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Synthesis of 2-(aryl)-5-(arylidene)-4-thiazolidinone derivatives with potential analgesic and anti-inflammatory activity

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Abstract A series of novel *N*-[5-(arylidene)-2-(aryl)-4-oxo-thiazolidin-3-yl]-4-biphenylcarboxamide derivatives was synthesized and evaluated for analgesic and anti-inflammatory activity. In this study, biphenyl-4-carboxylic acid hydrazide was converted to the corresponding aryl hydrazones using aryl aldehydes in the presence of catalytic amount of glacial acetic acid. The aryl hydrazones on reaction with thioglycolic acid in the presence of anhydrous zinc chloride yielded *N*-[2-(aryl)-4-oxo-thiazolidin-3-yl]-4-biphenylcarboxamide which further on reaction with aromatic aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid furnished the title compounds. All compound exhibited anti-inflammatory activity at the dose 10 mg/kg. The structures of all these newly synthesized compounds were confirmed by their elemental analyses (C, H, N) and spectral data (IR and ^{1}H NMR).

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Introduction

One of the main objectives of organic and medicinal chemistry is the design, synthesis, and production of molecules having a value as human therapeutic agents (Kumar *et al.*, 2011b). In the recent past, 4-thiazolidinone scaffold and its derivatives have attracted considerable attention of medicinal chemists and have become an important class of heterocyclic compounds because of their diverse biological activities such as anti-inflammatory (Kumar and Rajput, 2009; Ottana *et al.*, 2005; Geronikaki *et al.*, 2008), analgesic (Tandon *et al.*, 1985; Knutsen *et al.*, 2007) antimycobacterial (Kucukguzel *et al.*, 2002; Srivastav *et al.*, 2005), antimicrobial (Ozkirimli *et al.*, 2009; Bondock *et al.*, 2007; Madhukar *et al.*, 2009; Fuloria *et al.*, 2009), antiarrhythmic (Amr *et al.*, 2009), anti-HIV activity (Kucukguzel *et al.*, 2006; Barreca *et al.*, 2001), and anticonvulsant (Shiradkar *et al.*, 2007). An essential component in drug designing program is the syntheses of novel molecules, with better activity with lesser side effects. These observations promoted us to synthesize a new series of 4-thiazolidinones.

Thus, as a part of our ongoing research endeavors to search biologically active heterocyclic compounds containing sulfur and nitrogen atoms, we have synthesized some novel thiazolidin-4-ones and evaluated them for their anti-inflammatory, analgesic, and other biological activities in our laboratories (Kumar *et al.*, 2011a, b; Jain *et al.*, 2011; Sharma *et al.*, 2011). Moreover, it has been observed that thiazolidinone derivatives derived from biphenyl-4-carboxylic acid have shown promising anti-inflammatory and antibacterial activities (Deep *et al.*, 2010, 2011). Thus,

in the lights of these facts, we anticipated that the 2-(aryl)-5-(arylidene)-4-thiazolidinone derivatines may also possess commendable biological potential. Thus, it was decided to undertake biological evaluation of these compounds to determine their possible pharmacological potential. Hence, in this study, we report the synthesis with chemical characterization and anti-inflammatory and analgesic activities of some novel thiazolidin-4-ones derived from biphenyl-4-carboxylic acid.

