



SYNTHESIS OF NOVEL THIAZOLO-QUINAZOLINES AS ANTINOCICEPTIVE AND ANTI-INFLAMMATORY AGENTS

T.Panneer Selvam^{*}, C.R.Prakash¹, G.Saravanan², V.Karthick
and P.Dinesh Kumar

^{*}1Department of Pharmaceutical Chemistry, D.C.R.M. Charmacy College, Inkollu(A.P), India

²Medicinal Chemistry Research Laboratory, Bapatla College of Pharmacy, Bapatla(A.P), India

E-mail: tpsphc@gmail.com

ABSTRACT

A series of 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidene) thiazolo (2,3-b) quinazolin-3(2H)-one (**4a-4d**) and 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidene)-3-(4-nitrophenyl amino) thiazolo quinazoline (**5a-5d**) have been synthesized. All the newly synthesized compounds chemical structure were confirmed by IR, ¹H-NMR, mass spectroscopy and elemental analysis. The new compounds have been tested for their antinociceptive, anti-inflammatory activities. The results of studies indicate that the hydroxy substitution in the benzylidene ring increased the anti-inflammatory and antinociceptive activities.

Key words: Thiazolo quinazoline; Antinociceptive activity; Anti-inflammatory.

INTRODUCTION

Bacterial infections often produce pain and inflammation. In normal practice, two groups of agents (antinociceptive and anti-inflammatory) are prescribed simultaneously. Unfortunately, none of drug possesses these two activities in a single component. Therefore the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area¹⁻². On our going medicinal chemistry research program we found that quinazolines and condensed quinazolines exhibit potent central nervous system (CNS) activities like antinociceptive, anti-inflammatory³ and anticonvulsant⁴. Quinazolin-4(3H) ones with 2,3-disubstitution is reported to possess significant antinociceptive, anti-inflammatory and anticonvulsant activities⁵⁻⁸. On the other hand, some thiazole derivatives also have various biological properties like anti-inflammatory^{9,10} antimicrobial¹¹, anthelmintic¹² and immunorestitution¹³. These observation led to the conception that a novel series of 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(some substituted benzylidene) thiazolo(2,3-b) quinazolin-3-phenyl hydrazone derivatives were synthesized using different aromatic aldehydes by condensation with phenyl hydrazine in Schiff base mechanism and their chemical structure were confirmed by IR, ¹H-NMR, mass spectroscopy and elemental analysis. The main objective of the present study is to investigate the antinociceptive and anti-inflammatory activity of different substitute of thiazoloquinazoline derivatives.

EXPERIMENTAL

General experimental procedures

In the present study the eqimolar quantities of each (3.8g 0.039 mol) of cyclohexanone and salicylaldehyde (4.8g 0.039 mol) were taken in a beaker, to this sodium hydroxide solution was added to make the solution alkaline, shake and allow the mixture to stand tallises out or will so upon scratching the vessel with a glass rod. Filter off the solid, wash it with a little cold ethanol and recrystallise it from absolute ethanol.

A mixture of -hydroxy benzylidene cyclohexanone ring **1** (7.9g 0.039 mol) thiourea (3.0g 0.03 mol) and potassium hydroxide (2.5g) in ethanol (100 ml) was heated under reflux for 3h. The reaction mixture was

concentrated to half of its volume, dilute with water, then acidified with dil acetic acid and kept overnight. The solid thus obtained, was filtered, washed with water and crystallised from ethanol to give 4-hydroxy phenyl-3,4,5,6,7,8-hexahydro quinazolin-2-thione **2**

The chloroacetic acid (9.0g 0.096mol) was melted on a water bath and thione (2.3g 0.009mol) added to it portionwise to maintain its homogeneity. The homogeneous melt was further heated on a water bath for 30 min and kept overnight. The solid thus obtained was washed with water until neutral and crystallised from ethanol to give 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl) thiazolo (2,3-*b*)quinazolin-3(2*H*)-one **3**¹⁴.

