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Original article

2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides: Synthesis, reactions and biological activity

Asif Husain *, M.S.Y. Khan [1], S.M. Hasan [2], M.M. Alam [3]

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi 110 062, India

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Abstract

2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides (**1**–**17**) were prepared from 3-(4-phenoxy-benzoyl)propionic acid and aromatic aldehydes. Some of the selected butenolides were reacted with ammonia and benzylamine to give corresponding 3-arylidene-5-(4-phenoxy-phenyl)-2(3*H*)-pyrrolones (**18**–**23**) and 3-arylidene-5-(4-phenoxy-phenyl)-1-benzyl-2(3*H*)-pyrrolones (**24**–**29**) respectively, which were characterized on the basis of ^{1}H-, ^{13}C-NMR, Mass spectrometric data and elemental analysis results. These compounds were tested for anti-inflammatory and antimicrobial actions. The compounds, which showed significant anti-inflammatory activity, were screened for their analgesic and ulcerogenic activities. Five new compounds (**5**, **6**, **7**, **25** and **26**), out of 29 showed very good anti-inflammatory activity in the carrageenan induced rat paw edema test, with significant analgesic activity in the acetic acid induced writhing test together with negligible ulcerogenic action. Antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* as well as antifungal activity against *Candida albicans* were expressed as the corresponding minimum inhibitory concentration (MIC) values. Compound **21**, **22** and **23** showed excellent activity against *C. albicans* with MIC-10 μg/ml. Out of the above-mentioned compounds, **22** and **23** also showed good activity against *S. aureus* with MIC-20 and 15 μg/ml respectively.

Keywords: Butenolide; Aroylpropionic acid; Pyrrolone; Anti-inflammatory; Analgesic; Ulcerogenic; Antimicrobial activity

1. Introduction

The butenolide system as present in many cardiac glycosides shows strong oral cardiotonic activity [1]. Physiological activity of the natural lactones is known ever since santonin was used as an important anthelmintic and ascaricidal agent [2,3]. Besides the whole group of butenolide antibiotics [4], this moiety has been found to have some interesting activities [5–9] such as anticonvulsant, anti-inflammatory, analgesic, antitumor, antiviral, anticancer etc. The reactivity of γ-lactone ring present in the butenolide derivatives has been further exploited for the synthesis of nitrogen heterocycles of potential biological activity [10,11].

3-(4-Phenoxy-benzoyl) propionic acid is an example of well known aroyl propionic acid class of anti-inflammatory drugs [12] and some of them are available in the market (fenbufen, bucloxic acid, furobufen etc.), they have been reported to have comparatively more gastrointestinal side effects as compared to other NSAIDs [13–15]. We had examined in these laboratories the anti-inflammatory activity of a number of 2-arylidene-4-substituted phenyl butenolides and the results were encouraging [16,17]. 3-(4-Phenoxy-benzoyl) propionic acid is a good anti-inflammatory agent associated with gastrointestinal side effects [13]. It was therefore considered worthwhile to study various butenolide derivatives of 3-(4-phenoxy-benzoyl) propionic acid for their anti-inflammatory action. These butenolides were further exploited for the synthesis of nitrogen heterocycles (pyrrolones). In view of the

* Corresponding author. Tel.: +91 11 2605 9681/688x5647; fax: +91 11 1698 8874; mobile: +91 989 1116086.
E-mail addresses: drasifhusain@yahoo.com (A. Husain), msykhan@hotmail.com (M.S.Y. Khan), root@hamduni.ren.nic.in (S.M. Hasan), hamlucky@indiatimes.com (M.M. Alam).
[1] Tel.: +91 11 2605 9681/688x5890; fax: +91 11 1698 8874.
[2] Tel.: +91 11 2605 9681/688x5614; fax: +91 11 1698 8874.
[3] Tel.: +91 11 2605 9681/688x5660; fax: +91 11 1698 8874.

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reported antimicrobial activity of butenolides and pyrrolones, these compounds were also tested for their antibacterial and antifungal activity against some selected microbes.

2. Chemistry

Overall 29 new compounds **1**–**29** were prepared as outlined in Scheme 1. 2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides (**1**–**17**) were synthesized from 3-(4-phenoxy-benzoyl) propionic acid by reacting with aromatic aldehydes in presence of triethylamine in acetic anhydride. The required 3-(4-phenoxy-benzoyl) propionic acid was prepared by condensing diphenyl ether with succinic anhydride in presence of anhydrous aluminum chloride following Friedel-Craft's acylation reaction conditions. The 3-arylidene-5-(4-phenoxy-phenyl)-2(3*H*)-pyrrolones (**18**–**23**) were prepared by reacting butenolides with ammonia in absolute ethanol. The 3-arylidene-5-(4-phenoxy-phenyl)-1-benzyl-2(3*H*)-pyrrolones (**24**–**29**) were synthesized by reacting appropriate butenolides with benzylamine in dry benzene to give γ-ketobenzylamides, which were then lactamized in 6 N HCl to give the corresponding *N*-benzylpyrrolones. Calculations of δ values using incremental parameters for the hydrogen (semicyclic double bond) seems to suggest (*E*)-configuration. The structures assigned to the compounds **1**–**29** were supported by the results of elemental analysis as well as ^{1}H- and ^{13}C-NMR and Mass spectral data (Scheme 1).

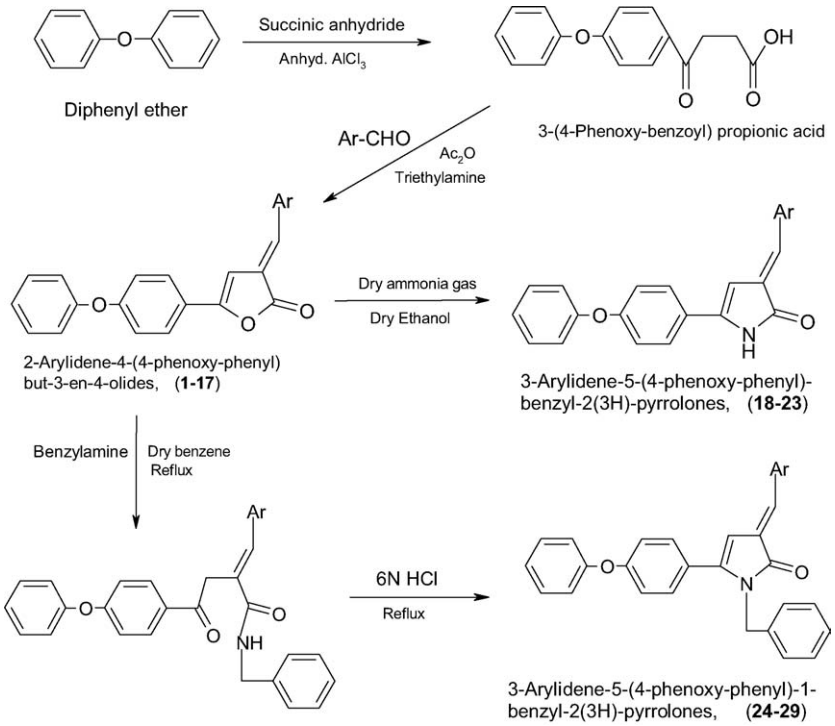
In the ^{1}H-NMR spectral data all the compounds showed two singlets of one proton each around δ 6.5 and δ 7.4 which could be assigned to the ring βH and the olefinic hydrogen of the arylidene substituent. However, deviations are observed when the Ar moiety is 2,6-dichlorophenyl and 9-anthracenyl. In these cases the ring hydrogen gets shifted upfield while the olefinic hydrogen is downfield possibly due to non-planarity of the Ar ring. In the ^{13}C-NMR spectral data all the compounds showed a peak around δ 98.5 that could be assigned to the olefinic carbon (C-5). Other peaks were observed at appropriate places.