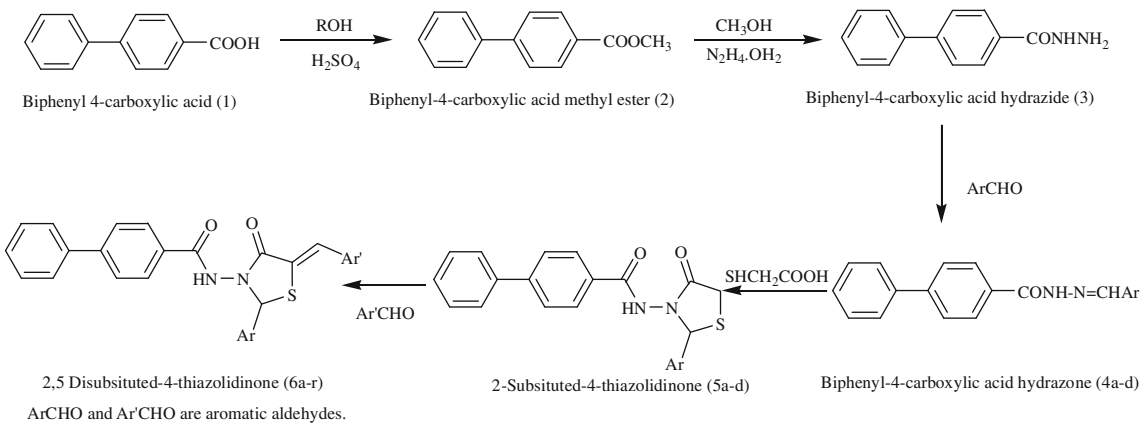
Results and discussion

We describe here a convenient approach for the preparation of *N*-[5-(arylidene)-2-(aryl)-4-oxo-thiazolidin-3-yl]-4-biphenylcarboxamide derivatives **6a–r**. All compounds were synthesized according to Scheme 1. At the first stage, Schiff's bases **4a–r** biphenyl-4-carboxylic acid hydrazide 3 and aromatic aldehydes were prepared. Further, reaction of these Schiff's bases with thioglycolic acid in DMF and in the presence of a small amount of $ZnCl_2$ yielded the *N*-[2-(aryl)-4-oxo-thiazolidin-3-yl]-4-biphenylcarboxamide derivatives **5a–r** which on further reaction with aromatic aldehydes in the presence of sodium acetate and glacial acetic acid yield the 2,3,5-trisubstituted-4-thiazolidinones. The synthesized compounds were characterized on the basis of their elemental analysis, IR and ^{1}H NMR. IR spectra of all compounds **6a–r** showed absorption band at around 3481–3298, 1665–1634, 1648–1402 cm^{-1} regions, conforming the presence of NH, C=O, C–N, respectively. ^{1}H NMR was more informative. In addition to the peak of biphenyl-4-carboxamido moiety, other characteristic signal were observed at δ 8.07–8.00 (1H, –NH), 7.31–6.94 (s, 1H, C=CH) and 4.98–4.32 (s, 1H, –NCHS), confirming the structure of thiazolidine ring. The elemental analysis, values are consistent with their predicted structure. The purpose of this study was to predict any molecular modification which might result in detection of new potential antirheumatic agents. A series of compounds were prepared and assayed in a variety of biological test for analgesic and anti-inflammatory activity. Compounds (**6a–r**) were investigated for in vivo antiinflammatory activity by carrageenan-induced rat paw edema method using *plethysmometer* and for in vivo analgesic activity by writhing method. All described 4-thiazolidinone derivatives were evaluated for anti-inflammatory activity and among them compounds **6l** and **6m** showed comparatively good percentage of inhibition of edema than the other synthesized compounds. Percentage inhibition observed with compound **6m** bearing a para methoxy and para chloro substitution was highest i.e., 71.83 and 57.90%, respectively, at 2 and 4-h time interval. The second most active compound of the series was compound **6l** with 71.21% inhibition at 4 h interval. However, at 2 h interval compound **6o** with two methoxy groups was observed to be second most active compound of the series. Similarly, all synthesized compounds were evaluated for analgesic activity. In the acetic acid-induced writhing, the entire test compounds showed the significant analgesic activity as compared to the standard drug. The compounds **6h** and **6p** bearing two electron withdrawing groups i.e., chloro and nitro (**6h**) and fluoro and chloro (**6p**) were found to be most potent with percentage protection of 46.25%. Next to these, compound **6g** bearing two nitro substitutions depicted 43.25% protection.

Experimental

All the chemical and solvents

All the chemicals and solvents used in this study were procured from Qualigens (Navi Mumbai, India), CDH (New Delhi, India), and SD Fines (Mumbai, India). Melting points were determined in open-glass capillaries on TEMPO



Scheme 1 Synthetic pathway for the formation of the title compounds

melting point apparatus and are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography (TLC). ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer using TMS as internal standard. Elemental analyses were carried out on Carlo Erba 1106 CHN Analyzer. IR spectra were recorded on Perkin Elmer Spectrum RXI FTIR spectrophotometer in KBr phase.

General procedure for synthesis of 4-thiazolidinone derivatives

*Synthesis of biphenyl-4-carboxylic acid methyl ester (**2**)*

A mixture of (0.25 M, 50 g) biphenyl-4-carboxylic acid (**1**) and excess of methanol (250 ml) with 1 ml of sulfuric acid was refluxed for 3–4 h in RBF. The mixture was cooled; the solid was separated by filtration and recrystallized from methanol.

*Synthesis of biphenyl-4-carboxylic acid hydrazide (**3**)*

A mixture of (0.2 M, 42.4 g) biphenyl-4-carboxylic acid methyl ester (**2**) and excess of hydrazine hydrate (0.30 M, 15 ml), ethanol (250 ml) was refluxed for about 3 h and cooled. The solid was separated by filtration and recrystallized from ethanol to afford biphenyl-4-carboxylic acid hydrazide.

*Synthesis of biphenyl-4-carboxylic acid hydrazone (**4a–r**)*

A mixture of (0.025 M, 5.3 g) biphenyl-4-carboxylic acid hydrazide (**3**) and required aromatic aldehydes (0.025 M) was refluxed in methanol (50 ml) in the presence of a catalytic amount of glacial acetic acid for about 2 h. The mixture was cooled; the solid was separated by filtration and recrystallized from methanol to give the corresponding hydrazones.

