Acta Poloniae Pharmaceutica – Drug Research, Vol. 67 No. 1 pp. 63–67, 2010 ISSN 0001-6837
Polish Pharmaceutical Society

SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SOME NOVEL BIPHENYL-4-CARBOXYLIC ACID 5-(ARYLIDENE)-2-(ARYL)-4-OXOTHIAZOLIDIN-3-YL AMIDES

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Abstract: Some new biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides have been synthesized and evaluated for anti-inflammatory activity. 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 the biphenyl-4-carboxylic acid 2-(aryl)-4-oxothiazolidin-3-yl amides, which again on reaction with aromatic aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid furnished the title compounds. The structures of all these newly synthesized compounds were confirmed by their analytical and spectral data which were in full agreement with proposed structures. All compounds were screened for anti-inflammatory activity employing carrageenan test at the dose of 10 mg/kg and exhibited significant activities.

Keywords: synthesis, biphenyl, 4-thiazolidinone, anti-inflammatory activity

The majority of currently marketed non-steroidal anti-inflammatory drugs (NSAIDs) are chemically hydroxylic acids as represented by indomethacin, ibuprofen with a carboxylic group and piroxicam with an enolic group. These NSAIDs are believed to exhibit their antiinflammatory activity by inhibiting the enzyme cyclooxygenase (COX), that catalyzes the biosynthesis of prostaglandins and thromboxane from arachidonic acid. The mechanism is correlated with unwanted side-effects such as gastrointestinal and renal toxicities (1).

Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal to the researchers of this field. On the other hand, 4-thiazolidinones have received considerable attention due to their wide range of biological activities. These derivatives are known to possess several promising pharmacological actions such as antimicrobial (2-6), analgesic (7), anti-inflammatory (8-9), anti-HIV (10), cytotoxic (11), and anticonvulsant (12), activities. Also, 4-thiazolidinones have been found as novel inhibitors of bacterial enzyme MurB, a key enzyme responsible for the synthesis of peptidoglycan (13). In the light of these observations, it was felt worthwhile to synthesisze a new series of 4-thiazolidinones and evaluate them for anti-inflammatory activity. The structures of all compounds have been confirmed by elemental and spectral analysis (IR and ^{1}H NMR).

EXPERIMENTAL

The purity of the synthesized compounds were ascertained by thin layer chromatography on silica gel G in various solvent systems using iodine vapors as detecting agent. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected. Elemental analyses were done using Carlo Erba 1106 CHN Analyzer. Infra-red spectra were recorded on Perkin Elmer Spectrum RXI FTIR spectrophotomer in KBr phase. Proton NMR spectra were recorded on Bruker Avance II 400 NMR Ultra Shield Spectrometer using DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Chemical shift values are expressed in δ ppm. All the compounds have been screened *in vivo* for their anti-inflammatory activity.

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Chemistry

A series of novel biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides have been synthesized. The reaction of acid hydrazide **(I)** with aromatic aldehydes yielded the corresponding hydrazones **(IIa-c)** which on further reaction with thioglycolic acid in methanol afforded the corresponding 2-substituted-4-thiazolidinones **(IIIa-c)**. The compounds **(IIIa-c)** were further reacted with aromatic aldehydes in the presence of few drops of glacial acetic acid to yield 2,5-disubstituted-4-thiazolidinones **(IVa-j)**. The synthesized 2,5-disubstituted-4-thiazolidinones were characterized on the basis of the spectral and analytical studies.

General method

Synthesis of hydrazone (**II**)

A mixture of biphenyl-4-carboxylic acid hydrazide (0.025 mol, 5.3 g) and required aromatic aldehydes (0.025 mol) 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 and the solid obtained was separated by filtration and recrystallized from methanol to give the corresponding hydrazones.

Synthesis of 2-substituted-4-thiazolidinone **(IIIa-c)**

A mixture of appropriate Schiff's base (0.015 mol) (**II**) and equimolar amount of thioglycolic acid (0.015 mol, 1.40 mL) in N,N-dimethylformamide (DMF) (50 mL), containing a pinch of anhydrous $ZnCl_2$ was refluxed for about 6 h. The reaction mixture was cooled and poured onto crushed ice. The solid thus obtained was filtered, washed with water and the product was recrystallized from rectified spirit.