The fragmentation pattern observed on electron impact mass spectrum can be summarized as follows:

The 2-arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides gave M^+ peak in reasonable intensities. The major fragment appears to be C_6H_5–O–C_6H_4–C≡O^+ arising from the heterocyclic oxygen and γ-carbon with its substituent. Subsequently it loses CO to give C_6H_5–O–$C_6H_4^+$. There appeared a peak at *m*/*z* 77 that corresponds to $C_6H_5^+$ Occasionally the aryl ring of the arylidene moiety also appeared as Ar^+. In the case of pyrrolones, the major fragmentation is through C_6H_5–O–C_6H_4–C≡N^+H, which is followed by loss of HCN to give C_6H_5–O–$C_6H_4^+$.

In case of *N*-benzylpyrrolones, loss of 91 mass units corresponding to benzyl moiety from the molecular ion is observed along with peaks at *m*/*z* 91, 77. Other pathway is via C_6H_5–O–C_6H_4–C≡N^+H arising from C-2 and its substituent, which appears to be novel. This also loses HCN to give C_6H_5–O–$C_6H_4^+$.

In case of aryl groups having chloro-substituent(s), the molecular ion peak or their fragments having halogen(s) appeared as cluster of peaks.



Scheme 1.

3. Pharmacological results and discussion

3.1. Anti-inflammatory activity

All the compounds were evaluated for in-vivo anti-inflammatory activity. Pedal inflammation in albino rats was induced by carrageenan in rat hind paw and the edema volume was measured by mercury displacement in a plethysmograph. Carrageenan induced rat paw oedema method [18] 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. The percentage inhibition of inflammation was calculated by applying Newbould formula [19].

The activity showed that compound **26** exhibited maximum anti-inflammatory activity (58.06%) and its activity was comparable with the standard drug indomethacin (64.51%) at a dose of 20 mg/kg P.O. Compound **5**, **6**, **13** and **25** showed good activity (45.16–51.61%). Results are presented in Table 1.

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

3.2. Analgesic activity

The analgesic activity of the synthesized compounds **4**, **5**, **6**, **7**, **12**, **13**, **24**, **25**, **26** and **27** was evaluated by acetic acid induced writhing test [20]. The activity showed that compound **6** exhibited maximum analgesic activity (58.79%) and its activity was comparable with the standard drug ibuprofen (62.33%) at a dose of 20 mg/kg P.O. Compound **5**, **7** and **26** showed good activity (51.33–53.17%). Results are presented in Table 2. Analysis of results showed that substitution of oxygen atom of butenolide ring with benzylamine moiety (*N*-benzylpyrrolones) resulted in decrease in activity. Substitution of one or more $-OCOCH_3$ group in arylidene moiety was also found to increase the activity. Compounds having trimethoxyl function at 3,4,5-position of arylidene moiety were found to have better analgesic activity as compared to those having one, two or no methoxyl functions.

3.3. Acute ulcerogenesis

The compounds, which showed significant anti-inflammatory activity, were screened for their ulcerogenic activity. The test was performed according to Cioli et al. [21]. The tested compounds showed ulcerogenic activity ranging from 0.16 to 0.76, whereas the standard drug ibuprofen showed high severity index of 1.97. The results indicate that compounds are almost devoid of ulcerogenic action. Results are presented in Table 2.

3.4. Antimicrobial activity

The antimicrobial studies were carried out on the synthesized compounds against the microorganism viz. *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* in meat peptone agar medium at a concentration of 100 μg/ml by cup plate method. Compounds inhibiting growth of one or more of the above microorganisms were further tested for minimum inhibitory concentration (MIC). The test was carried out according to the turbidity method [22].

Compound **21**, **22** and **23** showed excellent activity against *C. albicans* with MIC-10 μg/ml. Out of the above-mentioned compounds, **22** and **23** also showed good activity against *S. aureus* with MIC-20 and 15 μg/ml respectively. An analysis of results showed that these compounds were having better activity against *C. albicans* in comparison to *S. aureus* and *E. coli*. Introduction of nitrogen in place of oxygen atom (pyrrolones) in the butenolide ring enhanced antimicrobial action.

A solution of the compounds was prepared in dimethylformamide (DMF) 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 37° for 24 h and examined for turbidity. The tubes with highest dilution showing no turbidity was the MIC. Results are presented in Table 1.

4. Experimental protocols

4.1. Chemistry

Melting points (m.p.) were taken in open capillary tubes and are uncorrected. Microanalysis of the compounds was done on Perkin–Elmer model 240 analyzer and the values were found within ± 0.4% of the theoretical values. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian E-360 MHz or Bruker spectropsin DPX-300 MHz; chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. The splitting pattern abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. Spectral data are consistent with assigned structures. The progress of the reactions was monitored on TLC, which was performed on silica gel (Merck No. 5554). Dry solvents were used throughout.

4.1.1. Preparation of 3-(4-phenoxy-benzoyl) propionic acid

Succinic anhydride (10 g, 10 mmol) was reacted with diphenyl ether (17 g, 10 mmol) in presence of anhydrous alu-

Table 1
Antimicrobial and anti-inflammatory activity of the compounds **1–2 9**

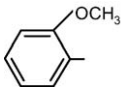
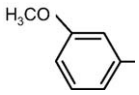
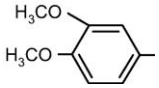
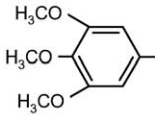
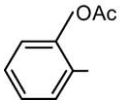
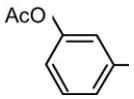
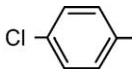
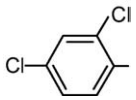
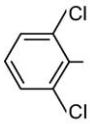
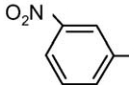
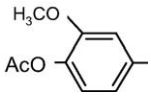
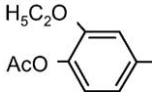
Compound	Ar	Antimicrobial activity (MIC *)			Anti-inflammatory activity (% inhibition in rat paw edema)		
		S. aureus	*E. coli*	*C. albicans*	Normal paw volume (x)	Paw oedema 5 h after carrageenan (a)	% Inhibition $(1 - a - x/b - y) \times 100$ of edema
1		–	–	>100	0.68 ± 0.03	0.92 ± 0.03	22.58
2		–	–	–	0.67 ± 0.03	0.92 ± 0.02	19.35
3		–	–	>100	0.69 ± 0.02	0.92 ± 0.02	25.80
4		–	–	–	0.68 ± 0.03	0.89 ± 0.04	32.25
5		>100	–	>100	0.70 ± 0.02	0.87 ± 0.03	45.16
6		–	–	–	0.72 ± 0.03	0.88 ± 0.03	48.38
7		–	–	–	0.70 ± 0.02	0.90 ± 0.05	35.48
8		>100	–	>100	0.67 ± 0.04	0.90 ± 0.04	25.80
9		50	–	50	0.69 ± 0.03	0.91 ± 0.03	29.03
10		>100	–	>100	0.68 ± 0.03	0.92 ± 0.05	22.58
11		50	>100	25	0.72 ± 0.02	0.95 ± 0.03	25.80
12		–	–	>100	0.69 ± 0.03	0.90 ± 0.04	32.25
13		–	–	–	0.71 ± 0.02	0.88 ± 0.03	45.16