*Synthesis of 2,3-disubstituted-4-thiazolidinone (**5a–r**)*

A mixture of (0.015 M) biphenyl-4-carboxylic acid hydrazone (**4a**–**r**) and required amount of thioglycolic acid (0.015 M, 1.40 ml) in DMF (50 ml), containing a pinch of anhydrous $ZnCl_2$ was refluxed for about 6 h. The reaction mixture was cooled and poured on to crushed ice. The solid thus obtained was filtered, washed with water, and the product was recrystallized from rectified spirit. Synthetic pathway for formation of title compounds is presented in Scheme 1. Characterization data of these compounds is provided in Table 1.

*Synthesis of 2,3,5-trisubstituted-4-thiazolidinone (**6a–r**)*

A mixture of (0.01 M) 2,3-disubstituted-4-thiazolidinone (**5a**–**r**) required aromatic aldehydes (0.01 M) and anhydrous sodium acetate in glacial acetic acid (20 ml) and refluxed for 5–7 h. After cooling, the solution was poured on crushed ice to precipitate the product. The product was recrystallized from rectified spirit.

*N-[2-(4-Chloro-phenyl)-5-benzylidene-4-oxo-thiazolidin-3yl]-biphenyl-4-carboxamide (**6a**)*

White crystal yield 71%, m.p 220°C. IR (KBr, cm^{-1}) 3477 (N–H *str* amide1), 3028 (C–H *str* aromatic), 1649 (C=O *str* amide1), 1603–1484 (C=C *str* aromatic), 1446–1402 (C–N *str*), 747–693(C–Cl).^{1}H NMR, (DMSO) δppm 8.24–7.40 (m, 9H, Ar H), 8.04 (s, 1H, –NH), 7.62–7.53 (m, 5H, Ar′ H), 7.50–7.38 (m, 4H, Ar H), 7.31 (s, 1H, C=CH), 4.68 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{21}ClN_2O_2S$: Calc C, 70.08; H, 4.26; N, 5.64. Found C, 70.12; H, 4.29; N, 5.67.

*N-[2-(4-Chloro-phenyl)-5-(3-nitro-benzylidene)-4-oxo-thiazolidin-3yl]-biphenyl-4-carboxamide (**6b**)*

Slightly yellow powder, yield 79%, m.p 250°C. IR (KBr, cm^{-1}) 3453 (N–H *str* amide1), 3051 (C–H *str* aromatic), 1657 (C=O *str* amide1), 1606–1484 (C=C *str* aromatic), 1404 (C–N *str*), 1544 (N–O *str*, NO_2), 779–604(C–Cl).^{1}H NMR, (DMSO) δppm 8.19–7.43(m, 4H, Ar′ H), 8.02 (s, 1H, –NH), 7.65–7.57(m, 9H, Ar H), 7.53–7.40 (m, 4H, Ar H), 7.28 (s, 1H, C=CH), 4.98 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{20}ClN_3O_4S$: Calc C, 64.26; H, 3.72; N, 7.75. Found C, 64.31; H, 3.69; N, 7.77.

*N-[2-(4-Chloro-phenyl)-5-(4-chloro-benzylidene)-4-oxo-thiazolidin-3yl]-biphenyl-4-carboxamide (**6c**)*

White powder, yield 81%, m.p 257°C. IR (KBr, cm^{-1}) 3481 (N–H *str* amide1), 3037 (C–H *str* aromatic), 1651 (C=O *str* amide1), 1606–1483 (C=C *str* aromatic), 1447–1402 (C–N *str*), 778–601(C–Cl).^{1}H NMR, (DMSO) δppm 8.21–7.44(m, 9H, Ar H), 8.02 (s, 1H, –NH), 7.62–7.55 (m, 4H, Ar′ H), 7.56–7.41 (m, 4H, Ar H), 7.13 (s, 1H, C=CH), 4.97 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{20}Cl_2N_2O_2S$: Calc C, 65.54; H, 3.79; N, 5.27. Found C, 65.51; H, 3.74; N, 5.29.

*N-[2-(4-Chloro-phenyl)-5-(3-bromo-benzylidene)-4-oxothiazolidin-3yl]-biphenyl-4-carboxamide (**6d**)*

White cystal, yield 79%, m.p 248°C. IR (KBr, cm^{-1}) 3410 (N–H *str* amide1), 3035 (C–H *str* aromatic), 1651 (C=O *str* amide1), 1606–1473 (C=C *str* aromatic), 1447–1403 (C–N *str*), 784–632 (C–Cl), 554–513 (C–Br).^{1}H NMR, (DMSO) δppm 8.31–7.42 (m, 9H, Ar H), 8.03 (s, 1H, –NH), 7.59–7.33 (m 4H, Ar′ H), 7.01 (s, 1H, C=CH), 7.41–7.19 (m 4H, Ar, H). Anal.: Calcd. for $C_{29}H_{20}BrClN_2O_2S$: Calc C, 60.48; H, 3.50; N, 4.86. Found C, 60.49; H, 3.48; N, 4.89.