Synthesis of 2,5-disubstituted-4-thiazolidinone **(IVa-l)**

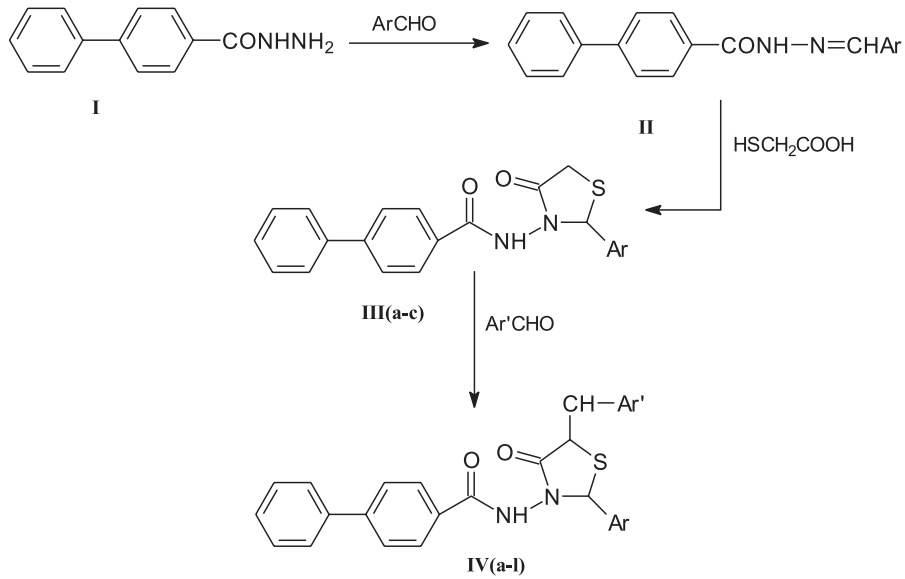
A suspension of 2-substituted-4-thiazolidinone (0.01 mol), aromatic aldehyde (0.01 mol) and anhydrous sodium acetate was prepared in glacial acetic acid and refluxed for 5 – 7 h. After cooling, the solution was poured on crushed ice to precipitate the product. The product was recrystallized from ethanol.

By adopting similar type of procedures, and employing equimolar quantities of reactants, twelve compounds were synthesized. Physical and analytical data of synthesized compounds are given in Table 1. Synthetic pathway for preparation of title compounds is shown in Scheme 1.

Spectral data

Biphenyl-4-carboxylic acid (5-benzylidene-4-oxo-2-phenylthiazolidin-3yl) amide (**IVa**)

IR (KBr, cm^{-1}): 3198 (N–H), 3028-2923 (C–H), 1634–1657 (C=O), 1605-1483 (C=C), 1446-1402 (C–N). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.43-7.38 (m, 9H, Ar H), 8.06 (s, 1H, -NH), 7.68-7.50 (m, 5H, Ar' H), 7.48-7.40 (m, 4H, Ar H), 7.32 (s, 1H, C=CH), 4.62 (s, 1H, -NCHS). Analysis: Calcd. for $C_{29}H_{22}N_2O_2S$: C, 75.30; H, 4.79; N, 6.06%; found: C, 75.26; H, 4.81; N, 6.01%.



Scheme 1. Preparation of biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxo-thiazolidin-3-yl amides (**IVa-l**).

Biphenyl-4-carboxylic acid [5-(3-nitrobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl] amide **(IVb)**

IR (KBr, cm^{-1}): 3253 (N–H), 3052 (C–H), 1657 (C=O), 1608-1485 (C=C), 1448-1435 (C–N),1581-1529 (N–O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.60-7.79 (m, 4H, Ar' H) , 8.05 (s, 1H, -NH), 7.78-7.47 (m 9H, Ar, H), 7.51 -7.42 (m, 5H, Ar H), 7.40 (s, 1H, C=CH), 3.34 (s, 1H, -NCHS). Analysis: Calcd. for $C_{29}H_{21}N_3O_4S$: C, 68.62; H, 4.17; N, 8.28%; found: C, 68.66; H, 4.21; N, 8.22%.

Biphenyl-4-carboxylic acid [5-(4-chlorobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl] amide **(IVc)**

IR (KBr, cm^{-1}): 3403 (N–H), 2933 (C–H), 1716-1681 (C=O), 1606-1485 (C=C), 1436-1422 (C–N), 749-698 (C–Cl). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.49-7.77 (m, 9H, Ar H), 8.04 (s, 1H, -NH), 7.47-7.40 (m, 5H, Ar H), 7.67-7.50 (m, 4H, Ar H), 7.41 (s, 1H, C=CH), 3.92 (s, 1H, -NCHS). Analysis: Calcd. for $C_{29}H_{21}ClN_2O_2S$: C, 70.08; H, 4.26; N, 5.64%; found: C, 70.02; H, 4.30; N, 5.66%.