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Table 1
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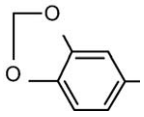
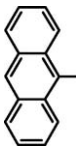
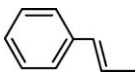
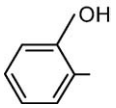
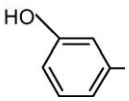
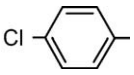
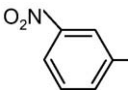
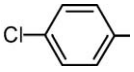
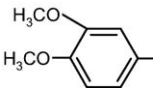
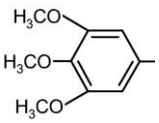
Compound	Ar	Antimicrobial activity (MIC *)			Anti-inflammatory activity (% inhibition in rat paw edema)		
		S. aureus	*E. coli*	*C. albicans*	Normal paw volume (x)	Paw oedema 5 h after carrageenan (a)	% Inhibition $(1 - a - x/b - y) \times 100$ of edema
14		50	>100	50	0.68 ± 0.03	0.95 ± 0.04	12.90
15		–	–	>100	0.68 ± 0.03	0.90 ± 0.03	29.03
16		>100	–	–	0.72 ± 0.03	0.97 ± 0.04	19.35
17		–	–	–	0.68 ± 0.04	0.91 ± 0.04	25.80
18		>100	>100	50	0.73 ± 0.02	0.98 ± 0.03	19.35
19		–	–	>100	0.69 ± 0.03	0.91 ± 0.03	29.03
20		50	>100	>100	0.67 ± 0.02	0.90 ± 0.04	25.80
21		25	50	10	0.68 ± 0.04	0.96 ± 0.02	09.67
22		20	50	10	0.66 ± 0.05	0.93 ± 0.04	12.90
23		15	25	10	0.69 ± 0.03	0.97 ± 0.05	09.67
24		>100	–	>100	0.70 ± 0.02	0.90 ± 0.05	35.48
25		–	–	–	0.71 ± 0.03	0.86 ± 0.03	51.61
26		–	–	–	0.74 ± 0.02	0.87 ± 0.03	58.06

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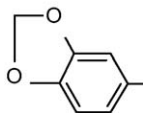
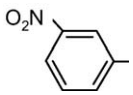
Table 1
(continued)

Compound	Ar	Antimicrobial activity (MIC *)			Anti-inflammatory activity (% inhibition in rat paw edema)		
		S. aureus	*E. coli*	*C. albicans*	Normal paw volume (x)	Paw oedema 5 h after carrageenan (a)	% Inhibition $(1 - a - x/b - y) \times 100$ of edema
27		–	–	>100	0.69 ± 0.03	0.90 ± 0.04	32.25
28		>100	>100	>100	0.68 ± 0.04	0.91 ± 0.04	25.80
29		50	>100	25	0.67 ± 0.03	0.91 ± 0.05	22.58
Indomethacin					0.70 ± 0.03	0.81 ± 0.03	64.51
Control					0.68 ± 0.02 (y)	0.99 ± 0.03 (b)	

* = in μg/ml; – = insignificant activity.

minum chloride (15 g, 11.25 mmol) 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 hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from acetone to give 9.6 g (65%) of the desired compound as a colorless solid, m.p. 172 °C which gave effervescence with sodium bicarbonate solution, ^{1}H-NMR ($CDCl_3$) δ 2.80 and 3.27 (t each, $2 \times CH_2$), 7.17 (m, 2H, H-2,6, phenyl), 7.22 (m, 1H, H-4, phenyl), 7.41 (m, 2H, H-3,5, phenyl), 6.98 and 7.97 (d each, $2 \times A_2B_2$ *p*-substituted phenyl).

*4.1.2. General procedure for the synthesis of 2-arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides (**1**–**17**)*

A solution of 3-(4-phenoxy-benzoyl) propionic acid (0.71 g, 3 mmol) and aromatic aldehyde (equimolar, 3 mmol) 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) to give **1**–**17**.

Table 2
Analgesic and ulcerogenic activity of the compounds **4**–**7**, **12**, **13**, **24**–**27**

Compound	Analgesic activity (% protection)	Ulcerogenic activity (severity index)
4	40.12	0.16
5	51.33	0.45
6	58.79	0.76
7	53.17	0.75
12	37.63	0.45
13	34.37	0.20
24	40.12	0.20
25	45.80	0.16
26	51.33	0.45
27	37.63	0.20
Control	–	0.00
Ibuprofen	62.33	1.97

*4.1.2.1. 2-Benzylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides (**1**).* Yield: 58%, m.p. 122 °C. ^{1}H-NMR ($CDCl_3$) δ 6.85 (s, 1H, butenolide ring), 7.03 and 7.72 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.05 (m, 4H, H-2,6, 2 × phenyl), 7.18 (m, 2H, H-4, 2 × phenyl), 7.37 (s, 1H, olefinic H), 7.42 (m, 4H, H-3,5, 2 × phenyl). ^{13}C-NMR ($CDCl_3$) δ 170.5 (C-1), 125.6 (C-2), 118.8 (C-3), 128.2 (C-4), 96.7 (C-5), 129.1 (C-6), 118.2 (C-7,11), 130.1 (C-8,10), 154.9 (C-9), 153.4 (C-12), 131.8 (C-13,17), 119.6 (C-14,16), 124.3 (C-15), 129.4 (C-1′), 126.9 (C-2′,6′), 129.8 (C-3′,5′), 131.2 (C-4′). MS: *m*/*z* 340 (M^+), 197, 169, 77. Anal. $C_{23}H_{16}O_3$ (C, H).

*4.1.2.2. 2-(2-Methoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**2**).* Yield: 54%, m.p. 118 °C. ^{1}H-NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.80 (s, 1H, butenolide ring), 6.94 (m, 1H, H-3, arylidene ring), 7.02 and 7.71 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.05 (m, 2H, H-2,6, phenyl), 7.18 (m, 1H, H-4, phenyl), 7.39 (m, 2H, H-4,5, arylidene ring), 7.42 (m, 2H, H-3,5, phenyl), 7.67 (dd, 1H, H-6, arylidene ring), 7.83 (s, 1H, olefinic H). ^{13}C-NMR ($CDCl_3$) δ 171.0 (C-1), 125.3 (C-2), 118.9 (C-3), 128.1 (C-4), 96.9 (C-5), 128.8 (C-6), 118.5 (C-7, 11), 130.6 (C-8,10), 155.5 (C-9), 153.8 (C-12), 132.2 (C-13,17), 119.4 (C-14,16), 124.1 (C-15,6′), 129.6 (C-1′), 155.1 (C-2′), 127.2 (C-3′), 130.2 (C-4′), 128.3 (C-5′), 56.4 (–OCH_3). MS: *m*/*z* 370 (M^+), 197, 169, 77. Anal. $C_{24}H_{18}O_4$ (C, H).