Table 1 Characterization data of synthesized compounds

Compound no.	Ar	Ar′	Mol. formula (mol. wt)	Yield% M.p (°C)		Microanalysis		
						C	H	N
6a	4-ClC_6H_4	C_6H_5–	$C_{29}H_{21}ClN_2O_2S$	71	Calc	70.08	4.26	5.64
			(497.01)	220	Found	70.12	4.29	5.67
6b	4-ClC_6H_4	3-$NO_2C_6H_4$	$C_{29}H_{20}ClN_3O_4S$	79	Calc	64.26	3.72	7.75
			(542.00)	250	Found	64.31	3.69	7.77
6c	4-ClC_6H_4	4-ClC_6H_4	$C_{29}H_{20}Cl_2N_2O_2S$	81	Calc	65.54	3.79	5.27
			(531.45)	257	Found	65.51	3.74	5.29
6d	4-ClC_6H_4	3-BrC_6H_4	$C_{29}H_{20}BrClN_2O_2S$	79	Calc	60.48	3.50	4.86
			(575.90)	248	Found	60.49	3.48	4.89
6e	4-ClC_6H_4	4-$OCH_3C_6H_4$	$C_{30}H_{23}ClN_2O_3S$	82	Calc	68.37	4.40	5.32
			(527.03)	262	Found	68.32	4.44	5.31
6f	3-$NO_2C_6H_4$	C_6H_5–	$C_{29}H_{21}N_3O_4S$	83	Calc	68.62	4.17	8.28
			(507.56)	221	Found	68.66	4.21	8.23
6g	3-$NO_2C_6H_4$	3-$NO_2C_6H_4$	$C_{29}H_{20}N_4O_6S$	87	Calc	63.04	3.65	10.14
			(552.26)	225	Found	63.09	3.67	10.18
6h	3-$NO_2C_6H_4$	4-ClC_6H_4	$C_{29}H_{20}ClN_3O_4S$	85	Calc	64.26	3.72	7.75
			(542.00)	202	Found	64.31	3.74	7.71
6i	3-$NO_2C_6H_4$	3-BrC_6H_4	$C_{29}H_{20}BrN_3O_4S$	69	Calc	59.39	3.44	7.17
			(586.46)	216	Found	59.41	3.47	7.13
6j	3-$NO_2C_6H_4$	4-$OCH_3C_6H_4$	$C_{30}H_{23}N_3O_5S$	71	Calc	67.03	4.31	7.82
			(537.59)	230	Found	67.01	4.36	7.78
6k	4-$OCH_3C_6H_4$	C_6H_5–	$C_{30}H_{24}N_2O_3S$	75	Calc	73.15	4.91	5.69
			(592.59)	245	Found	73.17	4.94	5.65
6l	4-$OCH_3C_6H_4$	3-$NO_2C_6H_4$	$C_{30}H_{23}N_3O_5S$	81	Calc	67.03	4.31	7.82
			(537.59)	238	Found	67.07	4.33	7.84
6m	4-$OCH_3C_6H_4$	4-ClC_6H_4	$C_{30}H_{23}ClN_2O_3S$	92	Calc	68.37	4.40	5.32
			(527.03)	242	Found	68.34	4.44	5.36
6n	4-$OCH_3C_6H_4$	3-BrC_6H_4	$C_{30}H_{23}BrN_2O_3S$	77	Calc	63.05	4.06	4.90
			(571.48)	235	Found	63.08	4.02	4.94
6o	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	$C_{31}H_{26}N_2O_4S$	88	Calc	71.24	5.01	5.36
			(522.61)	32	Found	71.28	5.05	5.39
6p	4-FC_6H_4	4-ClC_6H_4	$C_{29}H_{20}ClFN_2O_2S$	83	Calc	67.63	3.91	5.44
			(515.00)	247	Found	67.65	3.94	5.41
6q	4-FC_6H_4	3-BrC_6H_4	$C_{29}H_{20}BrFN_2O_2S$	82	Calc	62.26	3.60	5.01
			(559.45)	236	Found	62.28	3.61	4.99
6r	4-FC_6H_4	4-$OCH_3C_6H_4$	$C_{30}H_{23}FN_2O_3S$	87	Calc	70.57	4.54	5.49
			(510.58)	223	Found	70.61	4.57	5.52