Biphenyl-4-carboxylic acid [5-(3-bromobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl] amide **(IVd)**

IR (cm^{-1}, KBr): IR (KBr, cm^{-1}): 2993-2944 (C–H), 1717-1682 (C=O), 1605-1485 (C=C), 1436-1422 (C–N), 545 (C–Br). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.47-7.73 (m, 9H, Ar H), 8.07 (s, 1H, -NH), 7.46-7.42(m, 5H, Ar H), 7.69-7.48 (m, 4H, Ar H), 7.38 (s, 1H, C=CH), 4.24 (s, 1H, -NCHS). Analysis: Calcd. for $C_{29}H_{21}BrN_2O_2S$: C, 64.33; H, 3.91; N, 5.71%; found: C, 64.29; H, 3.96; N, 5.70%.

Biphenyl-4-carboxylic acid [5-(4-methoxybenzylidene)-4-oxo-2-phenylthiazolidin-3-yl] amide **(IVe)**

IR (KBr, cm^{-1}): 3269 (N–H), 3030-2927 (C–H), 1650 (C=O), 1607-1485 (C=C), 1447-1419 (C–N), 1253 (C–O–C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.41-7.46 (m, 9H, Ar H), 8.03 (s, 1H, -NH), 7.40-7.22 (m, 4H, Ar' H), 7.42 (s, 1H, C=CH), 7.38-7.26 (m, 5H, Ar, H), 5.18 (s, 1H, -NCHS), 3.52 (s, 1H, -OCH). Analysis: Calcd. for $C_{30}H_{24}N_2O_3S$: C, 73.13; H, 4.91; N, 5.69%; found: C, 73.11; H, 4.95; N, 5.72%.

Biphenyl-4-carboxylic acid [5-benzylidene-2-(3-bromophenyl)-4-oxothiazolidin-3-yl] amide **(IVf)**

IR (KBr, cm^{-1}): 3209 (N–H), 3030 (C–H), 1649 (C=O), 1606-1484 (C=C), 1447-1403 (C–N), 554-506 (C–Br). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.48-7.40 (m, 9H, Ar H), 8.04 (s, 1H, -NH), 7.68-7.38 (m, 5H, Ar' H), 7.48-7.28 (m, 4H, Ar H), 7.46 (s, 1H, C=CH), 3.09 (s, 1H, -NCHS). Analysis: Calcd. for $C_{29}H_{21}BrN_2O_2S$: C, 64.33; H, 3.91; N, 5.17%; found: C, 64.31; H, 3.96; N, 5.14%.

Biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(3-nitrobenzylidene)-4-oxo-thiazolidin-3-yl] amide **(IVg)**

IR (KBr, cm^{-1}): 3261 (N–H), 3034 (C–H), 1655 (C=O), 1528 (N–O), 1608-1483 (C=C),1445-1402 (C–N), 509 (C–Br). ^{1}H NMR (300 MHz, DMSO-d_6,

Table 1. Physical data of 2,5-disustituted-4-thiazolidinones

Compd. no.	Ar	Ar'	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)	R_f value
IVa	C_6H_5-	C_6H_5-	$C_{29}H_{22}N_2O_2S$	462.56	214-216	71.32	0.63
IVb	C_6H_5-	3-NO_2-C_6H_4-	$C_{29}H_{21}N_3O_4S$	507.56	217-219	78.14	0.71
IVc	C_6H_5-	4-Cl-C_6H_4-	$C_{29}H_{21}ClN_2O_2S$	497.01	223-224	82.26	0.59
IVd	C_6H_5-	3-Br-C_6H_4-	$C_{29}H_{21}BrN_2O_2S$	541.46	216-217	79.40	0.62
IVe	C_6H_5-	4-OCH_3-C_6H_4-	$C_{30}H_{24}N_2O_3S$	492.59	210-212	81.60	0.68
IVf	3-Br-C_6H_4-	C_6H_5-	$C_{29}H_{21}BrN_2O_2S$	541.46	228-230	78.46	0.92
IVg	3-Br-C_6H_4-	3-NO_2-C_6H_4-	$C_{29}H_{20}BrN_3O_4S$	586.46	238-239	78.40	0.88
IVh	3-Br-C_6H_4-	4-Cl-C_6H_4-	$C_{29}H_{20}BrClN_2O_2S$	575.90	225-227	81.20	0.79
IVi	3-Br-C_6H_4-	3-Br-C_6H_4-	$C_{29}H_{20}Br_2N_2O_2S$	620.35	245-248	78.62	0.82
IVj	3-Br-C_6H_4-	4-OCH_3-C_6H_4-	$C_{30}H_{23}BrN_2O_3S$	571.48	234-235	81.80	0.73
IVk	4-F-C_6H_4-	C_6H_5-	$C_{29}H_{21}FN_2O_2S$	480.55	242-243	79.34	0.78
IVl	4-F-C_6H_4-	3-NO_2-C_6H_4-	$C_{29}H_{20}FN_3O_4S$	525.55	235-237	78.86	0.84