General method of synthesis 4a-4d

A mixture of **3** (0.6g 0.002 mol), substituted benzaldehyde (0.002 mol) and anhydrous sodium acetate (0.2g 0.002 mol) in glacial acetic acid (10 ml) was heated under reflux for 4h. The reaction mixture was kept overnight and the solid, thus separated, was filtered, washed with water and recrystallized from ethanol to furnish 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidene) thiazolo (2,3-*b*) quinazolin-3(2*H*)-one **4a-4d**.

General method of synthesis 5a-5d

Equimolar quantities (0.004 mol) of compound **4a-4d** treated with thionyl chloride and DMF to get chloro derivative and then coupled with substituted anilines in DMF at 80°C and quenched in ice-water to get the product were separated by filtration, vacuum dried and recrystallized from warm ethanol to yields 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidene)-3-(4-nitrophenyl amino) thiazolo quinazoline (**5a-5d**)

Pharmacological Procedures

Animals

Male Swiss albino mice 25-35g were used. The animals were procured from C.L. Baid Metha College of Pharmacy, Chennai, India, and were maintained in colony cages at 25±2 °C, relative humidity of 45-55%, maintained under 12 h light and dark cycle and were fed with standard animal feed. Animals were maintained under standard conditions in an animal house approved by committee for the purpose of control and supervision on experiments on animals (CPCSEA). Institutional Animal Ethics Committee approved the experimental protocol. The entire animals were acclimatized for a week before use.

Antinociceptive Activity by Tail-flick method

Test for antinociceptive activity¹⁵ was performed by tail-flick technique using Wistar albino mice (25-35g) of either sex selected by random sampling technique Diclofenac sodium at dose level of 10 mg/kg was administered orally as reference drug for comparison. The test compound at a dose level of (100 mg/kg, *p.o*). The reaction time was recorded at 30min, 1, 2 and 3 h after the treatment. The cut off time was 10s. The percent antinociceptive activity (PAA) was calculated by the following,

$$PAA = \left[\frac{T_2 - T_1}{10 - T_1} \right] \times 100$$

Where T₁ is the reaction time (s) before treatment, T₂ is the reaction time (s) after treatment.

Carrageenan-induced hind paw edema model

Carrageenan-induced hind paw edema model was used for determination of anti-inflammatory activity¹⁶. Sixty minutes after the oral administration of synthesized compounds at one dose level (100 mg/kg), each mouse was injected with freshly prepared suspension of carrageenan (0.5mg/25µl) in physiological saline (154mM NaCl) into subplanter tissue of the right hind paw. As the control, 25µl saline solutions were injected into that of the left hind paw. Paw edema was measured by a gauge calipers (C.L. Baid Metha, Chennai, India) Mean values of treated groups were compared with those of a control group and analyzed by using statistical methods. Indomethacin (10 mg/kg) was used as the reference drug.

Acute toxicity studies

Acute toxicity test was performed for the entire synthesized compound to ascertain the LD50 values as per OECD guidelines¹⁷. Mice are treated with doses of 10,100,1000,1600,2000 and 5000 mg/kg of the synthesized drugs. The animals were kept under close observation over a period of 14 days. Restlessness, respiratory distress, convulsion, diarrhoea, motor activity, posture and reflexes were qualitatively determined. In addition internal organ (stomach, heart, lung, liver, kidney, etc.) were removed and examined macroscopically to detect internal lesions finally the weight of animal was monitored throughout the experiment doses were selected between the minimum effective dose and minimum non lethal dose.

Statistical Analysis

Data obtained from experiments were expressed as the mean standard error (\pm S.E.M). Statistical difference between the treated and the control groups were evaluated by ANOVA and Student-Newman-Keuls post hoc tests. P,0.05 was considered to be significant (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)

RESULTS AND DISCUSSION

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. The ¹H-NMR spectra were recorded on 300 MHz-Bruker DPX 200 NMR spectrometer (with TMS for ¹H as internal references). Mass spectra were recorded on Shimadzu GC MS QP 5000. Microanalyses for C, H, N were Performed in Heraeus CHN Rapid Analyzer. The purity of the compounds was checked by TLC on pre-coated SiO₂ gel (HF₂₅₄, 200 mesh) aluminum plates (E Merck) using benzene: petroleum ether (3:1) and visualized in UV chamber. IR, ¹H-NMR, Mass spectra and Elemental analysis were consistent with the assigned structures.

