Synthesis of Novel 6,7,8,9-Tetrahydro-5H-5-hydroxyphenyl-2-benzylidene-3-substituted Hydrazino Thiazolo (2,3-*b*) Quinazoline as Potent Antinociceptive and Anti-inflammatory Agents

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A series of 6,7,8,9-tetrahydro-5H-5-hydroxyphenyl-2-benzylidene-3-substituted hydrazino thiazolo (2,3-*b*) quinazolines have been synthesized to meet the structural requirements essential for anti-inflammatory and antinociceptive properties. The synthesized series of heterocycles, 6,7,8,9-tetrahydro-5H-5-hydroxyphenyl-2-benzylidene-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline by the reaction of 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl thiazolo (2,3-*b*) quinazolin-3(2*H*)-one with appropriate hydrazine hydrate and ketones/aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid as presented in Scheme 1. Their antinociceptive activity were evaluated by tail-flick technique, anti-inflammatory was evaluated by carrageenan-induced paw edema test and their ulcerogenicity index determined by reported protocol. The compounds exhibited the lowest ulcer index (0.51 ± 1.63 , 0.48 ± 1.28 and 0.50 ± 1.53 , respectively). The 6,7,8,9-tetrahydro-5H-5-hydroxy phenylhydroxy-2-benzylidene-3-(*N'*-3-pentylidene-hydrazino) thiazolo (2,3-*b*) quinazoline and 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(*N'*-2-pentylidene-hydrazino) thiazolo (2,3-*b*) quinazoline exhibited the most potent antinociceptive and anti-inflammatory activities.

Key Words: Thiazolo quinazoline, Benzylidene thiazolo quinazoline, Antinociceptive activity, Anti-inflammatory

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful drugs for the treatment of acute and chronic inflammation, pain, and fever. However, long-term NSAID use is associated with significant side effects of gastrointestinal lesions, bleeding, and nephrotoxicity. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area, the quinazolines and condensed quinazolines exhibit antinociceptive, anti-inflammatory activities.¹⁻¹⁴ On the other hand, the considerable biological and medicinal activities of thiazole derivatives have attracted continuing interest over the years because of their varied biological activities.^{15,16} These observation led to the conception that a novel series of 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline derivatives were synthesized using appropriate ketones/aldehydes by Schiff base mechanism and their chemical structure were confirmed by IR, ¹H-NMR, mass spectral and elemental analyses. These compounds were screened for their antinociceptive, anti-inflammatory activities.

Results and Discussion

Chemistry. The series of heterocycles, **6a-o** were synthesized by the reaction of **3** with appropriate hydrazine hydrate and ketones/aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid as presented in Scheme. The IR, ¹H-NMR, mass spectroscopy and elemental analyses for the new compound are in accordance with the assigned structures. The IR

Scheme

spectrum of compound **3** and **4** showed stretching bands of keto group at 1715 - 1740 cm^{-1} . In **5**, stretching and bending NH bands of thiazolo quinazoline moiety appear at 3300 - 3400 cm^{-1} , 1300 - 1350 cm^{-1} respectively. The absence of keto group absorption at 1715 - 1740 cm^{-1} and appearance of a strong intensity band in the IR spectra of compounds **5** in the range of 1610 - 1655 cm^{-1} attributable to C=N provides a strong evidence for the condensation and also confirms the formation of the azomethine **5**. The proton magnetic resonance spectra of thiazolo quinazoline and their corresponding derivatives have been recorded in CDCl_3 . In this **5** NH signal of 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-hydrazino thiazolo (2,3-*b*) quinazoline moiety appear at 7.26 (s) ppm respectively. The position and presence of NH signal in the ^1H -NMR spectra of final compounds confirms the secondary NH proton in thiazolo quinazoline moiety. This clearly envisages that the thiazole-3-one moiety involve in 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-hydrazino thiazolo (2,3-*b*) quinazoline formation. All these observed facts clearly demonstrate that the 3rd

position of keto group in thiazole ring is converted into secondary amino group as indicated in Scheme and confirms the proposed structure **5**.

Pharmacology. Evaluation of antinociceptive activity was performed by the tail-flick technique using Albino mice.^{17,18} The results of antinociceptive testing indicate that the test compounds exhibited moderate antinociceptive activity at 30 min of reaction time and an increase in activity at 1 h, which reached a peak level at 2 h. Decline in activity was observed at 3 h (Table 1). Compound **6a** with the N'-sec-butylidene substituent showed good activity, with increased lipophilicity (1-ethylpropylidene group (compound **6b**), it showed increased activity. Replacement of the 1-ethyl-propylidene group with its isomer 1-methyl-butylidene group (compound **6c**) retained the activity. Replacement of alkyl chain with a cycloalkyl group and an aryl alkyl group (compounds **6d** and **6e**, respectively) and aryl group (compounds **6f** and **6g**, **6h-6o**) also results in decreasing the activity. Placement of the electron-withdrawing group at N-3 aryl ring (compounds **6h-6l**) leads to further decrease of activity.