δ, ppm): 8.84-7.45 (m, 4H, Ar' H), 8.06-7.37 (m, 9H, Ar H), 8.00 (s, 1H, -NH), 7.54-7.32 (m, 4H, Ar H), 7.50 (s, 1H, C=CH), 4.59 (s, 1H, –NCHS). Analysis: Calcd. for $C_{29}H_{20}BrN_3O_4S$: C, 59.39; H, 3.44; N, 7.17%; found: C, 59.43; H, 3.47; N, 7.21%.

Biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(4-chlorobenzylidene)-4-oxo-thiazolidin-3-yl] amide **(IVh)**

IR (KBr, cm^{-1}): 3282 (N–H), 3036 (C–H), 1651 (C=O), 1607-1447 (C=C), 1447 (C–N), 780-603 (C–Cl), 513 (C–Br). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.45-7.48 (m, 9H, Ar H), 8.00 (s, 1H, -NH), 7.58 (s, 1H, C=CH), 7.52-7.46 (m 4H, Ar' H), 7.50-7.28 (m, 4H, Ar H), 3.02(s, 1H, -NCHS). Analysis: Calcd. for $C_{29}H_{20}BrClN_2O_2S$: C, 60.48; H, 3.50; N, 4.86%; found: C, 60.43; H, 3.54; N, 4.83%.

Biphenyl-4-carboxylic acid [5-(3-bromobenzylidene)-2-(3-bromophenyl)-4-oxo-thiazolidin-3-yl] amide **(IVi)**

IR (KBr, cm^{-1}): 3428 (N–H), 3044 (C–H), 1650 (C=O), 1607-1484 (C=C), 1447-1406 (C–N), 554-503 (C–Br). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.41-7.42 (m, 9H, Ar H), 8.03 (s, 1H, -NH), 7.62-7.30 (m 4H, Ar' H), 7.51 (s, 1H, C=CH), 7.46-7.26 (m 4H, Ar, H). Analysis: Calcd. for $C_{29}H_{20}Br_2N_2O_2S$: C, 56.15; H, 3.25; N, 4.52%; found: C, 56.20; H, 3.23; N, 4.57%.

Biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(4-methoxybenzylidene)-4-oxo-thiazolidin-3-yl] amide **(IVj)**

IR (KBr, cm^{-1}): 3428 (N–H), 3034 (C–H), 1650 (C=O), 1606-1473 (C=C), 1447-1403 (C–N), 1280-1253 (C–O–C), 553-531 (C–Br). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.05-7.44 (m, 9H, Ar H), 8.02 (s, 1H, -NH), 7.46-7.26 (m, 4H, Ar H), 7.41 (s, 1H, C=CH), 7.39-6.93 (m, 4H, Ar', H), 4.60 (s, 1H, -NCHS), 3.48 (s, 1H, -OCH). Analysis: Calcd. for $C_{30}H_{23}BrN_2O_3S$: C, 63.05; H, 4.06; N, 4.90%; found: C, 63.01; H, 4.08; N, 4.86%.

Biphenyl-4-carboxylic acid [5- benzylidene -2-(4-fluorophenyl)-4-oxothiazolidin-3-yl] amide **(IVk)**

IR (KBr, cm^{-1}): 3211 (N–H), 3038 (C–H), 1657 (C=O), 1606-1475 (C=C), 1445-1401 (C–N), 1233 (C–F). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.22-7.47 (m, 9H, Ar H), 8.03 (s, 1H, -NH), 7.56-7.37 (m, 5H, Ar' H), 7.34-7.12 (m, 4H, Ar H), 7.52 (s, 1H, C=CH), 3.58 (s, 1H, -NCHS). Analysis: Calcd. for $C_{29}H_{21}FN_2O_2S$: C, 72.48; H, 4.40; N, 5.83%; found: C, 72.45; H, 4.37; N, 5.85%.