The IR, ¹H-NMR, Mass Spectroscopy and Elemental analysis Datas were given below-

4a. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-hydroxy benzylidene) thiazolo (2, 3-b) quinazolin-3(2H)-one

IR : 3421 (O-H), 3098 (Ar-CH), 1722 (C=O), 1464 (C=C), 1342 (N-H) cm⁻¹; ¹H-NMR (CDCl₃): δ 6.98-7.56 (m, 8H, Ar-H), 6.62 (s, 1H, =CH), 5.84 (s, 1H, H-5), 5.36 (s, 1H, H-2', Ar-OH), 5.02 (s, 1H, H-4", Ar-OH), 1.62-2.56 (m, 8H, 4 \times CH₂); EI-MS (m/z, %): 404(M+); (Calcd. for C₂₃H₂₀N₂O₃S; 404.12); Anal. Calcd for C₂₃H₂₀N₂O₃S; C, 68.30; H, 4.98; N, 6.93; O, 11.86; S, 7.94; Found: C, 68.32; H, 4.96; N, 6.97; O, 11.84; S, 7.98.

4b. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methoxy benzylidene) thiazolo (2, 3-b) quinazolin-3(2H)-one

IR : 3476 (O-H), 3096 (Ar-CH), 1728 (C=O), 1468 (C=C), 1339 (N-H) cm⁻¹; ¹H-NMR (CDCl₃): δ 6.96-7.54 (m, 8H, Ar-H), 6.67 (s, 1H, =CH), 5.83 (s, 1H, H-5), 5.48 (s, 1H, Ar-OH), 3.75 (s, 3H -OCH₃), 1.58-2.62 (m, 8H, 4 \times CH₂); EI-MS (m/z, %): 418 (M+); (Calcd for C₂₄H₂₂N₂O₃S; 418.51). Anal. Calcd for C₂₄H₂₂N₂O₃S; C, 68.88; H, 5.30; N, 6.69; O, 11.47; S, 7.66; Found: C, 68.90; H, 5.33; N, 6.72; O, 11.51; S, 7.69.

4c. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methyl benzylidene) thiazolo (2, 3-b) quinazolin-3(2H)-one

IR : 3448 (O-H), 3049 (Ar-CH), 1694 (C=O), 1434 (C=C), 1297 (N-H) cm⁻¹; ¹H-NMR (CDCl₃): δ 6.86-7.74 (m, 8H, Ar-H), 6.72 (s, 1H, =CH), 5.76 (s, 1H, H-5), 5.54 (s, 1H, Ar-OH), 2.20 (s, 3H -CH₃), 1.62-2.32 (m, 8H, 4 \times CH₂); EI-MS (m/z, %): 402 (M+); (Calcd for C₂₄H₂₂N₂O₂S; 402.14). Anal. Calcd for C₂₄H₂₂N₂O₂S; C, 71.00; H, 5.51; N, 6.96; O, 7.95; S, 7.97; Found: C, 69.87; H, 5.32; N, 6.74; O, 7.58; S, 7.72.

4d. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-chloro benzylidene) thiazolo (2, 3-b) quinazolin-3(2H)-one

IR : 3415 (O-H), 3027 (Ar-CH), 1712 (C=O), 1503 (C=C), 1322 (N-H), 823 (C-Cl) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 7.12-7.56 (m, 8H, Ar-H), 6.82 (s, 1H, =CH), 5.74 (s, 1H, H-5), 5.56 (s, 1H, Ar-OH), 1.26-2.65 (m, 8H, 4 \times CH_2); EI-MS (m/z, %): 424 (M+2); (Calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_2\text{SCl}$; 422.09). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_2\text{SCl}$; C, 65.32; H, 4.53; N, 6.62; O, 7.57; S, 7.58; Cl, 8.38; Found: C, 65.36; H, 4.55; N, 6.63; O, 7.57; S, 7.61; Cl, 8.35.