Table 1. Analgesic activity of synthesized compounds (**6a-o**)

Compounds	Dose (mg/Kg)	Percentage analgesic activity ^a			
		30 min	1 h	2 h	3 h
6a	10	51 $\pm$ 1.12**	54 $\pm$ 1.27**	56 $\pm$ 1.43***	33 $\pm$ 1.36*
	20	64 $\pm$ 1.50***	68 $\pm$ 1.777***	71 $\pm$ 1.01***	37 $\pm$ 1.46*
6b	10	54 $\pm$ 1.37**	61 $\pm$ 1.70***	63 $\pm$ 1.60***	39 $\pm$ 1.07*
	20	69 $\pm$ 1.61***	71 $\pm$ 1.43***	77 $\pm$ 1.81	46 $\pm$ 1.43*
6c	10	51 $\pm$ 1.72**	60 $\pm$ 1.72***	62 $\pm$ 1.57***	31 $\pm$ 1.45*
	20	57 $\pm$ 1.36**	70 $\pm$ 1.53***	74 $\pm$ 1.82***	39 $\pm$ 1.36*
6d	10	39 $\pm$ 1.80*	47 $\pm$ 1.43*	53 $\pm$ 1.57**	31 $\pm$ 1.80*
	20	48 $\pm$ 1.17*	60 $\pm$ 1.91***	60 $\pm$ 1.43***	32 $\pm$ 1.50*
6e	10	38 $\pm$ 1.37*	46 $\pm$ 1.92*	56 $\pm$ 1.91**	29 $\pm$ 1.43*
	20	56 $\pm$ 1.60**	58 $\pm$ 1.39***	59 $\pm$ 1.51***	41 $\pm$ 1.17*
6f	10	42 $\pm$ 1.24*	46 $\pm$ 1.50*	47 $\pm$ 1.30*	28 $\pm$ 1.57*
	20	48 $\pm$ 1.67*	55 $\pm$ 1.46**	57 $\pm$ 1.27***	31 $\pm$ 1.70*
6g	10	42 $\pm$ 1.33*	50 $\pm$ 1.69**	54 $\pm$ 1.57**	27 $\pm$ 1.50*
	20	57 $\pm$ 1.29**	57 $\pm$ 1.57***	59 $\pm$ 1.40***	32 $\pm$ 1.26*
6h	10	31 $\pm$ 1.51*	33 $\pm$ 1.48*	38 $\pm$ 1.02*	31 $\pm$ 1.81*
	20	42 $\pm$ 1.91*	48 $\pm$ 1.50*	50 $\pm$ 1.00**	37 $\pm$ 1.44*
6i	10	33 $\pm$ 1.70	38 $\pm$ 1.27*	44 $\pm$ 1.90*	24 $\pm$ 1.44*
	20	51 $\pm$ 1.01**	52 $\pm$ 1.57**	55 $\pm$ 1.01**	34 $\pm$ 1.32*
6j	10	35 $\pm$ 1.67*	39 $\pm$ 1.03*	43 $\pm$ 1.43*	30 $\pm$ 1.67*
	20	47 $\pm$ 1.48*	50 $\pm$ 1.50**	51 $\pm$ 1.22**	35 $\pm$ 1.01*
6k	10	31 $\pm$ 1.36*	40 $\pm$ 1.54*	49 $\pm$ 1.02**	31 $\pm$ 1.43*
	20	43 $\pm$ 1.42*	50 $\pm$ 1.90**	52 $\pm$ 1.24**	36 $\pm$ 1.47*
6l	10	37 $\pm$ 1.61*	41 $\pm$ 1.27*	50 $\pm$ 1.51**	25 $\pm$ 1.91*
	20	42 $\pm$ 1.51*	52 $\pm$ 1.01**	55 $\pm$ 1.43**	35 $\pm$ 1.25*
6m	10	42 $\pm$ 1.26*	48 $\pm$ 1.53*	50 $\pm$ 1.91**	26 $\pm$ 1.60*
	20	56 $\pm$ 1.47**	61 $\pm$ 1.90***	65 $\pm$ 1.47***	31 $\pm$ 1.43*
6n	10	38 $\pm$ 1.91*	51 $\pm$ 1.50**	55 $\pm$ 1.37**	30 $\pm$ 1.61*
	20	51 $\pm$ 1.46**	55 $\pm$ 1.93**	60 $\pm$ 1.48**	36 $\pm$ 1.02*
6o	10	38 $\pm$ 1.77*	43 $\pm$ 1.02*	49 $\pm$ 1.54**	28 $\pm$ 1.91*
	20	51 $\pm$ 1.71**	56 $\pm$ 1.48**	61 $\pm$ 1.92**	39 $\pm$ 1.34*
Control		2 $\pm$ 0.33	6 $\pm$ 0.47	4 $\pm$ 0.57	4 $\pm$ 0.89
Diclofenac	10	25 $\pm$ 1.67*	31 $\pm$ 1.40*	33 $\pm$ 0.90*	31 $\pm$ 0.96*
	20	44 $\pm$ 0.93*	53 $\pm$ 1.14	60 $\pm$ 1.47***	37 $\pm$ 1.11*

^aData expressed as mean $\pm$ SD. Significance levels * p < 0.05, ** p < 0.01 and *** p < 0.001 as compared with the respective control.

Compound **6b** emerged as the most active antinociceptive agent and it is moderately more potent when compared with the reference standard diclofenac.

Anti-inflammatory activity was evaluated by the carrageenan induced paw edema test in rats.¹⁹ The anti-inflammatory activity data (Table 2) indicated that all the test compounds protected rats from carrageenan-induced inflammation moderately at 30 min of reaction time with increased activity at 1 h that reached a peak level at 2 h. Decline in activity was observed at 3 h. The compound **6c** exhibited the most potent anti-inflammatory activity of the series and it is moderately more potent when compared with the reference standard diclofenac sodium.