*4.1.2.3. 2-(3-Methoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**3**).* Yield: 52%, m.p. 104–106 °C. ^{1}H-NMR ($CDCl_3$) δ 3.87 (s, 3H, OCH_3), 6.97 (m, 1H, H-4, arylidene ring), 6.83 (s, 1H, butenolide ring), 7.03 and 7.73 (d, each, 2

× A_2B_2, *p*-disubstituted phenyl), 7.16 (m, 6H, 2 × phenyl), 7.37 (s, 1H, olefinic H), 7.39 (m, 2H, H-3,5, phenyl). ^{13}C-NMR ($CDCl_3$) δ 170.9 (C-1), 126.1 (C-2), 119.1 (C-3), 128.5 (C-4), 97.3 (C-5), 129.2 (C-6), 118.1 (C-7,11), 130.2 (C-8,10), 155.9 (C-9), 153.1 (C-12), 133.1 (C-13,17), 119.6 (C-14,16), 124.3 (C-15,6′), 129.6 (C-1′), 127.1 (C-2′), 153.2 (C-3′), 127.6 (C-4′), 128.9 (C-5′), 55.5 (–OCH_3). MS: *m*/*z* 370 (M^+), 197, 169, 77. Anal. $C_{24}H_{18}O_4$ (C, H).

*4.1.2.4. 2-(3,4-Dimethoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**4**).* Yield: 61%, m.p. 112–114 °C. ^{1}H-NMR ($CDCl_3$) δ 3.96 (s, 6H, 2 × OCH_3), 6.82 (s, 1H, butenolide ring), 6.95 (d, 1H, H-5, arylidene ring), 7.04 and 7.73 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.06 (m, 2H, H-2,6, phenyl), 7.11 (d, 1H, H-2, arylidene ring), 7.18 (m, 1H, H-4, phenyl), 7.30 (dd, 1H, H-6, arylidene ring), 7.35 (s, 1H, olefinic H), 7.42 (m, 2H, H-3,5, phenyl). ^{13}C-NMR ($CDCl_3$) δ 172.1 (C-1), 126.1 (C-2), 119.3 (C-3), 128.8 (C-4), 98.1 (C-5), 129.1 (C-6,1′), 118.3 (C-7,11), 130.6 (C-8,10), 156.4 (C-9), 153.4 (C-12), 132.8 (C-13,17), 119.7 (C-14,16), 124.5 (C-15), 126.9 (C-2′), 135.2 (C-3′), 130.1 (C-4′), 129.6 (C-5′), 127.2 (C-6′) 54.6 (–OCH_3). MS: *m*/*z* 400 (M^+), 197, 169, 77. Anal. $C_{25}H_{20}O_5$ (C, H).

*4.1.2.5. 2-(3,4,5-Trimethoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**5**).* Yield: 65%, m.p. 122–124 °C. ^{1}H-NMR ($CDCl_3$) δ 3.93 (s, 9H, 3 × OCH_3), 6.76 (s, 1H, butenolide ring), 6.84 (s, 2H, H-2,6, arylidene ring), 7.04 and 7.76 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.07 (m, 2H, H-2,6, phenyl), 7.18 (m, 1H, H-4, phenyl), 7.32 (s, 1H, olefinic H), 7.39 (m, 2H, H-3,5, phenyl). ^{13}C-NMR ($CDCl_3$) δ 170.8 (C-1), 127.5 (C-2), 118.6 (C-3), 128.8 (C-4), 99.2 (C-5), 129.1 (C-6), 118.1 (C-7,11), 130.2 (C-8,10), 155.8 (C-9), 153.1 (C-12), 131.9 (C-13,17), 119.6 (C-14,16), 124.2 (C-15), 129.4 (C-1′), 129.9 (C-2′,6′), 135.1 (C-3′), 134.7 (C-4′), 130.7 (C-5′), 54.1 (–OCH_3). MS: *m*/*z* 430 (M^+), 197, 169, 77. Anal. $C_{26}H_{22}O_6$ (C, H).

*4.1.2.6. 2-(2-Acetoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**6**).* Yield: 60%, m.p. 142 °C. ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3H, $OCOCH_3$), 6.81 (s, 1H, butenolide ring), 7.03 and 7.71 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.06 (m, 2H, H-2,6, phenyl), 7.36 (m, 3H, H-3,4,5, arylidene ring), 7.37 (s, 1H, olefinic H), 7.39 (m, 2H, H-3,5, phenyl). ^{13}C-NMR ($CDCl_3$) δ 168.5 (C-1), 126.7 (C-2), 118.6 (C-3), 128.2 (C-4), 97.7 (C-5), 129.0 (C-6,3′), 118.1 (C-7,11), 130.3 (C-8,10), 155.9 (C-9), 153.8 (C-12), 133.1 (C-13,17), 119.8 (C-14,16), 124.3 (C-15), 127.8 (C-1′), 157.2 (C-2′), 130.8 (C-4′), 128.8 (C-5′), 123.2 (C-6′), 20.6 (–OAc). MS: *m*/*z* 398 (M^+), 197, 77. Anal. $C_{25}H_{18}O_5$ (C, H).

*4.1.2.7. 2-(3-Acetoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**7**).* Yield: 62%, m.p. 146–148 °C. ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3H, $OCOCH_3$), 6.83 (s, 1H, butenolide ring), 7.08 and 7.76 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.07 (m, 2H, H-2,6, phenyl), 7.16 (m, 1H, H-4, arylidene ring), 7.18 (m, 1H, H-4, phenyl), 7.38 (s, 1H, olefinic H), 7.40 (m, 3H, H-2,5,6, arylidene ring), 7.66 (m, 2H, H-3,5, phenyl). ^{13}C-NMR ($CDCl_3$) δ 169.1 (C-1), 125.8 (C-2), 118.1 (C-3), 128.7 (C-4,5′), 97.3 (C-5), 129.1 (C-6,1′), 118.6 (C-7,11), 130.3 (C-8,10), 156.6 (C-9), 153.4 (C-12), 132.5 (C-13,17), 119.3 (C-14,16), 124.2 (C-15), 127.6 (C-2′), 158.3 (C-3′), 129.9 (C-4′), 124.5 (C-6′), 20.2 (–OAc). MS: *m*/*z* 398 (M^+), 197, 77. Anal. $C_{25}H_{18}O_5$ (C, H).

*4.1.2.8. 2-(4-Chlorobenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**8**).* Yield: 67%, m.p. 156–158 °C. ^{1}H-NMR ($CDCl_3$) δ 6.80 (s, 1H, butenolide ring), 7.04 and 7.76 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.06 (m, 2H, H-2,6, phenyl), 7.19 (m, 1H, H-4, phenyl), 7.34 (s, 1H, olefinic H), 7.40 (m, 2H, H-3,5, phenyl), 7.42 and 7.56 (d, each, 2 × A_2B_2, arylidene ring). ^{13}C-NMR ($CDCl_3$) δ 170.3 (C-1), 125.8 (C-2), 118.8 (C-3), 128.3 (C-4), 98.4 (C-5), 129.2 (C-6,1′), 118.2 (C-7,11), 130.1 (C-8,10), 156.4 (C-9), 153.3 (C-12), 132.7 (C-13,17), 119.5 (C-14,16), 124.5 (C-15), 126.8 (C-2′,6′), 129.6 (C-3′,5′), 135.6 (C-4′). MS: *m*/*z* 374 (M^+), 197, 77. Anal. $C_{23}H_{15}O_3Cl$ (C, H, Cl).