5a. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-hydroxy benzylidene)-3-(4-nitrophenyl amino) thiazolo quinazoline

IR : 3415 (O-H), 3060 (Ar-CH), 1534 (C=C), 1312 (N-H), 3310 (N-NH) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 6.98-7.36 (m, 12H, Ar-H), 6.53 (s, 1H, =CH), 5.82 (s, 1H, H-5), 5.40 (s, 1H, H-2', Ar-OH), 5.12 (s, 1H, H-4", Ar-OH), 7.78 (s, 1H, N-H), 1.59-2.47 (m, 8H, 4 \times CH_2); EI-MS (m/z, %): 526 (M+); (Calcd for $\text{C}_{29}\text{H}_{26}\text{N}_4\text{O}_4\text{S}$; 526.17). Anal. Calcd for $\text{C}_{29}\text{H}_{26}\text{N}_4\text{O}_4\text{S}$; C, 66.14; H, 4.98; N, 10.64; O, 12.15; S, 6.09; Found: C, 66.12; H, 4.96; N, 10.63; O, 12.13; S, 6.11.

5b. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methoxy benzylidene)-3-(4-nitrophenyl amino) thiazolo quinazoline

IR : 3464 (O-H), 3027 (Ar-CH), 1494 (C=C), 1326 (N-H), 3284 (N-NH) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 6.72-7.23 (m, 12H, Ar-H), 6.43 (s, 1H, =CH), 5.62 (s, 1H, H-5), 5.44 (s, 1H, Ar-OH), 3.78 (s, 3H - OCH_3), 7.76 (s, 1H, N-H), 1.46-2.42 (m, 8H, 4 \times CH_2); EI-MS (m/z, %): 540 (M+); (Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_4\text{S}$; 540.18). Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_4\text{S}$; C, 66.65; H, 5.22; N, 10.36; O, 11.84; S, 5.93;. Found: C, 66.67; H, 5.25; N, 10.38; O, 11.85; S, 5.96.

5c. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methyl benzylidene)-3-(4-nitrophenyl amino) thiazolo quinazoline

