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# Syntheses and reactions of some new 2-arylidene-4-(biphenyl-4-yl)-but-3-en-4-olides with a study of their biological activity

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2-Arylidene-4-(biphenyl-4-yl)but-3-en-4-olides also known as 3-arylidene-5-(biphenyl-4-yl)-2(3*H*)-furanones were prepared from 3-(4-phenyl-benzoyl) propionic acid and aromatic aldehydes. Some of the selected butenolides were reacted with ammonia and benzylamine to give corresponding pyrrolones and *N*-benzylpyrrolones respectively, which were characterized on the basis of $^1$H NMR and MS data and elemental analysis results. These compounds were tested for anti-inflammatory and anti-microbial actions. A few compounds were found to have promising anti-inflammatory activity while a fair in number of compounds showed a good anti-fungal activity and a promising antibacterial activity against *S. aureus* and *E. coli*.

## 1. Introduction

Physiological activity of the natural lactones is known ever since santonin was used as an important anthelmintic and ascaricidal agent [1, 2]. The butenolide system as present in many cardiac glycosides shows strong oral cardiotonic activity [3]. Even the simpler butyrolactone such as 3,3-diethylbutyrolactone shows anti-convulsant activity [4]. Besides the whole group of butenolide antibiotics [5], this moiety has been found to have some interesting activities [6, 7] such as anti-inflammatory, analgesic, antitumor, antiviral, anticancer etc.

The γ-lactone ring present in the butenolide derivatives is significantly reactive and was utilized for the synthesis of nitrogen hetrocycles of potential biological activity [8, 9].

In these investigations, we report the syntheses and reactions of 2-arylidene-4-(biphenyl-4-yl)but-3-en-4-olides following a literature procedure [10, 11] with slight modification, and a study of biological activity of the resulting products. We examined the anti-inflammatory activity of a number of 2-arylidene substituted phenyl but-3-en-4-olides and the results were encouraging [12].

3-(4-Phenyl-benzoyl) propionic acid is a known anti-inflammatory drug and is available under the name of fenbufen [13]. On oral administration, its active metabolite, biphenyl acetic acid, has been reported to have comparatively more gastro-intestinal side effects [14] than other NSAID's. It was therefore considered worthwhile to study various butenolide derivatives of 3-(4-phenyl-benzoyl) propionic acid for their anti-inflammatory action. In view of the reported antimicrobial activity of butenolides [5, 10] these compounds were also tested for their antibacterial and antifungal activity against some selected microbes.

## 2. Investigations, results and discussion

### *2.1. Synthesis of compounds 1–32*

These compounds were synthesized according to the Scheme. New 2-arylidene-4-(biphenyl-4-yl)but-3-en-4-olides (**1**–**20**) were synthesized from 3-(4-phenyl-benzoyl) propionic acid by reacting with aromatic aldehydes in the presence of triethylamine in acetic anhydride. Calculations of δ values using incremental parameters for the hydrogen (semicyclic double bond) seems to suggest (*E*)-configuration. The required 3-(4-phenyl-benzoyl) propionic acid was prepared by condensing biphenyl with succinic anhydride in the presence of anhydrous aluminium chloride following Friedel-Craft's acylation reaction conditions in 70% yield. The 3-arylidene-5-(biphenyl-4-yl)-2(3*H*)-pyrrolones **21**–**27** were prepared by reacting butenolides with ammonia in absolute ethanol in 58–82% yield. The 3-arylidene-5-(biphenyl-4-yl)-1-benzyl-2(3*H*)-pyrrolones **28**–**32** were synthesized by reacting appropriate butenolides with benzylamine in dry benzene to give γ-ketobenzylamides, which were then lactamized in 6N HCl to give the corresponding N-benzylpyrrolones in 64–74% yield. The structures assigned to the compounds **1**–**32** were supported by the results of elemental analyses as well as $^1$H NMR and MS data (Table 1–3).

