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SYNTHESIS OF 2-ARYLIDENE-4-(SUBSTITUTED ARYL) BUT-3-EN-4-OLIDES AND EVALUATION OF THEIR ANTIBACTERIAL AND ANTI-INFLAMMATORY ACTIVITIES

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ABSTRACT

Ten new 2-arylidene-4-(substituted aryl)but-3-en-4-olides have been synthesized by condensing β-(4-substituted benzoyl)propionic acid with appropriate aromatic aldehydes in presence of triethylamine (TEA). The compounds have been evaluated for their antimicrobial and anti-inflammatory activities. Their structures were established on the basis of elemental analysis, ^{1}H NMR and mass spectral data. Some of the compounds were found to have significant activity.

Key words: $\Delta^{\beta,\gamma}$-Butenolide, Antibacterial, anti-inflammatory.

INTRODUCTION

Butenolides, consisting of unsaturated γ-lactone ring, are well known heterocycles of biological interest. The γ-lactone ring is a part of variety of natural products like digitalis glycosides, sesquiterpene lactones, lignans and antibiotics[1]. Butenolides and their derivatives are known to have numerous important biological activities[2-5], which include anti-inflammatory, analgesic, antimicrobial, antitumour, cardiotonic and anticonvulsant. Research from our laboratories and elsewhere has shown that $\Delta^{\beta,\gamma}$-butenolides are furnished with antimicrobial and anti-inflammatory actions[6-8]. In continuation of these studies, we hereby report the synthesis, antibacterial and anti-inflammatory activities of ten new α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides. The compounds were synthesized by following the **Scheme 1** and their structures were established on the basis of elemental analysis, ^{1}H NMR and mass spectral data.

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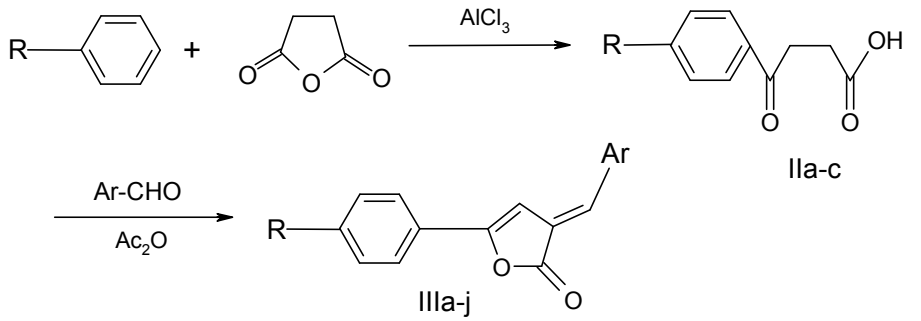
EXPERIMENTAL

Melting points were recorded in open glass capillaries and are uncorrected. Microanalyses were performed on Carlo Erba element analyzer and were within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded on Bruker 300MHz instrument in $CDCl_3$ using TMS as internal standard. Mass spectra of the compounds were recorded on JEOL-DX 303 instrument. Purity of the compounds was checked by TLC on silica gel G coated plates.

General procedure for the synthesis of β-(4-substituted benzoyl) propionic acids (IIa-c)

Succinic anhydride (0.1 mole) was condensed in presence of anhydrous aluminium chloride (0.1125 mole) with appropriate substituted benzenes (50 mL). The reaction mixture was refluxed for four hours and excess solvent was removed by steam distillation. It was purified by dissolving in sodium hydroxide solution (5% w/v), filtered and followed by addition of hydrochloric acid. A solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give **IIa-c** (Table 1).



Scheme 1. Protocol for synthesis of butenolide derivatives (IIIa-j)

General procedure for the preparation of α-arylidene–γ-aryl-$\Delta^{\beta,\gamma}$–butenolides (IIIa-j)

To a solution of compound **II** (3 mmol) and appropriate aromatic aldehyde (3 mmol) in acetic anhydride (10 mL), triethylamine (3-4 drops) was added and the reaction mixture was refluxed for four hours under anhydrous condition. After completion of reaction, the mixture was poured onto crushed ice and a coloured solid mass, which separated out, was filtered, washed, dried and crystallized from methanol : chloroform mixture (1 : 1) to give **IIIa-j** (Table 2).