*4.1.2.9. 2-(2,4-Dichlorobenzylidene)-4-(4-phenoxy-phenyl)-but-3-en-4-olides (**9**).* Yield: 56%, m.p. 198–200 °C. ^{1}H-NMR ($CDCl_3$) δ 6.81 (s, 1H, butenolide ring), 7.08 and 7.64 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.4 (m, 5H, phenyl), 7.68 (m, 4H, H-3,5,6, arylidene ring + olefinic H). ^{13}C-NMR ($CDCl_3$) δ 170.7 (C-1), 125.7 (C-2), 119.2 (C-3), 128.6 (C-4), 98.9 (C-5), 129.4 (C-6,5′), 118.1 (C-7,11), 130.1 (C-8,10), 155.9 (C-9), 153.5 (C-12), 132.3 (C-13,17), 119.5 (C-14,16), 124.3 (C-15), 129.9 (C-1′), 134.9 (C-2′), 127.1 (C-3′), 136.6 (C-4′), 126.9 (C-6′). MS: *m*/*z* 409 (M^+), 374, 197, 77. Anal. $C_{23}H_{14}O_3Cl_2$ (C, H, Cl).

*4.1.2.10. 2-(2,6-Dichlorobenzylidene)-4-(4-phenoxy-phenyl)-but-3-en-4-olides (**10**).* Yield: 66%, m.p. 106 °C. ^{1}H-NMR ($CDCl_3$) δ 6.21 (s, 1H, butenolide ring), 7.0 and 7.66 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.04 (m, 2H, H-3,5, arylidene ring), 7.18 (t, 1H, H-4, phenyl), 7.27 (m, 1H, H-4, arylidene ring), 7.28 (m, 2H, H-2,6, phenyl), 7.42 (s, 1H, olefinic H). ^{13}C-NMR ($CDCl_3$) δ 171.3 (C-1), 127.5 (C-2), 118.7 (C-3), 128.8 (C-4,5′), 98.3 (C-5), 129.2 (C-6), 118.3 (C-7,11), 130.6 (C-8,10), 156.4 (C-9), 153.1 (C-12), 132.8 (C-13,17), 119.6 (C-14,16), 124.8 (C-15), 129.8 (C-1′), 135.1 (C-2′), 128.2 (C-3′), 130.3 (C-4′), 136.9 (C-6′). MS: *m*/*z* 409 (M^+), 374, 197, 77. Anal. $C_{23}H_{14}O_3Cl_2$ (C, H, Cl).

*4.1.2.11. 2-(3-Nitrobenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**11**).* Yield: 62%, m.p. 194 °C. ^{1}H-NMR ($CDCl_3$) δ 6.04 (s, 1H, butenolide ring), 7.08 and 7.54 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.09 (m, 2H, H-2,6, phenyl), 7.21 (t, 1H, H-4, phenyl), 7.38 (s, 1H, olefinic H), 7.41 (m, 1H, H-5, arylidene ring), 7.66 (m, 2H, H-3,5, phenyl), 7.88 (dd, 1H, H-6, arylidene ring), 8.24 (dd, 1H, H-4, arylidene ring), 8.40 (d, 1H, H-2, arylidene ring). ^{13}C-NMR ($CDCl_3$) δ 166.5 (C-1), 125.9 (C-2), 118.1 (C-3), 129.1 (C-4), 98.3 (C-5),

129.5 (C-6,1′), 117.8 (C-7,11), 130.3 (C-8,10), 157.2 (C-9), 152.4 (C-12), 133.7 (C-13,17), 119.8 (C-14,16), 123.9 (C-15,6′), 127.2 (C-2′), 131.2 (C-3′), 127.6 (C-4′), 128.6 (C-5′). MS: *m/z* 385 (M^+), 197, 77. Anal. $C_{23}H_{15}O_5N$ (C, H, N).

*4.1.2.12. 2-(4-Acetoxy-3-methoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**12**).* Yield: 60%, m.p. 204 °C. ^{1}H-NMR ($CDCl_3$) δ 2.34 (s, 3H, $OCOCH_3$), 3.90 (s, 3H, OCH_3), 6.78 (s, 1H, butenolide ring), 7.04 and 7.71 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.06 (d, 1H, H-5, arylidene ring), 7.14 (m, 2H, H-2,6, phenyl), 7.19 (t, 1H, H-4, phenyl), 7.26 (m, 2H, H-2,6, arylidene ring), 7.38 (m, 2H, H-3,5, phenyl), 7.39 (s, 1H, olefinic H). ^{13}C-NMR ($CDCl_3$) δ 171.3 (C-1), 126.1 (C-2), 119.5 (C-3), 128.3 (C-4), 98.5 (C-5), 129.2 (C-6,4′), 118.3 (C-7,11), 130.7 (C-8,10), 156.4 (C-9), 153.4 (C-12), 132.3 (C-13,17), 119.8 (C-14,16), 124.8 (C-15), 129.9 (C-1′), 127.6 (C-2′), 133.6 (C-3′), 156.1 (C-5′), 125.6 (C-6′), 20.6 (OAc), 55.9 (–OCH_3). MS: *m/z* 428 (M^+), 386, 197, 77. Anal. $C_{26}H_{20}O_6$ (C, H).

*4.1.2.13. 2-(4-Acetoxy-3-ethoxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**13**).* Yield: 62%, m.p. 168 °C. ^{1}H-NMR ($CDCl_3$) δ 1.45 (t, 3H, $OCH_2\mathit{CH_3}$), 2.34 (s, 3H, $OCOCH_3$), 4.11 (q, 2H, $O\mathit{CH_2}CH_3$), 6.90 (s, 1H, butenolide ring), 7.15 (m, 2H, H-5,6, arylidene ring), 7.29 (m, 3H, H-2,6, phenyl + H-2 arylidene ring), 7.41 (s, 1H, olefinic H), 7.47 (m, 1H, H-4, phenyl), 7.64 (m, 2H, H-3,5, phenyl), 7.68 and 7.82 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl). ^{13}C-NMR ($CDCl_3$) δ 173.5 (C-1), 125.7 (C-2), 118.8 (C-3), 128.4 (C-4), 100.1 (C-5), 129.1 (C-6,4′), 118.4 (C-7,11), 130.5 (C-8,10), 155.8 (C-9), 153.2 (C-12), 133.3 (C-13,17), 119.5 (C-14,16), 124.8 (C-15), 129.6 (C-1′), 127.9 (C-2′), 132.8 (C-3′), 157.7 (C-5′), 126.2 (C-6′), 20.2 (OAc), 56.3 (–OC_2H_5). MS: *m/z* 442 (M^+), 197, 77. Anal. $C_{27}H_{22}O_6$ (C, H).

*4.1.2.14. 2-(2-Thienylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**14**).* Yield: 61%, m.p. 138 °C. ^{1}H-NMR ($CDCl_3$) δ 6.83 (s, 1H, butenolide ring), 7.04 and 7.70 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.05 (m, 2H, H-2,6, phenyl), 7.15 (m, 1H, H-5, thienyl), 7.18 (m, 1H, H-4, phenyl), 7.39 (m, 2H, H-3,5, phenyl), 7.40 (s, 1H, olefinic H), 7.56 (m, 1H, H-3, thienyl), 7.59 (m, 1H, H-4, thienyl). ^{13}C-NMR ($CDCl_3$) δ 170.5 (C-1), 125.9 (C-2), 117.7 (C-3), 128.7 (C-4), 96.7 (C-5), 129.3 (C-6), 118.2 (C-7,11), 130.6 (C-8,10), 157.3 (C-9), 154.2 (C-12), 131.9 (C-13,17), 119.7 (C-14,16), 124.9 (C-15), 130.1 (C-1′), 118.7 (C-2′,3′), 128.3 (C-4′). MS: *m/z* 346 (M^+), 197, 77. Anal. $C_{21}H_{14}O_3S$ (C, H, S).