The ulcer index of the test compounds (Table 3) revealed that the compounds with aliphatic substituents (compounds **6a-d**) showed negligible ulcer index, whereas those with aryl substituents (compounds **6e-g** and **6m-o**) exhibited little increase in ulcer index and the aryl substituents containing electron-withdrawing groups (compounds **6h-k**) exhibited higher ulcer index over other test compounds. When compared with the reference

standards aspirin (ulcer index 1.73 ± 0.41) and diclofenac (ulcer index 1.65 ± 0.59) the test compounds exhibited 35 - 50% of the ulcer index of the reference standards. The compound (**6a**), (**6b**) and (**6c**) exhibited the lowest ulcer index (0.51 ± 1.63 , 0.48 ± 1.28 and 0.50 ± 1.53 , respectively) among the test compounds, about one-third of the ulcer index of the reference standards aspirin and diclofenac. The compound 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(2-chloro-benzylidene hydrazino) thiazolo (2,3-*b*) quinazoline (**6h**) showed the highest ulcer index (0.78 ± 1.40) among the test compounds, about 50% of the ulcer index of the reference standards aspirin and diclofenac.

The literature survey revealed that the presence of alkyl groups exhibited more antinociceptive and anti-inflammatory activities over aryl groups. In this study, the most active compound **6b** exhibited 65 and 79% antinociceptive activity at 10 and 20 mg/kg dose level respectively at the reaction time of 2 h. Conversely, diclofenac sodium showed 45 and 62% antinociceptive activity at 10 and 20 mg/kg dose level, respectively,

Table 2. Anti-inflammatory activity of synthesized compounds (**6a-o**)

Compounds	Dose (mg/Kg)	Percentage Protection ^a			
		30 min	1 h	2 h	3 h
6a	10	$34 \pm 1.43^{**}$	$39 \pm 1.58^*$	$40 \pm 1.91^{**}$	$28 \pm 1.16^*$
	20	$46 \pm 1.26^{***}$	$49 \pm 1.62^{***}$	$54 \pm 1.51^{***}$	$32 \pm 1.26^*$
6b	10	$39 \pm 1.67^{**}$	$42 \pm 1.69^{**}$	$46 \pm 1.34^{***}$	$30 \pm 1.15^*$
	20	$51 \pm 1.87^{**}$	$58 \pm 1.47^{***}$	$61 \pm 1.87^{***}$	$34 \pm 1.60^*$
6c	10	$41 \pm 1.42^{**}$	$44 \pm 1.91^{***}$	$50 \pm 1.01^{**}$	$31 \pm 1.41^*$
	20	$54 \pm 1.91^{***}$	$61 \pm 1.27^{***}$	$64 \pm 1.90^{***}$	$36 \pm 1.23^*$
6d	10	$28 \pm 1.84^*$	$31 \pm 1.37^*$	$42 \pm 1.02^{**}$	$27 \pm 1.65^*$
	20	$39 \pm 1.02^{**}$	$44 \pm 1.65^{**}$	$48 \pm 1.02^{***}$	$29 \pm 1.43^*$
6e	10	$29 \pm 1.91^*$	$37 \pm 1.25^{**}$	$37 \pm 1.41^{**}$	$26 \pm 1.81^*$
	20	$38 \pm 1.17^{**}$	$45 \pm 1.54^{**}$	$47 \pm 1.28^{***}$	$32 \pm 1.90^*$
6f	10	$28 \pm 1.51^*$	$33 \pm 1.88^*$	$37 \pm 1.81^{**}$	$25 \pm 1.40^*$
	20	$36 \pm 1.22^*$	$38 \pm 1.01^*$	$43 \pm 1.87^{**}$	$34 \pm 1.41^*$
6g	10	$31 \pm 1.26^*$	$35 \pm 1.93^*$	$37 \pm 1.02^{**}$	$23 \pm 1.32^*$
	20	$35 \pm 1.92^*$	$41 \pm 1.54^{**}$	$42 \pm 1.91^{**}$	$29 \pm 1.54^*$
6h	10	$23 \pm 1.02^*$	$28 \pm 1.51^*$	$29 \pm 1.62^*$	$19 \pm 1.91^*$
	20	$31 \pm 1.43^*$	$34 \pm 1.27^*$	$35 \pm 1.02^*$	$28 \pm 1.54^*$
6i	10	$26 \pm 1.56^*$	$28 \pm 1.07^*$	$31 \pm 1.51^*$	$24 \pm 1.50^*$
	20	$34 \pm 1.51^{**}$	$38 \pm 1.91^{**}$	$40 \pm 1.57^{**}$	$34 \pm 1.27^*$
6j	10	$28 \pm 1.71^*$	$30 \pm 1.51^*$	$37 \pm 1.92^*$	$23 \pm 1.04^*$
	20	$34 \pm 1.91^*$	$41 \pm 1.50^{**}$	$42 \pm 1.16^{**}$	$30 \pm 1.92^*$
6k	10	$26 \pm 1.23^*$	$30 \pm 1.93^*$	$31 \pm 1.37^*$	$24 \pm 1.90^*$
	20	$35 \pm 1.26^*$	$36 \pm 1.71^{**}$	$42 \pm 1.87^{**}$	$33 \pm 1.50^*$
6l	10	$28 \pm 1.47^*$	$32 \pm 1.05^*$	$32 \pm 1.33^*$	$23 \pm 1.91^*$
	20	$33 \pm 1.57^*$	$37 \pm 1.01^{**}$	$38 \pm 1.54^{**}$	$32 \pm 1.92^*$
6m	10	31 ± 1.26	$35 \pm 1.54^*$	$37 \pm 1.88^{**}$	$24 \pm 1.70^*$
	20	$39 \pm 1.60^{**}$	$46 \pm 1.47^{**}$	$42 \pm 1.60^{**}$	$31 \pm 1.91^*$
6n	10	$28 \pm 1.27^*$	30 ± 1.04	$36 \pm 1.61^*$	$24 \pm 1.01^*$
	20	$39 \pm 1.58^{**}$	$41 \pm 1.65^{**}$	$42 \pm 1.01^{**}$	$30 \pm 1.63^*$
6o	10	$31 \pm 1.28^*$	$32 \pm 1.06^*$	$36 \pm 1.43^*$	$21 \pm 1.61^*$
	20	$38 \pm 1.54^{**}$	$43 \pm 1.79^{**}$	$44 \pm 1.63^{**}$	$31 \pm 1.56^*$
Control		5.1 ± 0.27	6.1 ± 0.25	5.7 ± 0.30	3.2 ± 0.91
Diclofenac	10	$20 \pm 0.61^*$	$26 \pm 1.56^*$	$37 \pm 1.95^*$	$21 \pm 0.91^*$
	20	$43 \pm 0.59^{**}$	$50 \pm 0.90^{***}$	$58 \pm 1.50^{***}$	$40 \pm 1.34^{**}$