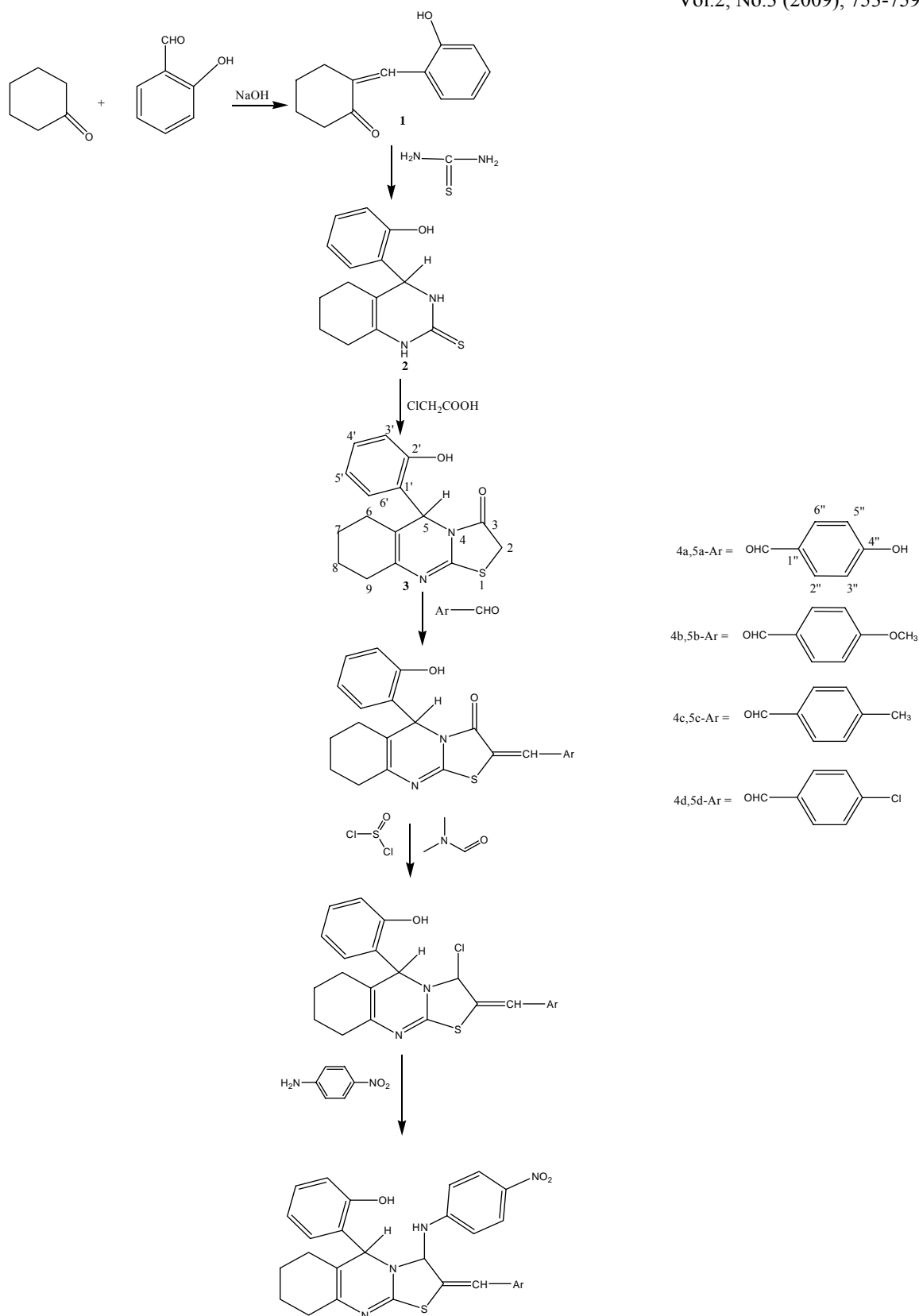
IR : 3438 (O-H), 3024 (Ar-CH), 1412 (C=C), 1332 (N-H), 3310 (N-NH) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 6.69-7.24 (m, 12H, Ar-H), 6.36 (s, 1H, =CH), 5.72 (s, 1H, H-5), 5.39 (s, 1H, Ar-OH), 2.28 (s, 3H, - CH_3), 7.69 (s, 1H, N-H), 1.36-2.41 (m, 8H, 4 \times CH_2); EI-MS (m/z, %): 524 (M+); (Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$; 524.19). Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$; C, 68.68; H, 5.38; N, 10.68; O, 9.15; S, 6.11; Found: C, 68.65; H, 5.36; N, 10.70; O, 9.18; S, 6.14.

5d 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-chloro benzylidene)-3-(4-nitrophenyl amino) thiazolo quinazoline

IR : 3446 (O-H), 3021 (Ar-CH), 1521 (C=C), 1324 (N-H), 3316 (N-NH), 820 (C-Cl) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 6.79-7.34 (m, 12H, Ar-H), 6.46 (s, 1H, =CH), 5.82 (s, 1H, H-5), 5.49 (s, 1H, Ar-OH), 7.79 (s, 1H, N-H), 1.26-2.32 (m, 8H, 4 \times CH_2); EI-MS (m/z, %): 544(M+2); (Calcd for $\text{C}_{29}\text{H}_{25}\text{ClN}_4\text{O}_3\text{S}$; 544.13). Anal. Calcd for $\text{C}_{29}\text{H}_{25}\text{ClN}_4\text{O}_3\text{S}$; C, 63.90; H, 4.62; N, 10.28; O, 8.81; S, 5.88; Cl, 6.50; Found: C, 63.93; H, 4.65; N, 10.30; O, 8.83; S, 5.86; Cl, 6.53.