*N-[2-(4-Chloro-phenyl)-5-(4-methoxy-benzylidene)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**6e**)*

Off white powder, yield 82%, m.p 262°C. IR (KBr, cm^{-1}) 3469 (N–H *str* amide1), 3032 (C–H *str* aromatic), 1653 (C=O *str* amide1), 1605–1484 (C=C *str* aromatic), 1447–1404 (C–N *str*), 1249 (C–O–C *str*), 776–607 (C–Cl). ^{1}H NMR, (DMSO) δppm 8.14–7.42 (m, 9H, Ar H), 8.02 (s, 1H, –NH), 7.45–7.22 (m, 4H, Ar H), 7.12 (s, 1H, C=CH), 7.39–6.92 (m, 4H, Ar′, H), 4.60 (s, 1H, –NCHS), 3.48 (s, 3H, $-OCH_3$). Anal.: Calcd. for $C_{30}H_{23}ClN_2O_3S$: Calc C, 68.37; H, 4.40; N, 5.32. Found C, 68.32; H, 4.44; N, 5.31.

*N-[2-(3-Nitro-phenyl)-5-benzylidene-4-oxo-thiazolidin-3-yl]-biphenyl-4-carboxamide (**6f**)*

Yellow powder, yield 83%, m.p 221°C. IR (KBr, cm^{-1}) 3429 (N–H *str* amide1), 3028 (C–H *str* aromatic), 1650 (C=O *str* amide1), 1606–1484 C=C *str* aromatic), 1446–1402 (C–N *str*), 1549 (N–O *str*, NO_2). ^{1}H NMR,

(DMSO) δppm 8.32–7.40 (m, 9H, Ar H), 8.04 (s, 1H, –NH), 7.78–7.33 (m, 4H, Ar′ H), 7.45–7.26 (m, 5H, Ar H), 7.01 (s, 1H, C=CH), 4.91 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{21}N_3O_4S$: Calc C, 68.62; H, 4.17; N, 8.28. Found C, 68.66; H, 4.21; N, 8.23.

*N-[2-(3-Nitro-phenyl)-5-(3-nitro-benzylidene)-4-oxo-thiazolidin-3-yl]-biphenyl-4-carboxamide (**6g**)*

Yellow crystal, yield 87%, m.p 225°C. IR (KBr, cm^{-1}) 3452 (N–H *str* amide1), 3050 (C–H *str* aromatic), 1657 (C=O *str* amide1), 1606–1483 (C=C *str* aromatic), 1435–1403 (C–N *str*), 1528(N–O *str*, NO_2). ^{1}H NMR, (DMSO) δppm 8.81–7.47 (m, 4H, Ar′ H), 8.04–7.39 (m, 9H, Ar H), 8.01 (s, 1H, –NH), 7.57–7.31 (m, 4H, Ar H), 7.04 (s, 1H, C=CH), 4.61 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{20}N_4O_6S$: Calc C, 63.04; H, 3.65; N, 10.14. Found C, 63.09; H, 3.67; N, 10.18.

*N-[2-(3-Nitro-phenyl)-5-(4-chlorobenzylidene)-4-oxo-thiazolidin-3-yl]-biphenyl-4-carboxamide (**6h**)*

Yellow crystal, yield 85%, m.p 202°C. IR (KBr, cm^{-1}) 3469 (N–H *str* amide1), 3056 (C–H *str* aromatic), 1654 (C=O *str* amide1), 1605–1484 (C=C *str* aromatic), 1447–1403 (C–N *str*), 1538 (N–O *str*, NO_2), 608–778 (C–Cl). ^{1}H NMR, (DMSO) δppm 8.25–7.47 (m, 9H, Ar H), 8.00 (s, 1H, –NH), 7.52–7.46 (m 4H, Ar H), 7.50–7.28 (m, 4H, Ar′ H), 7.18 (s, 1H, C=CH), 4.72 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{20}ClN_3O_4S$: Calc C, 64.26; H, 3.72; N, 7.75. Found C, 64.31; H, 3.74; N, 7.71.

*N-[2-(3-Nitro-phenyl)-5-(3-bromo-benzylidene)-4-oxo-thiazolidin-3-yl]-biphenyl-4-carboxamide (**6i**)*

Yellow powder, yield 69%, m.p 216°C. IR (KBr, cm^{-1}) 3361 (N–H *str* amide1), 3033 (C–H *str* aromatic), 1653 (C=O *str* amide1), 1608–1484(C=C *str* aromatic), 1417–1402 (C–N *str*), 1580–1529 (N–O *str*, NO_2), 624–508 (C–Br). ^{1}H NMR, (DMSO) δppm 8.33–7.42 (m, 9H, Ar H), 8.03 (s, 1H, –NH), 7.69–7.32 (m 4H, Ar H), 7.46–7.26 (m 4H, Ar′, H) 7.11 (s, 1H, C=CH), 4.79 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{20}BrN_3O_4S$: Calc C, 59.39; H, 3.44; N, 7.17. Found C, 59.41; H, 3.47; N, 7.13.