### *2.2. Biological studies*

The anti-inflammatory activity of the new compounds showed that the butenolides **6**, **8**, and the *N*-benzylpyrrolones **28**, **29** and **31** exhibited maximum activity (52.5–62%) at 20 mg/kg P.O. These compounds and a standard

**Scheme**

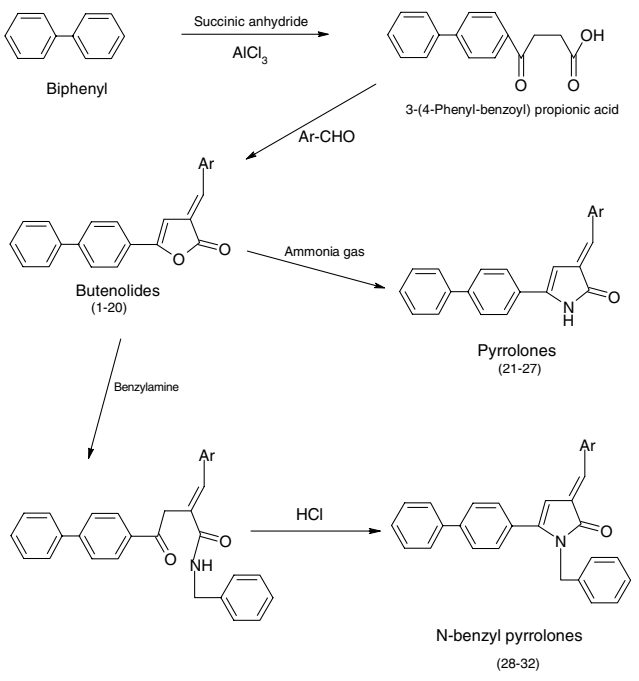
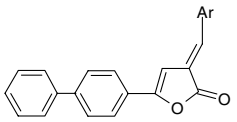


**Table 1: Compounds 1–20**



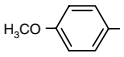
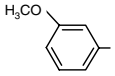
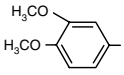
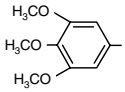
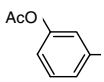
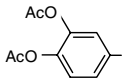
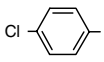
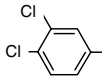
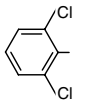
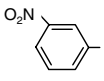
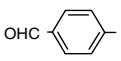
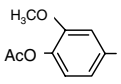
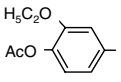
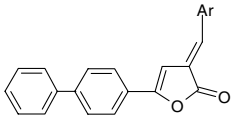
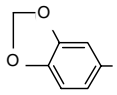
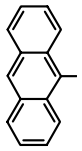
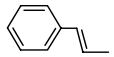
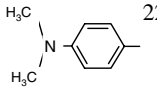