Anti-nociceptive and anti-inflammatory activity

In the present study, we have evaluated the antinociceptive activity by tail-flick and anti-inflammatory activity by carrageenan induced paw edema method. Among the synthesized compounds, compound **4d** showed better antinociceptive and anti-inflammatory activity when compare to 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-hydroxy benzylidene) thiazolo (2, 3-b) quinazolin-3(2H)-one **4a**, 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methoxy benzylidene) thiazolo (2, 3-b) quinazolin-3(2H)-one **4b** and 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methyl benzylidene) thiazolo (2, 3-b) quinazolin-3(2H)-one **4c** because presence of electron with drawing chloro group in its structure. Among all the eight compound synthesized compound 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-chloro benzylidene)-3-(4-nitrophenyl amino) thiazolo quinazoline **5d** produced more potent antinociceptive, anti-inflammatory activity against standard diclofenac sodium (Table-1). and indomethacin respectively (Table-2). This is mainly because of the addition of electron with drawing nitro substituent in third position of thiazolo quinazoline.



Scheme-1

Table-1: Antinociceptive Activity (Tail-Flick Technique)

Compound code	Dose (mg/kg)	30 min	1h	2h	3h
Control	-	2± 0.35	6±0.49	4±0.59	4±0.91
4a	100	43±1.83	49±0.29	54±2.54	35±0.47
4b	100	46±0.68	50±1.24	48±2.45	39±1.09
4c	100	43±0.34	46±1.15	49±0.96	39±0.67
4d	100	48±3.01*	56±1.33***	59±1.31**	41±0.72*
5a	100	58±1.38	59±1.26	61±1.45	42±1.27
5b	100	57±1.32*	63±1.42*	68±0.42*	52±1.39**
5c	100	49±0.96*	54±1.70*	59±1.68**	40±0.83**
5d	100	65±0.65*	8±1.36*	70±1.29**	56±1.37**
Diclofenac	10	37±1.69*	43±1.42***	45±0.92**	33±0.96**

Each value represents the mean±S.D (n=6). Significance levels * $P < 0.05$, $P < 0.01$ and *** $P < 0.001$ as compared with the respective control.

Table-2: Effect of the synthesized compounds and active principles on carrageenan-induced hind paws edema in mice

Test samples	Dose (mg/kg)	Swelling thickness ($\times 10^{-2}$ mm) \pm S.E.M (Inhibition %)			
		90 min	180 min	270 min	360 min
Control		35.2±3.5	41.4± 3.1	46.9± 3.7	52.3± 3.4
4a	100	37.5 ±3.9	45.8 ±3.4	51.0 ±3.2	58.2 ±3.6
4b	100	30.2 ±2.1(14.2)	35.0 ±2.5(15.5)	37.5 ±3.3(20.0)	41.5 ±2.8(20.7)
4c	100	38.2 ±3.7	43.3 ±3.9	52.5 ±3.8	55.6 ±4.3
4d	100	26.2 ±2.7(17.0)	37.3 ±2.4(16.6)	35.8 ±2.6(21.7)*	37.5 ±2.4(22.5)*
5a	100	30.5 ±2.8(13.4)	33.8 ±3.0(18.4)	36.9 ±3.2(21.3)	39.4 ±2.9(24.7)*
5b	100	29.2 ±2.7(17.0)	33.3 ±2.4(19.6)	35.8 ±2.6(23.7)*	39.5 ±2.4(24.5)*
5c	100	35.8 ±2.9	43.1± 3.3	44.6 ±3.0(4.9)	50.2 ±3.1(4.0)
5d	100	28.3 ±2.4(19.6)	32.7 ±2.7(21.0)	35.1 ±3.0(25.2)*	38.4 ±2.1(26.6)**
Indomethacin	10	28.2 ±2.3(19.9)	27.6 ±2.1(33.3)**	31.8 ±2.5(32.2)**	32.4 ±2.7(38.0)***

Data represent Mean \pm S.E.M (Standard Error Mean) (n = 6). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