*4.1.2.15. 2-(3,4-Methylenedioxybenzylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**15**).* Yield: 58%, m.p. 146 °C. ^{1}H-NMR ($CDCl_3$) δ 6.07 (s, 2H, OCH_2O), 6.80 (s, 1H, butenolide ring), 6.90 (d, 1H, H-5, arylidene ring), 7.04 and 7.1 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.09 (d, 1H, H-2, arylidene ring), 7.15 (m, 3H, H-2,6 phenyl + H-6 arylidene ring), 7.18 (m, 1H, H-4, phenyl), 7.31 (s, 1H, olefinic H), 7.40 (m, 2H, H-3,5, phenyl). ^{13}C-NMR ($CDCl_3$) δ 173.6 (C-1), 126.1 (C-2), 119.3 (C-3), 128.8 (C-4), 98.1 (C-5), 129.1 (C-6,1′), 118.3 (C-7,11), 130.6 (C-8,10), 156.4 (C-9), 153.4 (C-12), 132.8 (C-13,17), 119.8 (C-14,16), 124.5 (C-15), 126.7 (C-2′), 135.4 (C-3′), 130.3 (C-4′), 129.7 (C-5′), 127.1 (C-6′), 43.6 (–CH_2–). MS: *m/z* 384 (M^+), 197, 77. Anal. $C_{24}H_{16}O_5$ (C, H).

*4.1.2.16. 2-(9-Anthrylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**16**).* Yield: 58%, m.p. 128 °C. ^{1}H-NMR ($CDCl_3$) δ 5.96 (s, 1H, butenolide ring), 6.94 and 7.56 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.0 (m, 2H, H-2,6, phenyl), 7.15 (m, 1H, H-4, phenyl), 7.33 (m, 2H, H-3,5, phenyl), 7.51 (m, 4H, H-2,3,6,7, anthryl), 8.05 (m, 4H, H-1,4,5,8, anthryl), 8.36 (s, 1H, olefinic H), 8.4 (s, 1H, H-10, anthryl). ^{13}C-NMR ($CDCl_3$) δ 174.3 (C-1), 125.8 (C-2), 118.9 (C-3), 128.1 (C-4), 99.7 (C-5), 129.3 (C-6,1′), 118.2 (C-7,11), 130.1 (C-8,10), 154.9 (C-9), 153.4 (C-12), 131.8 (C-13,17), 119.6 (C-14,16), 125.1 (C-15), 128.9 (C-2′,14′), 119.7 (C-3′,13′), 127.2 (C-4′,5′,11′,12′), 126.2 (C-6′,8′,10′), 125.8 (C-7′,9′). MS: *m/z* 440 (M^+), 197, 177, 77. Anal. $C_{31}H_{20}O_3$ (C, H).

*4.1.2.17. 2-(Cinnamoylidene)-4-(4-phenoxy-phenyl)but-3-en-4-olides (**17**).* Yield: 54%, m.p. 166 °C. ^{1}H-NMR ($CDCl_3$) δ 6.48 (s, 1H, butenolide ring), 7.06 and 7.70 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.16 (m, 2H, H-2,6, phenyl), 7.19 (m, 1H, H-4, phenyl), 7.43 (m, 2H, H-3,5, phenyl), 7.65 (m, 7H, arylidene ring + 2 olefinic protons). ^{13}C-NMR ($CDCl_3$) δ 172.0 (C-1), 125.5 (C-2), 118.5 (C-3), 128.7 (C-4), 98.6 (C-5), 129.1 (C-6), 118.3 (C-7,11), 130.1 (C-8,10), 154.7 (C-9), 153.1 (C-12), 131.9 (C-13,17), 120.2 (C-14,16), 124.3 (C-15), 100.3 (C-18), 129.8 (C-1′), 127.3 (C-2′,6′), 129.4 (C-3′,5′), 131.2 (C-4′). MS: *m/z* 366 (M^+), 197, 77. Anal. $C_{25}H_{18}O_3$ (C, H).

*4.1.3. General procedure for the synthesis of 3-arylidene-5-(4-phenoxy-phenyl)-2(3H)-pyrrolones (**18**–**23**)*

Dry ammonia gas was passed into anhydrous ethanolic solution of butenolide (1.0 gm) for 1 h at room temperature, ethanol was distilled off under reduced pressure and the solid mass so obtained, was crystallized from methanol/acetone to give **18**–**23**.

*4.1.3.1. 3-Benzylidene-5-(4-phenoxy-phenyl)-2(3H)-pyrrolones (**18**).* Yield: 65%, m.p. 164–166 °C. ^{1}H-NMR ($CDCl_3$) δ 6.99 (s, 1H, pyrrolone ring), 7.04 and 7.70 (d, each, $2 \times A_2B_2$, *p*-disubstituted phenyl), 7.05 (m, 2H, H-2,6, phenyl), 7.18 (m, 1H, H-4, phenyl), 7.39 (m, 2H, H-3,5, phenyl), 7.46 (m, 3H, H-3,4,5, arylidene ring), 7.62 (m, 2H, H-2,6, arylidene ring), 7.63 (s, 1H, olefinic), 8.02 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 167.8 (C-1), 125.5 (C-2), 118.3 (C-3), 127.8 (C-4), 98.7 (C-5), 129.4 (C-6,1′), 119.1 (C-7,11), 130.2 (C-8,10), 157.5 (C-9), 150.8 (C-12), 134.1 (C-13,17), 119.5 (C-14,16), 124.4 (C-15), 127.1 (C-2′,6′), 129.8 (C-3′,5′), 131.4 (C-4′). MS: *m/z* 339 (M^+), 153, 77. Anal. $C_{23}H_{17}NO_2$ (C, H, N).

*4.1.3.2. 3-(2-Hydroxybenzylidene)-5-(4-phenoxy-phenyl)-2(3H)-pyrrolones (**19**).* Yield: 62%, m.p. 210 °C. ^{1}H-NMR ($CDCl_3$) δ 6.88 (s, 1H, pyrrolone ring), 6.91 (m, 2H, H-3,5, arylidene ring), 7.03 and 7.71 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.06 (m, 2H, H-2,6, phenyl), 7.16 (m, 1H, H-4, phenyl), 7.20 (t, 1H, H-4, arylidene ring), 7.20 (t, 1H, H-4, arylidene ring), 7.39 (m, 2H, H-3,5, phenyl), 7.46 (m, 3H, H-3,4,5, arylidene ring), 7.62 (m, 2H, H-2,6, arylidene ring), 7.63 (s, 1H, olefinic), 8.02 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 166.4 (C-1), 126.1 (C-2), 117.9 (C-3), 128.5 (C-4,5′), 96.9 (C-5), 129.1 (C-6,3′), 117.6 (C-7,11), 130.1 (C-8,10), 155.4 (C-9), 152.1 (C-12), 132.6 (C-13,17), 119.8 (C-14,16), 124.2 (C-15), 127.5 (C-1′), 158.3 (C-2′), 131.1 (C-4′), 123.6 (C-6′). MS: *m/z* 354 (M-1), 196, 77. Anal. $C_{23}H_{17}NO_3$ (C, H, N).