^aData expressed as mean $\pm$ SD. Significance levels * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ as compared with the respective control.

Table 3. Evaluation of ulcerogenicity Index

Compounds	Ulcer index ^a
6a	0.49 ± 1.61*
6b	0.46 ± 1.26*
6c	0.48 ± 1.51*
6d	0.52 ± 1.27*
6e	0.53 ± 1.57*
6f	0.56 ± 1.52*
6g	0.56 ± 1.90*
6h	0.76 ± 1.38*
6i	0.75 ± 1.45*
6j	0.68 ± 1.04*
6k	0.75 ± 1.67*
6l	0.71 ± 1.01*
6m	0.64 ± 1.36*
6n	0.63 ± 1.60*
6o	0.64 ± 1.61*
Control	0.13 ± 1.30*
Diclofenac	1.63 ± 0.57**
Aspirin	1.71 ± 0.39**

^aData expressed as mean ± SD. Significance levels *p < 0.05 and **p < 0.01 as compared with the respective control.

at the reaction time of 2 h. On the other hand, diclofenac sodium revealed 39 and 60% anti-inflammatory activity at the dose of 10 and 20 mg/kg, respectively, at the reaction of 2 h. The compound **6c** showed 52 and 66% anti-inflammatory activity at the dose of 10 and 20 mg/kg, respectively, at the reaction of 2 h. Interestingly, these compounds showed one third of ulcer index of the reference NSAID's aspirin and diclofenac.

Conclusions

This research examined the antinociceptive and anti-inflammatory activities of novel series of 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline **6a-o** prepared by the reaction of key intermediate **3** with benzaldehyde, hydrazine hydrate and appropriate ketones/aldehydes. The results of the antinociceptive and anti-inflammatory activities of the 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline series showed that moderate enhancement of activity. The compound **6b** emerged as the most active compound in exhibiting antinociceptive activity and the compound **6c** emerged as the most active compound in exhibiting anti-inflammatory activity and these compounds are moderately potent when compared with the reference standard diclofenac sodium. Hence, this series could be developed as a novel class of antinociceptive and anti-inflammatory agents. However, further structural modification is planned to increase the antinociceptive and anti-inflammatory activities with decreased ulcerogenicity.

Experimental

Chemistry. The synthetic strategy leading to the key intermediate and the target compounds are illustrated in the scheme. 6,7,8,9-tetrahydro-5H-5-(2'-hydroxy phenyl) thiazolo (2,3-*b*)

quinazolin-3(2H)-one **3** was prepared by the equimolar quantities of each (0.039 mol) of cyclohexanone and benzaldehyde (0.039 mol) were taken in a beaker, to this sodium hydroxide solution was added to make the solution alkaline, this was shaken and kept aside. The solid thus obtained, was filtered, washed with water and recrystallized from absolute ethanol. A mixture of 2-benzylidene cyclohexanone ring **1** (0.039 mol) thiourea (0.03 mol) and potassium hydroxide (2.5 g) 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 dilute acetic acid and kept overnight. The solid thus obtained, was filtered, washed with water and recrystallized from ethanol to give 3,4,5,6,7,8-hexahydro-4-phenyl quinazolin-2-thione **2**. The chloroacetic acid (0.096 mol) was melted on a water bath and thione (0.009 mol) added to it portion wise to maintain its homogeneity. The homogeneous mixture was further heated on a water bath for 30 min and kept overnight. The solid thus obtained was washed with water until neutralized and crystallized from ethanol to give 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl thiazolo (2,3-*b*) quinazolin-3(2H)-one **3**.²⁰ A mixture of **3** (0.002 mol), benzaldehyde (0.002 mol) and anhydrous sodium acetate (0.002 mol) in glacial acetic acid (10 mL) was heated under reflux for 4 h. The reaction mixture was kept overnight and the solid, thus separated, was filtered, washed with water and recrystallized from ethanol to furnish of 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene thiazolo (2,3-*b*) quinazolin-3(2H)-one **4**. Euqimolar quantities (0.004 mol) of compound **4** hydrazine hydrate (99%) (0.004 mol) were dissolved in 10 mL of warm ethanol and refluxed for 30 min. After standing for approximately 24 h at room temperature, the product were separated by filtration, dried under vacuo and recrystallized from warm ethanol to yield 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-hydrazino thiazolo (2,3-*b*) quinazoline **5**. A mixture of **5** (0.004 mol) and appropriate ketones/aldehydes (0.004 mol) in glacial acetic acid was refluxed for 38 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol to yields 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-substituted hydrazino thiazolo (2,3-*b*) quinazoline **6a-o**.