Table 1.Physical and analytical data of β-(4-substituted benzoyl)propionic acid (IIa-c)

Comp.	Name of the compound	R	Yield (%)	R_f value	M. P. (°C)	^{1}H NMR (δ-values)
IIa	β-(4-Chloro benzoyl) propionic acid	Cl-	62	0.68	124	2.81 & 3.38 (t, each, 2 x -CH_2), 7.45 & 7.92 (d, each, A_2B_2, phenyl).
IIb	β-(4-Ethyl benzoyl) propionic acid	C_2H_5-	52	0.7	110	1.25 (t, 3H $\underline{CH_3}CH_2$), 2.69 (q, 2H $CH_3\underline{CH_2}$), 2.80 & 3.30 (t, each, 2 x -CH_2), 7.27 & 7.85 (d, each, A_2B_2, phenyl).
IIc	β-(4-Methyl benzoyl) propionic acid	CH_3-	64	0.8	106	2.37 (s, 3H, -CH_3), 2.65 & 3.26 (t, each, 2 x -CH_2), 7.27 & 7.90 (d, each, A_2B_2, phenyl).

s = singlet; d = doublet; t = triplet; q = quartet.

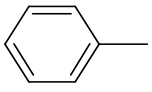
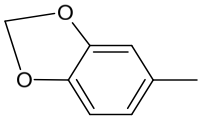
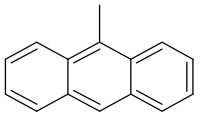
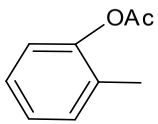
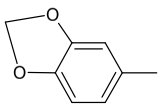
Antibacterial activity

The bacterial strains gram positive (*Staphylococcus aureus*) and gram negative (*Eschericia coli*) were used. The test was carried out according to turbidity method[9]. A solution of the compounds was prepared in dimethylformamide and a series of doubling dilutions prepared with sterile pipettes. To each of a series of sterile stoppered test tubes, a standard volume of nutrient broth medium was added. A control tube containing no antimicrobial agent was included. The inoculum consisting of an overnight broth culture of microorganisms was added to separate tubes. The tubes were incubated at 37ºC for 24 hours and examined for turbidity. The tube with highest dilution showing no turbidity was the MIC.

Anti-inflammatory activity

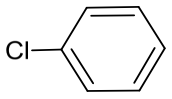
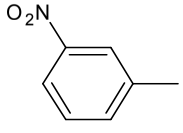
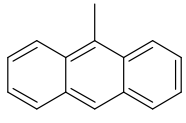
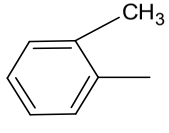
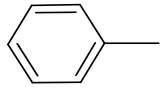
Carrageenan induced rat paw edema method[10] was employed for evaluating the anti-inflammatory activity of the compounds at a dose level of 20 mg/kg b.w. in albino rats (weighing 100-120 g) using indomethacin as a standard drug for comparison.

Table 2: Physical and analytical data of the α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides (IIIa-j)

Compd.	R	Ar	Yield (%)	R_f- value	M.P. (°C)	^{1}H NMR (δ-values)	Mass spectra (m/z)
IIIa	Cl-		62	0.76	146-48	6.93 (s, 1H, butenolide ring), 7.26 (s, = CH-), 7.44 (m, 5H, H-2,6, p-substituted phenyl + H-3,4,5, phenyl), 7.64 (m, 4H, H-3,5, p-substituted phenyl + H-2,6, phenyl).	282 (M^+), 139, 111
III b	Cl-		66	0.78	224-26	5.97 (s, 2H, -OCH_2O-),; 6.76 (s, 1H, butenolide ring), 7.16 (s, = CH-), 6.84 (s, 1H, H-5, aryl),; 7.08 (m, 2H, H-2,6, aryl),; 7.23 & 7.61 (d, each, A_2B_2, p-substituted phenyl).	326 (M^+), 139, 121
III c	Cl-		53	0.8	150-52	7.17 (s, butenolide ring); 7.38 (m, H-2, H-2′, H-3′, H-6, H-6′, H-7′); 7.92 (m, H-1′, H-3, H-4′, H-5, H-5′, H-8′); 8.34 (s, H-10′).	Not taken
III d	Cl-		58	0.82	126-28	6.80 (s, butenolide ring), 7.32 (s, = CH-), 7.20 (m, 4H, aryl), 7.46 & 7.60 (d each, A_2B_2, p substituted phenyl).	298 (M^+), 139
III e	H_5C_2-		56	0.76	176-78	1.19 (t, CH_3CH_2), 2.67 (q, CH_3CH_2); 5.99 (s, -OCH_2O-); 6.76 (s, butenolide ring), 7.19 (s, = CH-); 6.81 (s, H-5′), 7.08 (m, H-2′, H-6′), 7.23 & 7.60 (d each, 2x A_2B_2, p-substituted phenyl).	320 (M^+), 133, 105