| Compd. | Ar | Melting Point (°C) | Mass Spectral Data (m/z) | PMR Chemical shifts in δ values | | | |
|---|---|---|---|---|---|---|---|
| | | | | βH (ring H) | Olefinic H | Biphenyl protons | Ar protons |
| **1** |  | 162 | 324 ($M^+$), 181, 153, 77 | 6.97, s | 7.64, s | 7.47, m, 3 H, H-3,4,5; 7.63, m, 2 H, H-2,6; 7.63, 7.83, doubtlet each, $2 \times A_2B_2$ | 7.47, m, 3 H, H-3,4,5; 7.63, m, 2 H, H-2,6 |
| **2** |  | 186 | 354 ($M^+$), 181, 153, 77 | 6.94, s | 7.37, s | 6.67, 7.81, d (e), $2 \times A_2B_2$; 7.45,m, 5 H, Ph | 3.87, s, 3 H, $OCH_3$; 6.98, 7.61, d (e), $2 \times A_2B_2$ |
| **3** |  | 178 | 354 ($M^+$), 181, 153, 77 | 6.97, s | 7.43, s | 7.41, m, 2 H, H-2,6; 7.47, t, 1 H, H-4; 7.63, m, 2 H, H-3,5; 7.68, 7.83, d (e), $2 \times A_2B_2$ | 3.88, s, 3 H, $OCH_3$; 6.99, m, 1 H, H-4; 7.15, m, 1 H, H-2; 7.25, m, 1 H, H-5; H-6, merged with the protons in the multiplet centered at 7.43 |
| **4** |  | 150 | 384 ($M^+$), 181, 153, 77 | 6.92, s | 7.37, s | 7.44, m, 3 H, H-3,4,5; 7.63, m, 2 H, H-2,6; 7.68, 7.81, d (e), $2 \times A_2B_2$ | 3.96 two closely spaced singlets, $2 \times OCH_3$; 6.95, d, 1 H, H-5; 7.11, d, 1 H, H-2; 7.3, dd, 1 H, H-6 |
| **5** |  | 118 | 414 ($M^+$), 399, 181, 153, 77 | 6.88, s | 7.35, s | 7.44, m, 3 H, H-3,4,5; 7.61, m, 2 H, H-2,6; 7.67, 7.81, d (e), $2 \times A_2B_2$ | 3.93, s, 9 H, $3 \times OCH_3$; 6.85, s, 2 H, H-2,6 |
| **6** |  | 146 | 382 ($M^+$), 181, 153, 77 | 6.88, s | 7.39, s | 7.57, m, 5 H, Ph; 7.75, 7.82, d (e), $2 \times A_2B_2$ | 2.38, s, 3 H, $OCOCH_3$; 7.25, m, 4 H, H-3,4,5,6 |
| **7** |  | 142 | 382 ($M^+$), 340, 181, 153, 77 | 6.93, s | Merged with the protons in the multiplet centered at 7.47 | 7.47, m, 3 H, H-3,4,5; 7.63, m, 2 H, H-2,6.; 7.68, 7.84, d (e), $2 \times A_2B_2$ | 2.36, s, 3 H, $OCOCH_3$; 7.16, m, 1 H, H-4; 7.40, m, 3 H, H-2,5,6 |
| **8** |  | 162 | 440 ($M^+$), 356, 181, 153 | 6.91, s | 7.47, s | 7.48, m, 3 H, H-3,4,5; 7.62, m, 2 H, H-2,6; 7.68, 7.83, d (e), $2 \times A_2B_2$ | 2.33, 2.35, s (e), $2 \times OCOCH_3$; 7.29, d, 1 H, H-5; 7.41, m, 2 H, H-2,6 |
| **9** |  | 240 | 358 ($M^+$), 181, 153, 77 | 6.42, s | 7.32, s | 7.2, m, 3 H, H-2,4,6; 7.37, m, 2 H, H-3,5; 7.06, 7.85, d (e), $2 \times A_2B_2$ | 7.41, 7.50, d (e), $2 \times A_2B_2$ |
| **10** |  | 204 | 393 ($M^+$), 181, 153, 77 | 6.4, s | 7.9, s | 7.48, m, 3 H, H-3,4,5; 7.62, m 2 H, H-2,6; 7.62; 7.70, d (e), $2 \times A_2B_2$ | 7.33, dd, 1 H, H-5; 7.79, m, 1 H, H-3; 8.04, d, 1 H, H-6 |
| **11** |  | 180 | 393 ($M^+$), 358, 181, 153 | 6.34, s | 7.40, s | 7.43, m, 3 H, H-3,4,5; 7.48, m, 2 H, H-2,6; 7.66, 7.78, d (e), $2 \times A_2B_2$ | 7.29, m, 1 H, H-4; 7.61, m, 2 H, H-3,5 |
| **12** |  | 192 | 369 ($M^+$), 181, 153 | 6.61, s | 7.73, s | 7.47,m, 2 H, H-2,6; 7.69, m, 3 H, H-3,4,5; 7.66, 7.82, d (e), $2 \times A_2B_2$ | 7.39, m, H-5; 8.05, dd, H-6; 8.19, m, H-4; 8.46, d, 1 H, H-2 |
| **13** |  | 180 | 352 ($M^+$), 181, 153, 77 | 6.98, s | 7.48, s | 7.42, m, 3 H, H-3,4,5; 7.65, m, 2 H, H-2,6; 7.78, 7.98, d (e), $2 \times A_2B_2$ | 7.71, 7.86, d (e), $2 \times A_2B_2$.; 10.07, s, 1 H, −CHO |
| **14** |  | 152 | 412 ($M^+$), 181, 153, 77 | 6.91, s | Merged with the protons in the multiplet centered at 7.44 | 7.44, m, 4 H, H-2,4,6 + olefinic proton; 7.64, m, 2 H, H-3,5; 7.68, 7.82, d (e), $2 \times A_2B_2$ | 2.35, s, 3 H, $OCOCH_3$; 3.91, s, 3 H, $OCH_3$; 7.15, d, 1 H, H-5; 7.16, d, 1 H, H-2; 7.29, dd, 1 H, H-6. |
| **15** |  | 158 | 426 ($M^+$), 384, 181, 153 | 6.89, s | 7.37, s | 7.48, m, 3 H, H-3,4,5; 7.62, 2 H, H-2,6; 7.68, 7.81, d (e), $2 \times A_2B_2$ | 1.44, t, 3 H, $OCH_2\underline{CH_3}$; 4.10, q, 2 H, $O\underline{CH_2}CH_3$, 2.34, s, 3 H, $OCOCH_3$; 7.12, m, 2 H, H-2,5; 7.26, dd, 1 H, H-6 |
| **16** |  | 184 | 330 ($M^+$), 181, 153, 77 | 6.94, s | 7.5, s | 7.43, m, 3 H, H-3,4,5; 7.62, m, 2 H, H-2,6; 7.68, 7.81, d (e), $2 \times A_2B_2$ | 7.14, m, 1 H, H-4; 7.4, m, 1 H, H-3; 7.63, m, 1 H, H-5 |