Table 2. Antiinflammatory activity of title compounds

Compd. no.	% anti-inflammatory activity 2 h	4 h
IVa	28.18	43.97
IVb	33.13	47.06
IVc	32.82	44.90
IVd	31.73	44.59
IVe	35.61	47.68
IVf	44.90	50.47
IVg	42.42	48.61
IVh	42.42	51.09
IVi	44.59	55.73
IVj	43.04	52.02
IVk	41.56	50.06
IVl	45.12	53.08
Standard drug (Diclofenac sodium)	54.18	79.26

Biphenyl-4-carboxylic acid [2-(4-fluorophenyl)-5-(3-nitrobenzylidene)-4-oxo-thiazolidin-3-yl] amide **(IVl)**

IR (KBr, cm^{-1}): 3245 (N–H), 3033 (C–H), 1651 (C=O), 1522 (N–O), 1605-1483 (C=C),1445-1402 (C–N), 1226 (C–F). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.77-7.48 (m, 4H, Ar' H), 8.11-7.35 (m, 9H, Ar H), 8.01 (s, 1H, -NH), 7.57-7.35, 4H, Ar H), 7.49 (s, 1H, C=CH), 4.31 (s, 1H, –NCHS). Analysis: Calcd. for $C_{29}H_{20}FN_3O_4S$: C,66.28; H, 3.84; N, 8.00%; found: C, 66.25.43; H, 3.80; N, 6.03%.

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 method as described by Winter et al. (14). Diclofenac sodium was used as a standard drug. Albino rats of either sex (150-200 g) were divided into groups consisting of six animals each. Animals were fastened for 12 h before the experiment and only water was allowed. Control group received vehicle sodium carboxymethyl cellulose (CMC) (0.5 % w/v) 0.5 mL per rat, and the standard group received diclofenac sodium 10 mg kg^{-1} body mass suspended in 0.5% w/v of CMC. All the remaining

groups received the test compounds at the same dose *via* oral route. All the suspensions for oral dose were prepared in the same vehicle and were administered as a constant volume of 0.5 mL per rat. After one hour of the administration of the test compounds and diclofenac sodium, 0.1 mL of 1% w/v suspension of carrageenan was injected in to the subplanatar of left paw of the test animals. The paw volume was measured using plethismometer at suitable time intervals. The difference between initial and subsequent observations gave the edema volume for the corresponding time. The anti-inflammatory activity (percentage inhibition of inflammation) of standard drug and the test compounds was calculated as per following formulas:

$$\text{Edema } (\Delta T) = T_t - T_O$$

$$\% \text{ Inflammation} = \Delta T/T_O \times 100$$

$$\text{Anti-inflammatory activity } (\% \text{ Inhibition}) = 100 - \% \text{ inflammation}$$

where T_t = the right hind paw thickness at time t, T_O = the right hind paw thickness before subplantar injection of carrageenan.

Percentage inhibition of inflammation by standard drug and the synthesized compounds has been presented in Table 2.

RESULTS AND DISCUSSION

The synthesized compounds were characterized by suitable methods such as spectroscopic evaluation like IR, ^{1}H NMR and elemental analysis. Data obtained were found to be in good agreement with the calculated values of proposed structures. The newly synthesized compounds were subjected to preliminary testing for their anti-inflammatory activity. The percentage reduction in inflammation the after 2 h and 4 h of administration of carageenan was recorded. All the compounds have exhibited significant anti-inflammatory activity. The compound **IVi**, with a substitution of bromine on both the aromatic rings, was found to be the most potent anti-inflammatory agent with percentage inhibition of 44.59 and 55.73 at 2 h and 4 h, respectively. It was followed by compound **IVl** bearing bromo and nitro substitutions depicting percentage inhibition of 45.12 and 53.08, respectively.

CONCLUSION

In conclusion, the present investigation describes synthesis of a novel series of biphenyl-4-carboxylic acid-5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides and their evaluation for anti-inflammatory activity. In general, the compounds bearing electron withdrawing substitutents were found to be more active than the others, indicating probable interaction of such groups with receptor sites. The promising activity of compounds **IVi** and **IVl** along with the other activity data obtained during the study can be useful for establishing the structure-activity relationship studies and for the development of newer and potent anti-inflammatory compounds.

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Received: 05. 07. 2009