*4.1.3.3. 3-(3-Hydroxybenzylidene)-5-(4-phenoxy-phenyl)-2(3H)-pyrrolones (**20**).* Yield: 65%, m.p. 202 °C. ^{1}H-NMR ($CDCl_3$) δ 6.91 (s, 1H, pyrrolone ring), 7.04 and 7.68 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.20 (m, 3H, H-2,4,6, phenyl), 7.21 (m, 1H, H-5, arylidene ring), 7.37 (m, 2H, H-3,5, phenyl), 7.92 (dd, 1H, H-6, arylidene ring), 8.05 (m, 1H, H-4, arylidene ring), 8.18 (d, 1H, H-2, arylidene ring), 7.74 (s, 1H, olefinic), 8.63 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 170.3 (C-1), 125.2 (C-2), 118.8 (C-3), 128.9 (C-4), 99.1 (C-5), 128.5 (C-6,5′), 118.2 (C-7,11), 131.4 (C-8,10), 155.8 (C-9), 152.7 (C-12), 132.1 (C-13,17), 119.8 (C-14,16), 125.2 (C-15), 129.4 (C-1′), 127.9 (C-2′), 158.6 (C-3′), 130.3 (C-4′), 124.1 (C-6′), MS: *m/z* 354 (M-1), 196, 77. Anal. $C_{23}H_{17}NO_3$ (C, H, N).

*4.1.3.4. 3-(4-Chlorobenzylidene-5-(4-phenoxy-phenyl)-2(3H)-pyrrolones (**21**).* Yield: 68%, m.p. 240 °C. ^{1}H-NMR ($CDCl_3$) δ 6.42 (s, 1H, pyrrolone ring), 7.06 and 7.58 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.20 (m, 3H, H-2,4,6, phenyl), 7.32 (s, 1H, olefinic), 7.37 (m, 2H, H-3,5, phenyl), 7.41 and 7.50 (d, each, 2 × A_2B_2, arylidene ring), 8.2 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 172.0 (C-1), 125.9 (C-2), 117.7 (C-3), 127.6 (C-4), 97.8 (C-5), 129.1 (C-6,1′), 118.3 (C-7,11), 130.2 (C-8,10), 155.7 (C-9), 154.8 (C-12), 131.9 (C-13,17), 118.6 (C-14,16), 124.1 (C-15), 126.3 (C-2′,6′), 129.4 (C-3′,5′), 136.2 (C-4′). MS: *m/z* 373 (M^+), 196, 77. Anal. $C_{23}H_{16}NO_2Cl$ (C, H, N, Cl).

*4.1.3.5. 3-(3-Nitrobenzylidene-5-(4-phenoxy-phenyl)-2(3H)-pyrrolones (**22**).* Yield: 66%, m.p. 226 °C. ^{1}H-NMR ($CDCl_3$) δ 6.44 (s, 1H, pyrrolone ring), 7.08 and 7.55 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.19 (m, 1H, H-5, phenyl), 7.40 (m, 3H, H-2,4,6, phenyl), 7.50 (s, 1H, olefinic), 7.62 (m, 2H, H-3,5, phenyl), 7.90 (dd, 1H, H-6, arylidene ring), 8.20 (m, 1H, H-4, arylidene ring), 8.51 (d, 1H, H-2, arylidene ring), 8.60 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 174.2 (C-1), 125.7 (C-2), 118.1 (C-3), 129.7 (C-4), 98.0 (C-5), 129.2 (C-6,1′), 117.8 (C-7,11), 130.5 (C-8,10), 157.1 (C-9), 151.4 (C-12), 134.2 (C-13,17), 119.8 (C-14,16), 123.5 (C-15), 127.8 (C-2′), 131.5 (C-3′), 127.2 (C-4′), 128.2 (C-5′), 124.2 (C-6′). MS: *m/z* 383 (M-1), 337, 196, 77. Anal. $C_{23}H_{17}N_2O_4$ (C, H, N).

*4.1.3.6. 3-(2-Thienylidene-5-(4-phenoxy-phenyl)-2(3H)-pyrrolones (**23**).* Yield: 68%, m.p. 216 °C. ^{1}H-NMR ($CDCl_3$) δ 6.97 (s, 1H, pyrrolone ring), 7.15 (m, 2H, H-3,4, thienyl), 7.47 and 7.85 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.40 (m, 2H, H-3,5, phenyl), 7.65 (m, 4H, H-2,4,6 phenyl + H-5 thienyl), 7.68 (s, 1H, olefinic), 8.18 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 168.5 (C-1), 126.1 (C-2), 118.3 (C-3), 128.5 (C-4,4′), 96.7 (C-5), 129.3 (C-6), 118.8 (C-7,11), 130.1 (C-8,10), 156.9 (C-9), 153.2 (C-12), 132.1 (C-13,17), 119.6 (C-14,16), 124.7 (C-15), 130.9 (C-1′), 119.2 (C-2′,3′). MS: *m/z* 345 (M^+), 196, 77. Anal. $C_{21}H_{15}NO_2S$ (C, H, N, S).

*4.1.4. General procedure for the synthesis 3-arylidene-5-(4-phenoxy-phenyl)-1-benzyl-2(3H)-pyrrolones (**24**–**29**)*

Synthesis of these compounds involved the following two steps:

- 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 a solid mass so obtained was washed with petroleum ether and dried. The compound obtained was used without crystallization.
- 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 a solid mass so obtained was collected, washed with water and crystallized from methanol to give **24**–**29**.

*4.1.4.1. 3-(4-Chlorobenzylidene)-5-(4-phenoxy-phenyl)-1-benzyl-2(3H)-pyrrolones (**24**).* Yield: 48%, m.p. 108 °C. ^{1}H-NMR ($CDCl_3$) δ 4.85 (s, 2H, CH_2), 6.17 (s, 1H, pyrrolone ring), 6.96 and 7.59 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.20 and 7.43 (d, each, 2 × A_2B_2, arylidene ring), 7.25 (m, 6H, H-3,4,5 phenyl + H-3,4,5 benzyl), 7.39 (s, 1H, olefinic), 7.40 (m, 4H, H-2,6 phenyl + H-2,6 benzyl). ^{13}C-NMR ($CDCl_3$) δ 175.5 (C-1), 126.4 (C-2), 116.8 (C-3), 127.5 (C-4), 99.2 (C-5), 129.5 (C-6,1′), 118.8 (C-7,11,14,16), 130.7 (C-8,10), 155.1 (C-9), 153.7 (C-12), 132.3 (C-13,17), 123.6 (C-15), 126.9 (C-2′,6′), 129.1 (C-3′,5′), 133.6 (C-4′), 44.6 (C-1″), 132.6 (C-2″), 127.1 (C-3″,7″), 128.8 (C-4″), 119.3 (C-5″), 128.2 (C-6″). MS: *m/z* 463 (M^+), 196, 91, 77. Anal. $C_{30}H_{22}NO_2Cl$ (C, H, N, Cl).