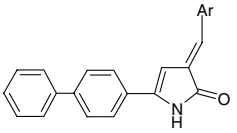
**Table 1 Cont.**

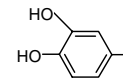
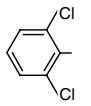
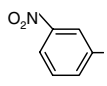
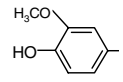



| Compd. | Ar | Melting Point (°C) | Mass Spectral Data (m/z) | PMR Chemical shifts in δ values | | | |
|---|---|---|---|---|---|---|---|
| | | | | βH (ring H) | Olefinic H | Biphenyl protons | Ar protons |
| **17** |  | 220 | 368 ($M^+$), 181, 153, 77 | 6.90, s | 7.35, s | 7.47, m, 3 H, H-3,4,5; 7.64, m, 2 H, H-2,6; 7.67, 7.82, d (e), $2 \times A_2B_2$ | 6.06, s, 2 H, $CH_2$; 6.89, d, 1 H, H-5; 7.16, m, 2 H, H-2,6 |
| **18** |  | 222 | 424 ($M^+$), 181, 153, 77 | 6.90, s | 7.60, s | 7.34, m, 1 H, H-4; 7.43, m, 2 H, H-3,5; 7.52, m, 2 H, H-2,6; 7.54, 7.66, d (e), $2 \times A_2B_2$ | 7.55, m, 4 H, H-2,3,6,7; 8.09,m, 4 H, H-1,4,5,8; 8.54, s, 1 H, H-10 |
| **19** |  | 150 | 350 ($M^+$), 181, 153, 77 | 6.48, s | 7.36, s | 7.55, m, 5 H, Ph.; 7.56, 7.70, d (e), $2 \times A_2B_2$ | 7.55,m, 5 H, Ph proton + 2 olefinic protons |
| **20** |  | 220 | 367 ($M^+$), 181, 153, 77 | 6.96, s | 7.57, s | 7.5, m, 5 H, Ph; 7.56, 7.79, d (e), $2 \times A_2B_2$ | 3.07, 6 H, $-N(CH_3)_2$; 6.71, 7.64, d (e), $2 \times A_2B_2$ |

s = singlet; d (e) = doublet each; dd = double doublet; t = triplet; q = quatret; m = multiplet
† = corresponding isotopic molecular ions peaks were observed due to chlorine atom(s)