*N-[5-(4-Methoxy-benzylidene)-2-(3-nitro-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**6j**)*

Yellow powder, yield 71%, m.p 230°C. IR (KBr, cm^{-1}) 3400 (N–H *str* amide1), 3039 (C–H *str* aromatic), 1655 (C=O *str* amide1), 1605–1484 (C=C *str* aromatic), 1412 (C–N *str*), 1546 (N–O *str*, NO_2), 1269–1248 (C–O–C *str*). ^{1}H NMR, (DMSO) δppm 8.15–7.49 (m, 9H, Ar H), 8.02 (s, 1H, –NH), 7.48–7.22 (m, 4H, Ar H), 7.39–6.93 (m, 4H, Ar′, H), 7.00 (s, 1H, C=CH) 4.65(s, 1H, –NCHS), 3.51 (s, 3H, $–OCH_3$). Anal.: Calcd. for $C_{30}H_{23}N_3O_5S$: Calc C, 67.03; H, 4.31; N, 7.82. Found C, 67.01; H, 4.36; N, 7.78.

*N-[5-Benzylidene-2-(4-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-biphenyl-4-carboxamide (**6k**)*

White crystal, yield 75%, m.p 245°C. IR (KBr, cm^{-1}) 3431 (N–H *str* amide1), 3028 (C–H *str* aromatic), 1634 (C=O *str* amide1), 1607–1484 (C=C *str* aromatic), 1446–1408 (C–N *str*), 1280 (C–O–C *str*). ^{1}H NMR, (DMSO) δppm 8.21–7.32 (m, 9H, Ar H), 8.04 (s, 1H, –NH), 7.40–7.21 (m, 4H, Ar H), 6.94 (s, 1H, C=CH), 7.18–6.99 (m, 4H, Ar′, H), 4.62 (s, 1H, –NCHS), 3.41 (s, 3H, $–OCH_3$). Anal.: Calcd. for $C_{30}H_{24}N_2O_3S$: Calc C, 73.15; H, 4.91; N, 5.69. Found C, 73.17; H, 4.94; N, 5.65.

*N-[2-(4-Methoxy-phenyl)-5-(3-nitro-benzylidene)-4-oxo-thiazolidin-3-yl]-biphenyl-4-carboxamide (**6l**)*

Off yellow crystal, yield 81%, m.p 238°C. IR (KBr, cm^{-1}) 3357 (N–H *str* amide1), 3052 (C–H *str* aromatic), 1656 (C=O *str* amide1), 1607–1483 (C=C *str* aromatic), 1446–1402 (C–N *str*), 1528 (N–O *str*, NO_2), 1269–1211 (C–O–C *str*). ^{1}H NMR, (DMSO) δppm 8.63–7.39 (m, 4H, Ar′ H), 8.11–7.36 (m, 9H, Ar H), 8.03 (s, 1H, –NH), 7.57–7.31 (m, 4H, Ar H), 7.09 (s, 1H, C=CH), 4.51 (s, 1H, –NCHS) 3.46 (s, 3H, $–OCH_3$). Anal.: Calcd. for $C_{30}H_{23}N_3O_5S$: C, 67.03; H, 4.31; N, 7.82. Found C, 67.07; H, 4.33; N, 7.84.

*N-[5-(4-Chloro-benzylidene)-2-(4-methoxy-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**6m**)*

Off white powder, yield 92%, m.p 242°C. IR (KBr, cm^{-1}) 3432 (N–H *str* amide1), 3036 (C–H *str* aromatic), 1651 (C=O *str* amide1), 1606–1483 (C=C *str* aromatic), 1447–1403(C–N *str*), 1268 (C–O–C *str*), 778–603 (C–Cl). ^{1}H NMR, (DMSO) δppm 8.31–7.48 (m, 9H, Ar H), 8.02 (s, 1H, –NH), 7.51–7.44 (m, 4H, Ar′ H), 7.50–7.28 (m 4H, Ar H), 7.03 (s, 1H, C=CH), 4.77 (s, 1H, –NCHS) 3.49 (s, 3H, $–OCH_3$). Anal.: Calcd. for $C_{30}H_{23}ClN_2O_3S$: Calc C, 68.37; H, 4.40; N, 5.32. Found C, 68.34; H, 4.44; N, 5.36.