REFERENCES

1. VanRyn J, Botting RM. New insights into the mode of action of antiinflammatory drugs. *Inflamm Res.*, **44**, 1-10 (1995).
2. VanRyn J, Trummlitz G, Pairet M. COX-2 selectivity and inflammatory processes. *Curr Med Chem.*, **7**, 1145-61 (2000).
3. Alagarsamy V, Revathi R, Vijayakumar S, Ramseshu K V. Synthesis and pharmacological investigation of some novel 2,3-disubstituted quinazolin-4(3H)-ones as antinociceptive and

- antiinflammatory agents. *Pharmazie.*, **58**,4-8 (2003).
- Alagarsamy V, Thangathirupathy A, Mandal SC, Rajasekaran S, Vijayakumar S, Revathi R, et al. Pharmacological evaluation of 2-substituted (1,3,4) thiazolo quinazolines. *Indian J Pharm Sci.*, **68**, 108-11 (2006).
 - Bhalla M, Srivatava VK, Bhalla TN, Shanker K. Anti-inflammatory and antinociceptive activity of indolyl quinazolones and their congeners. *Arzneimittelforschung.*, **43**:595-600 (1993).
 - Zappala M, Grasso S, Micale N, Zuccala G, Menniti FS, Ferreri G, et al. 1Aryl-6,7-methylenedioxy-3H-quinazolin-4-ones as anticonvulsant agents. *Bioorg Med Chem Lett.*, **13**, 4427-30 (2003).
 - Chao Q, Deng L, Shih H, Leoni LM, Genini D, Carson DA, et al. Substituted isoquinolines and quinazolines as potential antiinflammatory agents. Synthesis and biological evaluation of inhibitors of tumor necrosis factor. *J Med Chem.*, **42**, 3860 -73 (1999).
 - Alagarsamy V, Muthukumar V, Pavalarani N, Vasanthanathan P, Revathi R. Synthesis, antinociceptive and anti-inflammatory activities of some novel 2,3disubstituted quinazolin-4(3H)-ones. *Biol Pharm Bull.*, **26**, 557 -9 (2003).
 - Tajana A, Portioli F, Nardi D, Magistretti M J. New alkylamino, dialkylamino, and arylalkylamino acetylhydrazones with anti-inflammatory activity. *Boll. Chim. Farm.*, **118**, 397 (1979).
 - Verma M, Gujrati VR, Sharma M, Bhalla TN, Saxena AK, Sinha JN, Bhargava KP, Shanker K. Synthesis and Anti-inflammatory activities of substituted arylamino (*N'*-benzylidene) acetylhydrazides and derivatives. *Arch. Pharm.*, **317**, 890 (1984).
 - Shukla JS, Synthesis of 4-(5-substituted-arylidene-4-thiazolidino-2-thione)-6,8-substituted quinazolines as potential anthelmintic agents. *J. Indian Chem. Soc.*, **66**, 209 (1989).
 - Malesic M, Krbovcic A, Golobio A, Golic L, Stanovnik B. The synthesis and transformation of some 3-thiocarbamoylthiazolidines. *J. Heterocyclic Chem.*, **34**, 43 (1997).
 - McDonald LA, Foster MP, Phillips DR, Ireland CN. Towicyclamides A and B, new cyclic peptides from the ascidian *lissoclinum patella*: Studies on the solution and solid state conformation. *J. Org. Chem.*, **57**, 4616 (1992).
 - Sharma R, Kumar S, Pujari HK, *Indian J. Chem.*, **30B**, 425-426 (1991).
 - Yesilada, E, Kupeli, E, Clematis vittalba L. aerial part exhibits potent anti-inflammatory, antinociceptive and antipyretic effects. *J of Ethnopharmacology.*, **110**, 504-515 (2007).
 - Kulkarni SK. *Life Sci.*, **27**, 185-188 (1980).
 - OECD. *Guidance Document on Acute Oral Toxicity. Environmental Health and Safety Monograph Series on Testing and Assessment No. 24* (2000).

(Received: 29 August 2009

Accepted: 13 September 2009

RJC-443)