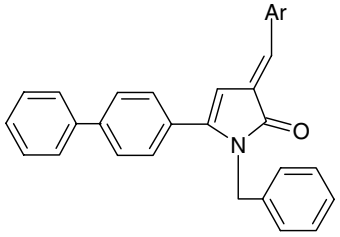
**Table 2: Compounds 21–27**

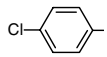
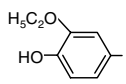
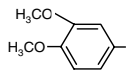
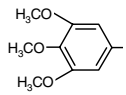



| Compd. | Ar | Melting Point (°C) | Mass Spectral Data (m/z) | PMR Chemical shifts in δ values | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | βH (ring H) | Olefinic H | Biphenyl protons | Ar protons | NH |
| **21** |  | 236 | 369 ($M^+$), 153, 77 | 6.99 | 7.63 | 7.46, m, 3 H, H-3,4,5; 7.62, m, 2 H, H-2,6; 7.68, 7.84, d (e), $2 \times A_2B_2$ | 7.46, m, 3 H, H-3,4,5; 7.62, m, 2 H, H-2,6 | 7.86 |
| **22** |  | 164 | 322 ($M^+$), 180, 153, 77 | 6.58 | 7.74 | 7.45, m, 3 H, H-3,4,5; 7.67, m, 2 H, H-2,6; 7.64, 7.81, d (e), $2 \times A_2B_2$ | 6.91, m, 2 H, H-3,5; 7.20, t, 1 H, H-4; 7.35, m, 1 H, H-6 | 7.63 |
| **23** |  | 245 | 391 ($M^+$), 356, 181, 153, 77 | 6.91 | 8.02 | 7.46, m, 3 H, H-3,4,5; 7.63, m, 2 H, H-2,6; 7.67, 7.84, d (e), $2 \times A_2B_2$ | 6.96, d, 1 H, H-5; 7.23, m, 2 H, H-2,6 | 7.91 |
| **24** |  | 222 | 355 ($M^+$), 181, 153, 77 | 6.96 | 8.07 | 7.39, m, 3 H, H-3,4,5; 7.62, m, 2 H, H-2,6; 7.60, 7.68, d (e), $2 \times A_2B_2$ | 7.41, m, 2 H, H-3,5; 7.46, m, 1 H, H-4 | 8.06 |
| **25** |  | 218 | 338 ($M^+$), 181, 153, 77 | 6.61 | 7.73 | 7.47, m, 2 H, H-2,6; 7.69, m, 3 H, H-3,4,5; 7.66, 7.82, d (e), $2 \times A_2B_2$ | 7.39, m, 1 H, H-5; 8.05, dd, 1 H, H-6; 8.19, m, 1 H, H-4; 8.46, d, 1 H, H-2 | 7.52 |
| **26** |  | 200 | 328 ($M^+$), 300, 181, 153 | 6.56 | 7.59 | 7.36, m, 2 H, H-2,6; 7.47, t, 1 H, H-4; 7.62, m, 2 H, H-3,5; 7.60, 7.70, d (e) $2 \times A_2B_2$ | 3.96, s, 3 H, $OCH_3$; 6.99, d, 1 H, H-5; 7.14, d, 1 H, H-2; 7.31, dd, 1 H, H-6 | 8.02 |
| **27** |  | 260 | 367 ($M^+$), 321, 180, 153 | 6.97 | 7.65 | 7.47, 7.85, d (e) $2 \times A_2B_2$; 7.4, m, 2 H, H-3,5; 7.65, m, 5 H, H-2,4,6 + olefinic proton + H-5 (thiophene) | 7.15, m, 2 H, H-3,4; H-5 merged with the protons in multiplet centered at 7.65 | 8.06 |

s = singlet; d (e) = doublet each; dd = double doublet; t = triplet; q = quatret; m = multiplet
† = corresponding isotopic molecular ions peaks were observed due to chlorine atoms.