*N-[5-(3-Bromo-benzylidene)-2-(4-methoxy-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**6n**)*

White powder, yield 77%, m.p 235°C. IR (KBr, cm^{-1}) 3408 (N–H *str* amide1), 3036 (C–H *str* aromatic), 1650 (C=O *str* amide1), 1607–1473 (C=C *str* aromatic), 1447–1404 (C–N *str*), 1279–1218(C–O–C *str*), 553–503(C–Br). ^{1}H NMR, (DMSO) δppm 8.13–7.45 (m, 9H, Ar H), 8.03 (s, 1H, –NH),

7.61–7.41 (m, 4H, Ar′ H), 7.12–7.09 (m 4H, Ar H), 6.98 (s, 1H, C=CH), 4.65 (s, 1H, –NCHS) 3.51 (s, 3H, $–OCH_3$). Anal.: Calcd. for $C_{30}H_{23}BrN_2O_3S$: Calc C, 63.05; H, 4.06; N, 4.90. Found C, 63.08; H, 4.02; N, 4.94.

*N-[5-(4-Methoxy-benzylidene)-2-(4-methoxy-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**6o**)*

White powder, yield 88%, m.p 232°C. IR (KBr, cm^{-1}) 3312 (N–H *str* amide1), 2925 (C–H *str* aromatic), 1651 (C=O *str* amide), 1606–1484 (C=C *str* aromatic), 1417(C–N *str*), 1275–1253 (C–O–C *str*). ^{1}H NMR, (DMSO) δppm 8.22–7.43 (m, 9H, Ar H), 8.07 (s, 1H, –NH), 7.59–7.39 (m, 4H, Ar′ H), 7.52–7.31 (m 4H, Ar H), 7.12 (s, 1H, C=CH), 4.79 (s, 1H, –NCHS) 3.51 (s, 6H, $–OCH_3$). Anal.: Calcd. for $C_{31}H_{26}N_2O_4S$: Calc C, 71.24; H, 5.01; N, 5.36. Found C, 71.28; H, 5.05; N, 5.39.

*N-[5-(4-Chloro-benzylidene)-2-(4-fluoro-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxylic acid amide (**6p**)*

White crystal, yield 83%, m.p 247°C. IR (KBr, cm^{-1}) 3317 (N–H *str* amide1), 3035 (C–H *str* aromatic), 1665 (C=O *str* amide1), 1606–1474 (C=C *str* aromatic), 1447–1411 (C–N *str*), 1233 (C–F), 608–778 (C–Cl). ^{1}H NMR, (DMSO) δppm 8.25–7.39 (m, 9H, Ar H), 8.03 (s, 1H, –NH), 7.59–7.36 (m, 4H, Ar′ H), 7.33–7.11 (m, 4H, Ar H), 7.09 (s, 1H, C=CH), 4.58 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{20}ClFN_2O_2S$: Calc C, 67.63; H, 3.91; N, 5.44. Found C, 67.65; H, 3.94; N, 5.41.

*N-[5-(3-Bromo-benzylidene)-2-(4-fluoro-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**6q**)*

Off white crystal, yield 82%, m.p 236°C. IR (KBr, cm^{-1}) 3298 (N–H *str* amide1), 3037 (C–H *str* aromatic), 1651 (C=O *str* amide1), 1605–1486 (C=C *str* aromatic), 1448–1402 (C–N *str*), 1226 (C–F), 554–502(C–Br). ^{1}H NMR, (DMSO) δppm 8.47–7.50(m, 9H, Ar H), 8.12–7.35 (m, 4H, Ar′ H), 8.02 (s, 1H, –NH), 7.51–7.35, (m, 4H, Ar H), 7.21 (s, 1H, C=CH), 4.32 (s, 1H, –NCHS). Anal.: Calcd. for $C_{29}H_{20}BrFN_2O_2S$: Calc C, 62.26; H, 3.60; N, 5.01. Found C, 62.28.; H, 3.61; N, 4.99.

*N-[5-(4-Methoxy-benzylidene)-2-(4-fluoro-phenyl)-4-oxothiazolidin-3-yl]-biphenyl-4-carboxamide (**6r**)*

White crystal, yield 87%, m.p 223°C. IR (KBr, cm^{-1}) 3366 (N–H *str* amide1), 3031 (C–H *str* aromatic), 1656 (C=O *str* amide1), 1604–1483 (C=C *str* aromatic), 1441–1412 (C–N *str*), 1221 (C–F), 1276–1251 (C–O–C *str*). ^{1}H NMR, (DMSO) δppm 8.42–7.55(m, 9H, Ar H), 8.25–7.37 (m, 4H, Ar H),), 8.05 (s, 1H, –NH), 7.52–7.25, (m, 4H, Ar′ H), 7.03 (s, 1H, C=CH), 4.33 (s, 1H, –NCHS), 3.98 (s, 3H, $–OCH_3$). Anal.: Calcd. for $C_{30}H_{23}FN_2O_3S$: Calc C, 70.57; H, 4.54; N, 5.49. Found C, 70.61; H, 4.57; N, 5.52.

