planter region of left hind paw of animals. Immediately, the paw volume was measured using plethysmometer (initial paw volume, Vc). Thereafter, the paw volume was measured after 1 and 3 h after carrageenan administration. The difference between initial and subsequent readings gave the change in edema volume for the corresponding time.

Edema volume of control (Vc) and volume of treated (Vt) were used to calculate percentage (%) inhibition and (%) edema volume by using following formula.

% Inhibition = [1- (Vt/Vc)] × 100

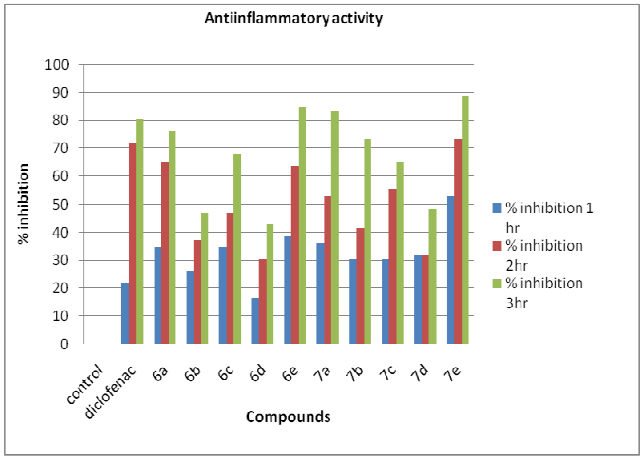
% Edema volume = 100 × (Edema volume after drug treatment/Initial volume)

Table 5: Carragenan induced rat paw edema

	Paw volume (ml) ± SEM			%Inhibition		
Time	**1 hr**	**2 hr**	**3 hr**	**1 hr**	**2 hr**	**3 hr**
Control	2.4	2.4	2.4			
Diclofenac	1.86±0.03	0.66±0.06	0.46±0.03	22.22	72.22	80.55
6a	1.56±0.03	0.83±0.03	0.56±0.03	34.72	65.27	76.38
6b	1.76±0.03	1.50±0.05	1.26±0.03	26.38	37.5	47.22
6c	1.56±0.03	1.26±0.03	0.76±0.03	34.72	47.22	68.05
6d	2.00±0.16	1.66±0.03	1.36±0.03	16.66	30.55	43.05
6e	1.46±0.03	1.86±0.03	0.36±0.08	38.88	63.88	84.72
7a	1.53±0.06	1.13±0.03	0.40±0.05	36.11	52.77	83.33
7b	1.66±0.08	1.40±0.05	0.63±0.03	30.55	41.66	73.61
7c	1.66±0.06	1.06±0.03	0.83±0.03	30.55	55.55	65.27
7d	1.63±0.08	1.63±0.03	1.23±0.03	31.94	31.94	48.61
7 e	1.13±0.03	0.63±0.03	0.26±0.08	52.77	73.61	88.88

No.of animal used per group: 3
Dose of standard and test compounds: 50 mg /kg
SEM= Standard error of mean

Figure: Bar Diagram showing% inhibition



Results and Discussion:

- synthesized compounds were screened for invivo anti-inflammatory activity by inhibition of carragenan induced rat paw edema method at the dose of 50 mg /kg orally
- Significant anti inflammatory activity was observed with inhibition in edema in the range of 43.0 5% to 88.88% after 3 h.
- The standard drug diclofenac has shown 80.55% inhibition after 3 h.
- Among all the screened compound **(7e)** was found to be the most potent in the series with 88.88% inhibition after 3 h & **(6 d)** was found to be the least potent in the series with 43.05% inhibition after 3 hr .

ACKNOWLEDGEMENT:

The author Apexa D Patel is thankful to the project guide Prof. Dr. C.N. Patel and prof. I. S. Rathod. Also thankful to the staff members of Shri Sarvajanik Pharmacy College, Mehsana, Gujarat to fulfil the project successfully. Also thankful to the Quality Assurance Department of Shri Sarvajanik Pharmacy College, Mehsana for UV and IR spectral data, Oxygen Healthcare, Ahmedabad for Mass spectral data and MS University for NMR spectral datas.

REFERENCES:-

1) Morrow D J, Goodman and Gilman's. The Pharmacological Basis Of therapeutics; 10th Edn; Mc Graw-Hill pub, New York, 2001, pp 669-87.
2) Rang H P., Dale M M., Ritter J M., Moore P K. Pharmacology. 5th Edn; Churchill Livingstones pub, New York, 2003, pp 217-243.
3) Mohan H. In Textbook of Pathology. Inflammation and Healing; 3rd Edn; Jaypee brothers medical publishers Ltd.,1998, pp 133-90.
4) Malkowski M G, Ginell S L, Smith W L, Garavito R M. "The productive confirmation of arachidonic acid bound to prostaglandin synthase." Science Reports. 2000, 289, pp1933-937.
5) P X Franklin, Ajay D Pillai, Parendu D Rathod,Swapnil Yerande."2-amino-5-thiazolyl motif: A novel scaffold for designing anti-inflammatory agents of diverse structure." Eur. J. Of Med.Chem.2008, 43, pp 129-134
6) Hantzch, A weber, J H Ueber verbindungen des. "Thiazoles" Berdtsch chem Ges. 1987, 20 (2), 3118-3132.
7) Rajan S Giri, Hardik M Thaker, Tony Girando. "Design,synthesis and characterization of novel 2-(2, 4 – disubstituted – thiazole – 5 - yl) - 3 –aryl - 3H - quinazoline-4-one derivatives as inhibitors of NF-KB and AP-1 mediated transcription activation

and as potential anti-inflammatory agents." Eur. J. Of Med. Chem.2009, 44, pp 2184-2189.

8) 532-55-8 CAS MSDS (Benzoyl isothiocyanate), Sept.2010 www.us.chemicalbook.com/Chemical Product Property_us_CB8116176.aspc

9) Haviv F, Denel R W, Michaels R J, "2-[(phenylthio) methyl] pyridine derivatives, new anti-inflammatory agents." J.Med.Chem.1983, 26, 218-222.

10) Winter C A, Risely EA, NussG W, "Carageenan induced edema hind paw of the rats as an assay for antiinflammatory drugs." Proc. Soc. Expt. Bio. Med.1962, 1, 544-547.