The melting points were taken in open capillary tube and are uncorrected. IR spectra were recorded with KBr pellets (ABB Bomem FT-IR spectrometer MB 104 ABB Limited Bangaluru, India). Proton (¹H) NMR spectra (Bruker 400 NMR spectrometer Mumbai, India) were recorded with TMS as internal references. Mass spectral data were recorded with a quadrupol mass spectrometer (Shimadzu GC MS QP 5000, Chennai, India), and microanalyses were performed using a vario EL V300 elemental analyzer (Elemental Analysen systeme GmbH Chennai, India). The purity of the compounds was checked by TLC on pre-coated SiO₂ gel (HF₂₅₄, 200 mesh) aluminium plates (E. Merck) using ethyl acetate: benzene (1:3) and visualized in UV chamber. IR, ¹H-NMR, mass spectral datas and elemental analyses were consistent with the assigned structures of all the compounds.

¹H NMR spectra were recorded for all the targeted compounds. The ¹H NMR spectra were recorded for the representative key intermediate **3**. The 6,7,8,9-tetrahydro-5H-5-hydroxy phenyl thiazolo quinazolin-3-ones. Cream solid; Yield: 83%;

mp 142 - 144 °C; IR cm^{-1} : 3402 (phenolic OH), 3012 (Cycloalkane C-H), 3079 (Ar-CH), 1727 (C=O), 1615 (C=C); $^1\text{H-NMR}$ (CDCl_3) δ 6.74-7.76 (m, 4H, Ar-H), 9.91 (s, 1H; Ar-OH), 5.75 (s, 1H, H-5), 3.40 (s, 2H, CH_2 , thiazole ring), 1.64-2.35 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 300 (M^+); (Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$; 300.48). Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$; C, 63.98; H, 5.37; N, 9.33; Found: C, 63.86; H, 5.41; N, 9.39.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-thiazolo (2,3-b) quinazolin-3(2H)-one (4): Pale Yellow solid; Yield: 75%; mp 146 - 148 °C; IR cm^{-1} : 3474 (O-H), 3100 (Cycloalkane C-H), 3059 (Ar-CH), 1742 (C=O), 1613 (C=C); $^1\text{H-NMR}$ (CDCl_3) δ 6.82-7.46 (m, 9H, Ar-H), 9.74 (s, 1H, Ar-OH), 5.86 (s, 1H, H-5), 6.57 (s, 1H, =CH), 1.82-2.24 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 388 (M^+); (Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$; 388.48). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$; C, 71.11; H, 5.19; N, 7.21; Found: C, 71.18; H, 5.24; N, 7.27.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-hydrazino thiazolo (2,3-b) quinazoline (5): Dark brown solid; Yield: 69%; mp 169 - 171 °C; IR cm^{-1} : 3442 (O-H), 3076 (Cycloalkane C-H), 3144 (Ar-CH), 1618 (C=C); 3378 (N-H); 1341 (N-H); 1654 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.74-7.86 (m, 10H, Ar-H), 5.56 (s, 1H, H-5), 6.38 (s, 1H, =CH), 7.26 (s, 2H, NH_2), 1.90-2.42 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 402 (M^+); (Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$; 402.51). Ana. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$; C, 68.63; H, 5.51; N, 13.92; Found: C, 68.56; H, 5.59; N, 13.97.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-2-butyldene-hydrazino) thiazolo (2,3-b) quinazoline (6a): Yellow solid; Yield: 78%; mp 176 - 178 °C; IR cm^{-1} : 3476 (O-H), 2912 (Cycloalkane C-H), 3078 (Ar-CH), 1534 (C=C); 2868 (C-H in CH_3); 1656 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.82-7.46 (m, 9H, Ar-H), 9.84 (s, 1H, Ar-OH), 5.18 (s, 1H, H-5), 6.18 (s, 1H, =CH), 1.80-2.32 (m, 8H, $4 \times \text{CH}_2$), 1.4 (q, 2H, CH_2CH_3), 1.82 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 2.64 (s, 3H, CH_3); EI-MS (m/z) 456 (M^+); (Calcd for $\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; 456.2). Ana. Calcd for $\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; C, 71.02; H, 6.18; N, 12.27; Found: C, 71.14; H, 6.06; N, 12.21.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-3-pentylidene-hydrazino) thiazolo (2,3-b) quinazoline (6b): Pale yellow crystals; Yield: 72%; mp 164 - 166 °C; IR cm^{-1} : 3448 (O-H), 2987 (Cycloalkane, C-H), 3065 (Ar-CH), 1541 (C=C); 2833 (C-H in CH_3); 1649 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.44-7.88 (m, 9H, Ar-H), 9.76 (s, 1H, Ar-OH), 5.08 (s, 1H, H-5), 6.20 (s, 1H, =CH), 1.76-2.46 (m, 8H, $4 \times \text{CH}_2$), 1.52 (q, 4H, CH_2CH_3), 1.92 (t, $J = 7.0$ Hz, 6H, CH_2CH_3); EI-MS (m/z) 470 (M^+); (Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$; 470.63). Ana. Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$; C, 71.46; H, 6.43; N, 11.90; Found: C, 71.41; H, 6.48; N, 11.97.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-2-pentylidene-hydrazino) thiazolo (2,3-b) quinazoline (6c): Creamy crystals; Yield: 68%; mp 178 - 180 °C; IR cm^{-1} : 3437 (O-H), 2952 (Cycloalkane C-H), 3068 (Ar-CH), 1544 (C=C); 2870 (C-H in CH_3); 1660 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.72-7.36 (m, 9H, Ar-H), 9.94 (s, 1H, Ar-OH), 5.22 (s, 1H, H-5), 6.24 (s, 1H, =CH), 1.82-2.36 (m, 8H, $4 \times \text{CH}_2$), 0.91 (t, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.33 (sext, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.84 (t, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.68 (s, 3H, CH_3); EI-MS (m/z) 470 (M^+); (Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$; 470.63). Ana. Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$; C, 71.46; H, 6.43; N, 11.90; Found: C, 71.41; H, 6.49; N, 11.98.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-cyclohexylidene-hydrazino) thiazolo (2,3-b) quinazoline (6d): Yellow crystals; Yield: 82%; mp 182 - 184 °C; IR cm^{-1} : 3431 (O-H), 2924 (Cycloalkane C-H), 3028 (Ar-CH), 1544 (C=C); 1666 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.92-7.86 (m, 9H, Ar-H), 9.97 (s, 1H, Ar-OH), 5.26 (s, 1H, H-5), 6.24 (s, 1H, =CH), 1.60-2.04 (m, 18H, $9 \times \text{CH}_2$); EI-MS (m/z) 470 (M^+); (Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$; 470.63). Ana. Calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$; C, 71.46; H, 6.43; N, 11.90; Found: C, 71.31; H, 6.37; N, 11.83.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-1-phenylethylidene-hydrazino) thiazolo (2,3-b) quinazoline (6e): Yellow solid; Yield: 84%; mp 146 - 148 °C; IR cm^{-1} : 3447 (O-H), 2928 (Cycloalkane C-H), 3098 (Ar-CH), 1542 (C=C); 2918 (C-H in CH_3); 1606 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.62-7.16 (m, 14H, Ar-H), 9.89 (s, 1H, Ar-OH), 5.06 (s, 1H, H-5), 6.06 (s, 1H, =CH), 1.74-2.38 (m, 8H, $4 \times \text{CH}_2$), 2.74 (s, 3H, CH_3); EI-MS (m/z) 504 (M^+); (Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; 504.65). Ana. Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; C, 73.78; H, 5.59; N, 11.10; Found: C, 73.71; H, 5.64; N, 11.17.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-1-oxo-indolin-2-one-3-ylidene-hydrazino) thiazolo (2,3-b) quinazoline (6f): Pale yellow solid; Yield: 70%; mp 156 - 158 °C; IR cm^{-1} : 3452 (O-H), 2934 (Cycloalkane C-H), 3086 (Ar-CH), 1538 (C=C); 1616 (C=N), 1338 (C-N), 1726 (C=O); $^1\text{H-NMR}$ (CDCl_3) δ 6.60-7.18 (m, 13H, Ar-H), 9.84 (s, 1H, Ar-OH), 5.16 (s, 1H, H-5), 6.12 (s, 1H, =CH), 1.78-2.32 (m, 8H, $4 \times \text{CH}_2$), 8.06 (s, 1H, NH); EI-MS (m/z) 531 (M^+); (Calcd for $\text{C}_{31}\text{H}_{25}\text{N}_5\text{O}_2\text{S}$; 531.63). Ana. Calcd for $\text{C}_{31}\text{H}_{25}\text{N}_5\text{O}_2\text{S}$; C, 70.04; H, 4.74; N, 13.17; Found: C, 70.07; H, 4.76; N, 13.19.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-benzylidene-hydrazino) thiazolo (2,3-b) quinazoline (6g): Creamy crystals; Yield: 72%; mp 159 - 160 °C; IR cm^{-1} : 3450 (O-H), 2934 (Cycloalkane C-H), 3048 (Ar-CH), 1568 (C=C); 1608 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.90-7.68 (m, 14H, Ar-H), 9.84 (s, 1H, Ar-OH), 5.22 (s, 1H, H-5), 6.34 (s, 1H, =CH), 8.1 (s, 1H, CH), 1.61-2.10 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 490 (M^+); (Calcd for $\text{C}_{30}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$; 490.92). Ana. Calcd for $\text{C}_{30}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$; C, 73.44; H, 5.34; N, 11.42; Found: C, 73.41; H, 5.37; N, 11.48.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(2-chloro-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6h): Brown crystals; Yield: 77%; mp 162 - 164 °C; IR cm^{-1} : 3441 (O-H), 2926 (Cycloalkane C-H), 3056 (Ar-CH), 1562 (C=C); 1598 (C=N), 816 (C-Cl); $^1\text{H-NMR}$ (CDCl_3) δ 6.80-7.58 (m, 13H, Ar-H), 5.32-9.71 (s, 1H, Ar-OH), (s, 1H, H-5), 6.38 (s, 1H, =CH), 8.12 (s, 1H, CH), 1.66-2.20 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 527 (M^+); (Calcd for $\text{C}_{30}\text{H}_{25}\text{ClN}_4\text{O}_2\text{S}$; 525.06). Ana. Calcd for $\text{C}_{30}\text{H}_{25}\text{ClN}_4\text{O}_2\text{S}$; C, 68.62; H, 4.80; N, 6.75; Found: C, 68.76; H, 4.72; N, 6.79.