**Table 3: Compounds 28–32**




| Compd. | Ar | Melting Point (°C) | Mass Spectral Data (m/z) | PMR Chemical shifts in δ values | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | βH (ring H) | Olefinic H | Biphenyl protons | Ar protons | N-Benzyl moiety |
| **28** |  | 140 | 447 ($M^+$), 356,180, 91, 77 | 6.25, s | 7.38, s | 7.39, 7.6, d(e), $2 \times A_2B_2$, 7.46, m, 3 H, H-3,4,5; 7.6, m, 2 H, H-2,6 | 7.39, 7.6, d(e), $2 \times A_2B_2$ | 4.89, 2 H, $CH_2$; 7.11, m, 2 H, H-2,6; 7.24, m, 3 H, H-3,4,5 |
| **29** |  | 160 | 473 ($M^+$), 382, 180, 153, 121, 91, 77 | 6.25, s | Merged with the protons in the multiplet centered at 7.37 | 7.13, m, 2 H, H-2,6; 7.27, m, 1 H, H-4; 7.46, m, 2 H, H-3,5; 7.37, 7.59, d(e) $2 \times A_2B_2$ | 1.48, t, 3 H, $\underline{CH_3}-CH_2-$, 4.15, q, 2 H, $CH_3-\underline{CH_2}-$; 6.98, d, 1H. H-5; 7.6, m, 2 H, H-2,6 | 4.89, s, 2 H, $CH_2$; 7.27, m, 3 H, H-3,4,5; 7.46, m, 2 H, H-2,6 |
| **30** |  | 134 | 473 ($M^+$), 382, 180, 91, 77 | 6.2, s | 7.49, s | 7.39, 7.61, d (e), $2 \times A_2B_2$; 7.46, m, 3 H, H-3,4,5; 7.59, m, 2 H, H-2,6 | 3.90, closely spaced doublet, 6 H, $2 \times OCH_3$; 6.92, d, 1 H, H-5 | 4.89, s, 2 H, $CH_2$; 7.02–7.32, m, 7 H, 5 potons of benzyl ring + H-2,6 (Ar) |
| **31** |  | 160 | 503 ($M^+$), 180, 91, 77 | 6.23, s | 7.22, s | 7.37, 7.60, d (e), $2 \times A_2B_2$; 7.46, m, 3 H, H-3,4,5; 7.60, m, 2 H, H-2,6 | 3.90, s, 9 H, $3 \times OCH_3$; 6.90, s, 2 H, H-2,6 | 4.88, s, 2 H, $CH_2$; 7.11, m, 2 H, H-2,6; 7.22, m, 4 H, H-3,4,5 + olefinic proton |
| **32** |  | 136 | 419 ($M^+$), 180, 153, 91, 77 | 6.32, s | 7.59, s | 7.24, 7.60, d (e), $2 \times A_2B_2$; 5H of phenyl merged with the protons in the multiplet centered at 7.46 | 7.12, m, 1 H, H-4; 7.22, m, 1 H, H-3; 7.64, m, 1 H, H-5 | 4.89, s, 2 H, $CH_2$; 7.46, m, 10 H, protons of phenyl + benzyl ring. |

s = singlet; d (e) = doublet each; dd = double doublet; t = triplet; q = quatret; m = multiplet
† = corresponding isotopic molecular ions peaks were observed due to chlorine atoms.

drug (indomethacin) exhibited nearly equipotent activity (Table 4). It is significant that none of these compounds showed ulcerogenic activity, which is a common feature with similar compounds.