Cont…

Table 2: Physical and analytical data of the α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides (IIIa-j)

Compd.	R	Ar	Yield (%)	R_f value	M.P. (°C)	^{1}H NMR (δ-values)	Mass spectra (m/z)
III f	H_5C_2-		68	0.72	140-42	1.19 (t, CH_3CH_2), 2.62 (q, CH_3CH_2); 6.76 (s, butenolide ring), 7.23 (s, = CH-), 7.20 (m, H-3′, H-5′); 7.48 (m, H-2′, H-6′); 7.36 & 7.62 (d each, 2x A_2B_2, p-substituted phenyl).	310 (M^+), 133, 105
III g	H_5C_2-		62	0.75	96-98	1.29 (t, CH_3CH_2); 2.72 (q, CH_3CH_2); 6.89 (s, butenolide ring); 7.4 (s, = CH-); 7.67 (m, H-5′); 7.29 & 8.25 (d, H-4′, H-6′); 8.50 (s, H-2′); 7.32 & 7.73 (d each, 2x A_2B_2, p-substituted phenyl).	321(M^+), 133, 105
III h	H_5C_2-		48	0.88	156-58	1.20 (t, CH_3CH_2); 2.6 (q, CH_3CH_2); 7.0 (s, butenolide ring); 7.18 (s, = CH-); 7.39 (m, H-2′, H-2, H-3′, H-6′, H-6, H-7′); 7.9 (m, H-1′, H-3, H-4′, H-5′, H-5, H-8′); 8.35 (s, H-10′).	Not taken
III i	H_5C_2-		56	0.76	119-21	1.19 (t, CH_3CH_2); 2.59 (q, CH_3CH_2); 2.34 (s, CH_3); 6.80 (s, butenolide ring); 7.31 (s, = CH-); 7.19 (m, H-2′, H-3′, H-4′, H-5′); 7.46 & 7.61 (d each, 2x A_2B_2, p-substituted phenyl).	290 (M^+), 133, 105
III j	H_3C-		65	0.75	86-88	2.4 (s, CH_3); 6.73 (s, butenolide ring); 7.38 (s, = CH-), 7.30 & 7.41 (d each, 2x A_2B_2, p-substituted phenyl), 7.48 (m, 5H, phenyl),.	262 (M^+), 119

s = singlet; d = doublet; t = triplet; q = quatret; m = multiplet

The percentage inhibition of inflammation was calculated by applying Newbould formula[11]. The ulcerogenic activity was carried out by the reported method[12]. None of these compounds showed ulcerogenic activity.

Table 3. Biological activity

Comp.	Antibacterial activity (Minimum inhibitory concentration*)		Anti-inflammatory activity (% inhibition in rat paw oedema)		
	S. aureus	***E. coli***	**Normal paw volume (x)**	**Paw oedema 3 hr after carragenan (a)**	**% inhibition (1- a-x/b-y) 100 of oedema**
IIIa	>100	>100	0.70 ± 0.03	0.93 ± 0.03	25.80
IIIb	-	-	0.65 ± 0.03	0.92 ± 0.02	12.90
IIIc	25	50	0.73 ± 0.03	0.95 ± 0.04	29.03
IIId	50	25	0.68 ± 0.03	0.81 ± 0.03	58.06
IIIe	-	-	0.65 ± 0.03	0.90 ± 0.02	19.35
IIIf	25	12.5	0.73 ± 0.03	0.95 ± 0.04	29.03
IIIg	>100	>100	0.72 ± 0.02	0.86 ± 0.03	54.83
IIIh	10	25	0.71 ± 0.04	0.96 ± 0.05	19.35
IIIi	>100	-	0.71 ± 0.02	0.88 ± 0.03	45.16
IIIj	-	>100	0.67 ± 0.03	0.93 ± 0.04	16.12
Nitrofurazone 12.5		6.5			
Indomethacin			0.73 ± 0.03	0.85 ± 0.03	61.30
Control			0.68 ± 0.02 (y)	0.99 ± 0.03(b)	

* = in μg/mL; - = insignificant activity

RESULTS AND DISCUSSION

The newly synthesized butenolides showed interesting profile of antibacterial and anti-inflammatory activity. In antibacterial test, compound **IIIf** showed very good activity

against *E. coli* (MIC-12.5 μg/mL) and good activity against *S. aureus* (MIC-25 μg/mL). In anti-inflammatory test, the most active compound was **IIId**, which showed 58.06 % inhibition comparable with the standard drug indomethacin (61.3 %) at a dose level of 20 mg/kg body weight. It is significant that none of these compounds showed ulcerogenic activity, which is a common feature with NSAIDs.

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