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(4-chloro-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6i): Yellow solid; Yield: 79%; mp 144 - 146 °C; IR cm^{-1} : 3467 (O-H), 2928 (Cycloalkane C-H), 3058 (Ar-CH), 1566 (C=C); 1590 (C=N), 826 (C-Cl); $^1\text{H-NMR}$ (CDCl_3) δ 6.76-7.52 (m, 13H, Ar-H), 9.87 (s, 1H, Ar-OH), 5.34 (s, 1H, H-5), 6.36 (s, 1H, =CH), 8.22 (s, 1H, CH), 1.68-2.28 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 527 (M^+); (Calcd for $\text{C}_{30}\text{H}_{25}\text{ClN}_4\text{O}_2\text{S}$; 525.06). Ana. Calcd for $\text{C}_{30}\text{H}_{25}\text{ClN}_4\text{O}_2\text{S}$; C, 68.62; H, 4.80; N, 6.75; Found: C, 68.65; H, 4.83; N, 6.77.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(2-nitro-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6j): Creamy crystals; Yield: 77%; mp 166 - 168 °C; IR cm^{-1} : 3461 (O-H), 2930 (Cycloalkane C-H), 3048 (Ar-CH), 1542 (C=C); 1584 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.72-7.58 (m, 13H, Ar-H), 9.81 (s, 1H, Ar-OH), 5.24 (s, 1H, H-5), 6.22 (s, 1H, =CH), 8.44 (s, 1H, CH), 1.52-2.18 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 535 (M^+); (Calcd for $\text{C}_{30}\text{H}_{25}\text{N}_5\text{O}_3\text{S}$; 535.62). Ana. Calcd for $\text{C}_{30}\text{H}_{25}\text{N}_5\text{O}_3\text{S}$; C, 67.27; H, 4.70; N, 13.08; Found: C, 67.21; H, 4.76; N, 13.14.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(4-nitro-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6k): Pale yellow crystals; Yield: 71%; mp 142 - 144 °C; IR cm^{-1} : 3464 (O-H), 2922 (Cycloalkane C-H), 3066 (Ar-CH), 1538 (C=C); 1562 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.68-7.52 (m, 13H, Ar-H), 9.87 (s, 1H, Ar-OH), 5.32 (s, 1H, H-5), 6.12 (s, 1H, =CH), 8.32 (s, 1H, CH), 1.40-2.20 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 535 (M^+); (Calcd for $\text{C}_{30}\text{H}_{25}\text{N}_5\text{O}_3\text{S}$; 535.62). Ana. Calcd for $\text{C}_{30}\text{H}_{25}\text{N}_5\text{O}_3\text{S}$; C, 67.27; H, 4.70; N, 13.08; Found: C, 67.32; H, 4.72; N, 13.19.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(4-methoxy-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6l): Brown solid; Yield: 75%; mp 150 - 152 °C; IR cm^{-1} : 3438 (O-H), 2968 (Cycloalkane C-H), 3050 (Ar-CH), 1550 (C=C); 1560 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.75-7.56 (m, 13H, Ar-H), 9.82 (s, 1H, Ar-OH), 5.22 (s, 1H, H-5), 6.35 (s, 1H, =CH), 8.44 (s, 1H, CH), 1.80-2.60 (m, 8H, $4 \times \text{CH}_2$), 3.73 (s, 3H, OCH_3); EI-MS (m/z) 520 (M^+); (Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; 520.64). Ana. Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; C, 71.51; H, 5.42; N, 10.76; Found: C, 71.57; H, 5.34; N, 10.71.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(2-methyl-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6m): Creamy crystals; Yield: 80%; mp 136 - 138 °C; IR cm^{-1} : 3449 (O-H), 2972 (Cycloalkane C-H), 3054 (Ar-CH), 1548 (C=C); 1568 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.70-7.52 (m, 13H, Ar-H), 9.96 (s, 1H, Ar-OH), 5.33 (s, 1H, H-5), 6.36 (s, 1H, =CH), 8.64 (s, 1H, CH), 1.88-2.66 (m, 8H, $4 \times \text{CH}_2$), 3.73 (s, 3H, CH_3); EI-MS (m/z) 504 (M^+); (Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; 504.65). Ana. Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; C, 73.78; H, 5.59; N, 11.10; Found: C, 73.81; H, 5.67; N, 11.17.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(4-methyl-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6n): Creamy crystals; Yield: 82%; mp 148 - 150 °C; IR cm^{-1} : 3447 (O-H), 2976 (Cycloalkane C-H), 3060 (Ar-CH), 1554 (C=C); 1574 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.77-7.57 (m, 13H, Ar-H), 9.81 (s, 1H, Ar-OH), 5.38 (s, 1H, H-5), 6.40 (s, 1H, =CH), 8.60 (s, 1H, CH), 1.90-2.70 (m, 8H, $4 \times \text{CH}_2$), 3.75 (s, 3H, CH_3); EI-MS (m/z) 504 (M^+); (Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; 504.65). Ana. Calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$; C, 73.78; H, 5.59; N, 11.10; Found: C, 73.71; H, 5.52; N, 11.13.