Structure activity relationship studies showed that substitution of the oxygen atom of the butenolide ring with NH (pyrrolones) resulted in a marked decrease in activity, while substitution of the oxygen atom with a benzylamine moiety (*N*-benzyl-pyrrolones) markedly increased activity. Compounds having a trimethoxy function at 3,4,5-position of the arylidene moiety were found to have better anti-inflammatory activity than those having one, two or no methoxyl functions. Substitution of one or more $-OCOCH_3$ groups in the arylidene moiety did also increase activity.

The antimicrobial studies were carried out on the synthesized compounds against the microorganisms *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans.* Compounds inhibiting growth of one or more of the above microorganisms at a concentration of 100 μg/ml were further tested for minimum inhibitory concentration (MIC).

Compounds **10**, **24**, **25** and **27** showed excellent activity against *Candida albicans* with MIC 2 μg/ml. Out of the above mentioned compounds, compound **25** and **27** also showed good activity against *Staphylococcus aureus* with a MIC of 5 μg/ml. The pyrrolones **23** and **26** were found to be active against *Escherichia coli* (MIC 10 μg/ml).

An analysis of results showed that these compounds have better activity against *Candida albicans* in comparison to *Staphylococcus aureus* and *Escherichia coli.* Introduction of nitrogen instead of the oxygen atom (pyrrolones) in the butenolide ring enhanced antimicrobial action.

## 3. Experimental

Melting points were determined in open capillary tubes and are uncorrected. Analytical data of C, H, O, N, and S were within ±0.4% of the theoretical values. $^1$H NMR spectra were recorded on Varian E-360 MHz or Bruker spectropsin DPX-300MHz with tetramethylsilane as internal standard in solvent $CDCl_3$. MS were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. TLC were carried out using silica gel (Merck No. 5554). Dry solvents were used throughout. The spectral data of the compounds are listed in Table 1–3.

### *3.1. Chemistry*

#### *3.1.1. 3-(4-Phenyl-benzoyl) propionic acid*

Succinic anhydride (0.1 mol) was reacted with biphenyl (0.1 mol) in the presence of anhydrous aluminium chloride (0.1125 mol) in dry nitrobenzene (50 ml). The reaction mixture was refluxed for 2 h and excess nitrobenzene was removed by steam distillation. It was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochlo-

**Table 4: Biological activity**

| Compd. | Antimicrobial Activity (Minimum Inhibitory Concentration*) | | | Anti-inflammatory activity (% Inhibition in rat paw oedema) |
|---|---|---|---|---|
| | *S. aureus* | *E. coli* | *C. albicans* | |
| **1** | – | – | >100 | 29.2 |
| **2** | – | – | – | 36.36 |
| **3** | – | – | – | 38.2 |
| **4** | – | – | – | 40.74 |
| **5** | – | >100 | >100 | 42.0 |
| **6** | – | >100 | >100 | 52.5 |
| **7** | – | – | 50 | – |
| **8** | >100 | >100 | 50 | 58.2 |
| **9** | 25 | >100 | 15 | 28.52 |
| **10** | 15 | 20 | 2 | 29.63 |
| **11** | 15 | 20 | 15 | 28.52 |
| **12** | 25 | 20 | 15 | – |
| **13** | – | – | – | 35.3 |
| **14** | – | – | – | 40.2 |
| **15** | – | – | – | 28.52 |
| **16** | – | – | – | 32.0 |
| **17** | – | – | >100 | – |
| **18** | – | – | – | 28.52 |
| **19** | >100 | >100 | 15 | – |
| **20** | – | – | – | – |
| **21** | – | – | >100 | 18.33 |
| **22** | >100 | >100 | – | – |
| **23** | 20 | 10 | 15 | 20.2 |
| **24** | >100 | 25 | 2 | 18.52 |
| **25** | 5 | 15 | 2 | – |
| **26** | 15 | 10 | 25 | 28.52 |
| **27** | 5 | 20 | 2 | – |
| **28** | – | – | – | 55 |
| **29** | >100 | – | – | 62 |
| **30** | 25 | 50 | 25 | 32.33 |
| **31** | – | >100 | >100 | 56.2 |
| **32** | >100 | 25 | 25 | 32.5 |
| Indomethacin | | | | 61.2 |