Anti-inflammatory screening

All the experimental procedures and protocols used in the study were reviewed by the Institutional Animal Ethics Committee and were in accordance with the guidelines of the CPCSEA, Ministry of Forests and Environment, Govt. of India. Anti-inflammatory activity of all title compounds was carried out by carrageenan-induced rat paw edema test. (Winter *et al.*, 1962). Albino rats of either sex (150–200 g) were divided into different groups, each containing six individuals. Animals were fasted for 12 h before experiment and only water was allowed. While the first group was a control one and received vehicle sodium CMC (0.5% w/v) 0.5 ml per rat, the second group received diclofenac sodium 10 mg/1 kg body mass. All the remaining groups received orally the test compounds at the same dose. All the suspensions for oral dose were prepared in the vehicle mentioned above and administered in a constant volume of 0.5 ml per rat. After 1 h of the administration of the test compound and diclofenac sodium 0.1 ml of 1% w/v suspension of carrageenan was injected into the subplanatar of left paw of control and test animals. Immediately, the paw volume was measured using plethismometer (initial paw volume), there after the paw volume was measured every half an hour till 3 h. The difference between initial and subsequent readings gave the edema volume for the corresponding time. The percent anti-inflammatory activity was calculated according to the formula as given below:

$$\text{Percentage of inhibition of oedema} = (1 - V_t/V_c)100,$$

where V_t and V_c are the volume of edema in right paw of rats in the drug treated and control group, respectively.

Analgesic activity

Writhing test

Acetic acid-induced writhing model was employed to evaluate the analgesic activity (Kazunaga *et al.*, 1980). The test compounds, standard, and vehicle were administered orally to the mice and thereafter, 30 min later 0.7% acetic acid solution was injected intraperitoneally. Diclofenac sodium was used as standard drug. The mice were placed in separate boxes under observation immediately after acetic acid injection and the numbers of abdominal constrictions were counted over a period of 20 min.

Table 2 Anti-inflammatory and analgesic activity of title compounds

Compound no.	Anti-inflammatory activity (%)			Analgesic activity		
	Dose (mg/kg)	2 h	4 h	Dose (mg/kg)	Mean number of writhing ± SEM	Protection (%)
6a	10	48.92	55.11	10	31.83 ± 1.07**	20.43
6b	10	45.21	56.35	10	29 ± 1.15**	27.50
6c	10	46.14	55.34	10	30.83 ± 1.01**	22.93
6d	10	44.56	54.80	10	32.83 ± 1.42**	17.93
6e	10	45.83	53.87	10	28.16 ± 1.49**	29.60
6f	10	38.09	47.99	10	23.66 ± 1.05**	40.85
6g	10	39.63	51.37	10	22.66 ± 1.52**	43.35
6h	10	39.94	49.23	10	21.5 ± 1.14**	46.25
6i	10	38.70	50.78	10	25 ± 1.59**	37.50
6j	10	37.78	48.92	10	24.83 ± 1.32**	37.93
6k	10	45.83	68.74	10	24.66 ± 1.13**	38.35
6l	10	47.68	71.21	10	25.5 ± 1.08**	36.25
6m	10	57.90	71.83	10	27.16 ± 1.90**	32.10
6n	10	46.75	69.05	10	26.66 ± 1.24**	33.35
6o	10	49.54	70.28	10	23.83 ± 1.24**	40.43
6p	10	43.64	52.92	10	21.5 ± 1.14**	46.25
6q	10	41.76	52.08	10	25 ± 1.59**	37.50
6r	10	45.82	53.62	10	24.83 ± 1.32**	37.93
Diclofenac sodium	10	54.18	79.26	10	12.6 ± 0.71**	68.50

Values of paw thickness are mean ± SEM from six animals in each group, $P < 0.05$

** $P < 0.01$, compared with control

The percentage protection was calculated by employing following formula and the results have been presented in Table 2.

$$\% \text{ Protection} = 100 - \frac{\text{No .of writhes in test}}{\text{No. of writhes in control}} \times 100.$$

Results of anti-inflammatory and analgesic screening have been shown in Table 2.

Conclusions

In conclusion, this investigation describes the preparation and biological evaluation of a series of novel thiazolidinones. The synthesized compounds were characterized by suitable analytical techniques such as IR, NMR, and elemental analysis and the data obtained was in full agreement of the proposed structures. Evaluation of their potential for biological activities such as antiinflammatory and analgesic activity was carried out and most of the synthesized compounds exhibited moderate to significant anti-inflammatory and analgesic activities in vivo. Hence the compounds are suitable candidates for further exploration and some more derivatives can be synthesized to get an insight into the structure activity relationship of these compounds to be employed as biologically useful agents.

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