6,7,8,9-Tetrahydro-5H-5-hydroxy phenyl-2-benzylidene-3-(N'-(2-phenyl-benzylidene hydrazino) thiazolo (2,3-b) quinazoline (6o): Pale brown solid; Yield: 78%; mp 152 - 154 °C; IR cm^{-1} : 3445 (O-H), 2988 (Cycloalkane C-H), 3088 (Ar-CH), 1572 (C=C); 1584 (C=N); $^1\text{H-NMR}$ (CDCl_3) δ 6.90-7.70 (m, 19H, Ar-H), 9.96 (s, 1H, Ar-OH), 5.36 (s, 1H, H-5), 6.32 (s, 1H, =CH), 1.84-2.52 (m, 8H, $4 \times \text{CH}_2$); EI-MS (m/z) 566 (M^+); (Calcd for $\text{C}_{36}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$; 566.71). Ana. Calcd for $\text{C}_{36}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$;

C, 76.30; H, 5.34; N, 9.89; Found: C, 76.35; H, 5.37; N, 9.93.

Pharmacology. The synthesized compounds were evaluated for antinociceptive, anti-inflammatory and ulcerogenic index. The test compounds and the standard drugs were administered in the form of a suspension (using 1% carboxymethylcellulose as a vehicle) by oral route of administration for antinociceptive and anti-inflammatory. For ulcerogenicity studies, the drug was administered by intraperitoneally as suspension in 10% v/v Tween 80. Each group consisted of six animals. The animals were procured from the C.L.Baid metha college of pharmacy (Chennai, India), and were maintained in colony cages at 25 ± 2 °C, relative humidity 45 - 55%, under a 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee has approved the protocol adopted for the experimentation of animals.

Antinociceptive activity. Test for antinociceptive activity was performed by tail-flick technique using Wistar albino mice (25 - 35 g) of either sex selected by a random sampling technique.^{21,17} Diclofenac sodium at a dose level of 10 and 20 mg/kg was administered orally as the reference drug for comparison. The test compounds at two dose levels (10 and 20 mg/kg) were administered orally. The reaction time was recorded at 30 min and 1, 2 and 3 h after the treatment, and the cut-off time was 10 seconds. The percentage antinociceptive activity (PAA) was calculated by the following formula:

$$\text{PAA} = [T_2 - T_1/10 - T_1] \times 100$$

Where T_1 is the reaction time (s) before treatment and T_2 is the reaction time (s) after treatment.

Anti-inflammatory activity. Anti-inflammatory activity was evaluated by carrageenan-induced paw edema test in rats.¹⁸ Diclofenac sodium 10 and 20 mg/kg were administered as a standard drug for comparison. The test compounds were administered at two dose levels (10 and 20 mg/kg). The paw volumes were measured using the mercury displacement technique with the help of a plethysmograph immediately before and 30 min and 1, 2 and 3 h after carrageenan injection. The percentage inhibition of paw edema was calculated using the following formula:

$$\text{Percent inhibition I} = 100[1 - (a - x)/(b - y)]$$

Where x is the mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group), a is the mean paw volume of rats after the administration of carrageenan in the test group (drug treated), b is the mean paw volume of rats after the administration of carrageenan in the control group and y is the mean paw volume of rats before the administration of carrageenan in the control group.

Evaluation of ulcerogenicity index. Ulceration in rats was induced as described by reported protocol.²² Albino rats of the Wistar strain weighing 150 - 200 g of either sex were divided into various groups each of six animals. The control groups of animals were administered only 10% v/v Tween 80 suspension intraperitoneally. Two groups were administered with aspirin

(German Remedies) and diclofenac sodium intraperitoneally at a dose of 20 mg/kg once daily for 3 days. The remaining group of animals was administered with test compounds intraperitoneally at a dose of 20 mg/kg. On the fourth day, pylorus was ligated as per the method.²² Animals were fasted for 36 h before the pylorus ligation procedure. Four hours after the ligation, animals were sacrificed. The stomach was removed and opened along with the greater curvature. Ulcer index was determined by the method²³ and is recorded in Table 3.

Statistical analysis. Statistical analysis of the biological activity of the synthesized compounds on animals was evaluated using a one-way analysis of variance (ANOVA). In all cases, post hoc comparisons of the means of individual groups were performed using Tukey's test. A significance level of $p < 0.05$ denoted significance in all cases. All values are expressed as mean $\pm$ SD (standard deviations). For statistical analysis, we have used GRAPHPAD PRISM version 3.0. (Graph Pad Software Inc, San Diego, CA, USA).

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