* = in μg/ml; – = insignificant activity

ric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give a colorless product, m.p. 180 °C, yield 70%, $^1$H NMR (ppm): 2.82 and 3.37 (t each, $2 \times CH_2$), 7.45 (m, 3 H, H-3,4,5 phenyl), 7.64 (m, 2 H, H-2, 6 phenyl), 7.70 and 8.07 (d each, $2 \times A_2B_2$ p-substituted phenyl).

*3.1.2. General procedure for the synthesis of 2-arylidene-4-(biphenyl-4-yl)-but-3-en-4-olides* (**1**–**20**)

A solution of an aromatic aldehyde (3 mmol) and 3-(4-phenyl-benzoyl) propionic acid (equimolar) in acetic anhydride (15 ml) with triethylamine (3–4 drops) was refluxed for 4 h under anhydrous conditions. After completion of reaction, the contents were poured into crushed ice in small portions while stirring. A solid mass separated out, which was filtered, washed with water and crystallized from a mixture of methanol:chloroform (1 : 1).

*3.1.3. General procedure for the synthesis of 3-arylidene-5-(biphenyl-4-yl)-2(3H)-pyrrolones* (**21**–**27**)

Dry ammonia gas was passed into anhydrous ethanolic solution of butenolide (1.0 g) for 1 h at room temperature, ethanol was distilled off under reduced pressure and the solid mass obtained was crystallized from methanol/acetone to give TLC pure coloured compound.

*3.1.4. General procedure for the synthesis 3-arylidene-5-(biphenyl-4-yl)-1-benzyl-2(3H)-pyrrolones* (**28**–**32**)

Synthesis of these compounds involved two steps:

*3.1.4.1. Synthesis of γ-ketobenzylamide*

Butenolide (3 mmol) and benzylamine (4 mmol) were refluxed in dry benzene for 2 h. On completion of reaction, excess benzene was distilled off and the solid mass obtained was washed with petroleum ether and dried. The compound obtained was used without crystallisation.

*3.1.4.2. Lactamization of γ-ketobenzylamide*

γ-Ketobenzylamide (3 mmol) was refluxed in 6 N hydrochloric acid (20 ml) for 1 h. The contents were then cooled and the solid mass obtained was collected, washed with water and recrystallized from methanol.

### *3.2. Biological evaluation*

*3.2.1. Anti-inflammatory activity*

A freshly prepared suspension of carrageenan (0.05 ml of 1% solution in 0.9% saline) was injected under the planter aponeurosis of the right paw of rats according to the method of Winter et al. [15]. One group of six rats was kept as a control and the animals of the other groups were pretreated with test drugs given orally 30 min before carrageenan injection. The foot volume was measured before and 3 h after carrageenan injection by a plethysmograph. The mean increase in the paw volume in each group was calculated according to the following formula:

$$\text{Anti-inflammatory activity (\% inhibition)} = 1 - \text{Vt/Vc} \times 100$$

Where Vt and Vc are the oedema volumes in the drug-treated and the control groups. Indomethacin was used as standard drug for comparison.

*3.2.2. Antimicrobial activity*

Gram positive (*Staphylococcus aureus*), and gram negative (*Escherichia coli*) bacterial strains and a yeast (*Candida albicans*) were used. The test was carried out according to the turbidity method [16]. A solution of the compounds was prepared in dimethylformamide (DMF) and a series of doubling dilutions was 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 37 °C for 24 h and examined for turbidity. The tubes with the highest dilution showing no turbidity determined MIC.

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