*4.1.4.2. 3-(3,4-Dimethoxybenzylidene)-5-(4-phenoxy-phenyl)-1-benzyl-2(3H)-pyrrolones (**25**).* Yield: 65%, m.p. 132 °C. ^{1}H-NMR ($CDCl_3$) δ 3.90 (s, 6H, 2 × –OCH_3), 4.89 (s, 2H, CH_2), 6.20 (s, 1H, pyrrolone ring), 6.92 (d, 1H, H-5, arylidene ring), 6.93 and 7.61 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.02–7.32 (m, 7H, 5H of benzyl + H-2,6 arylidene ring), 7.46 (m, 3H, H-3,4,5, phenyl), 7.49 (s, 1H, olefinic), 7.59 (m, 2H, H-2,6, phenyl). ^{13}C-NMR ($CDCl_3$) δ 170.8 (C-1), 126.2 (C-2), 119.1 (C-3,5″), 128.3 (C-4,4″), 97.6 (C-5), 128.7 (C-6,6″), 118.6 (C-7,11), 130.8 (C-8,10), 155.1 (C-9), 152.5 (C-12), 133.2 (C-13,17), 119.5 (C-14,16), 125.1 (C-15), 129.1 (C-1′), 127.1 (C-2′,6′), 134.8 (C-3′), 130.5 (C-4′), 129.6 (C-5′), 44.2 (C-1″), 132.6 (C-2″), 127.4 (C-3″,7″), 53.9

(–OCH_3). MS: *m/z* 489 (M^+), 196, 91, 77. Anal. $C_{32}H_{27}NO_4$ (C, H, N).

*4.1.4.3. 3-(3,4,5-Trimethoxybenzylidene)-5-(4-phenoxy-phenyl)-1-benzyl-2(3H)-pyrrolones (**26**).* Yield: 62%, m.p. 142 °C. ^{1}H-NMR ($CDCl_3$) δ 3.90 (s, 9H, 3×–OCH_3), 4.88 (s, 2H, CH_2), 6.23 (s, 1H, pyrrolone ring), 6.90 (s, 2H, H-2,6, arylidene ring), 6.87 and 7.60 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.11 (m, 2H, H-2,6, benzyl), 7.27 (m, 4H, H-3,4,5 phenyl + 1H olefinic), 7.44 (m, 3H, H-3,4,5, phenyl), 7.60 (m, 2H, H-2,6, phenyl). ^{13}C-NMR ($CDCl_3$) δ 168.5 (C-1), 127.8 (C-2), 118.1 (C-3), 128.6 (C-4), 100.1 (C-5), 128.7 (C-6), 118.8 (C-7,11), 130.7 (C-8,10,2′,6′), 155.2 (C-9), 154.6 (C-12), 132.5 (C-13,17), 119.8 (C-14,16), 124.3 (C-15), 129.3 (C-1′), 134.4 (C-3′), 135.1 (C-4′), 130.3 (C-5′), 45.4 (C-1″), 131.8 (C-2″), 127.3 (C-3″,7″), 128.1 (C-4″), 119.4 (C-5″), 128.7 (C-6″), 54.3 (–OCH_3). MS: *m/z* 519 (M^+), 196, 91, 77. Anal. $C_{33}H_{29}NO_5$ (C, H, N).

*4.1.4.4. 3-(3,4-Methylenedioxybenzylidene)-5-(4-phenoxy-phenyl)-1-benzyl-2(3H)-pyrrolones (**27**).* Yield: 60%, m.p. 170–172 °C. ^{1}H-NMR ($CDCl_3$) δ 4.85 (s, 2H, CH_2), 6.02 (s, 2H, –OCH_2O–), 6.10 (s, 1H, pyrrolone ring), 6.85 (d, 1H, H-5, arylidene ring), 6.92 and 7.26 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.10 (m, 7H, 5H, phenyl + H-2,6 arylidene), 7.25 (m, 5H, benzyl), 7.60 (s, 1H, olefinic). ^{13}C-NMR ($CDCl_3$) δ 169.5 (C-1), 126.1 (C-2), 119.8 (C-3,5″), 128.2 (C-4,4″), 97.8 (C-5), 129.5 (C-6,1′), 118.6 (C-7,11), 130.7 (C-8,10), 155.8 (C-9), 153.7 (C-12), 132.4 (C-13,17), 119.2 (C-14,16), 124.9 (C-15), 126.8 (C-2′), 134.8 (C-3′), 130.1 (C-4′), 129.2 (C-5′), 127.3 (C-6′,3″,7″), 43.3 (C-1″), 132.1 (C-2″), 128.6 (C-6″), 45.6 (–CH_2–). MS: *m/z* 473 (M^+), 196, 91, 77. Anal. $C_{31}H_{23}NO_4$ (C, H, N).

*4.1.4.5. 3-(3-Nitrobenzylidene)-5-(4-phenoxy-phenyl)-1-benzyl-2(3H)-pyrrolones (**28**).* Yield: 63%, m.p. 116 °C. ^{1}H-NMR ($CDCl_3$) δ 4.87 (s, 2H, CH_2), 6.20 (s, 1H, pyrrolone ring), 6.97 and 7.28 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.05 (m, 4H, H-2,6 phenyl + H-2,6 benzyl), 7.25 (m, 5H, H-3,5 phenyl + H-3,4,5 benzyl), 7.47 (s, 1H, olefinic), 7.60 (t, 1H, H-5, arylidene), 7.9 (d, 1H, H-4, arylidene), 8.2 (dd, 1H, H-6, arylidene), 8.5 (t, 1H, H-2, arylidene). ^{13}C-NMR ($CDCl_3$) δ 168.1 (C-1), 126.5 (C-2), 118.9 (C-3,5″), 129.2 (C-4,4″), 99.6 (C-5), 129.6 (C-6,1′), 117.9 (C-7,11), 130.5 (C-8,10), 156.4 (C-9), 152.7 (C-12), 134.8 (C-13,17), 119.5 (C-14,16), 124.4 (C-15), 127.6 (C-2′,4′), 131.7 (C-3′,2″), 128.6 (C-5′,6″), 123.5 (C-6′), 44.8 (C-1″), 127.3 (C-3″,7″). MS: *m/z* 474 (M^+), 446, 428, 383, 196, 91. Anal. $C_{30}H_{22}N_2O_4$ (C, H, N).

*4.1.4.6. 3-(2-Thienylidene)-5-(4-phenoxy-phenyl)-1-benzyl-2(3H)-pyrrolones (**29**).* Yield: 58%, m.p. 156 °C. ^{1}H-NMR ($CDCl_3$) δ 6.97 (s, 1H, pyrrolone ring), 7.15 (m, 2H, H-3,4, thienyl), 7.47 and 7.85 (d, each, 2 × A_2B_2, *p*-disubstituted phenyl), 7.40 (m, 2H, H-3,5, phenyl), 7.65 (m, 4H, H-2,4,6 phenyl + H-5 thienyl), 7.68 (s, 1H, olefinic), 8.18 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ 169.5 (C-1), 126.3 (C-2), 118.3 (C-3), 128.5 (C-4,4″), 97.3 (C-5), 129.6 (C-6), 118.8 (C-7,11), 131.1 (C-8,10), 156.6 (C-9), 153.8 (C-12), 132.3 (C-13,17), 119.3 (C-14,16), 124.2 (C-15), 130.2 (C-1′), 117.5 (C-2′,3′), 128.1 (C-4′,6″), 44.6 (C-1″), 130.8 (C-2″), 127.9 (C-3″,7″), 119.7 (C-5″). MS: *m/z* 435 (M^+), 196, 77. Anal. $C_{28}H_{21}NO_2S$ (C, H, N, S).

4.2. Pharmacology

4.2.1. Anti-inflammatory activity

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. Animals were divided in groups with six animals in each group. The dose administered was 20 mg/kg body weight. Stock solution containing 4 mg/ml of the drug was prepared and administered orally 0.5 ml/100 g body weight of the animal. One group was kept as a control and the animals of 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 plethysmograph. The percentage inhibition of inflammation was calculated by applying Newbould formula [19]. Indomethacin was used as standard drug for comparison.

4.2.2. Analgesic activity

Analgesic activity was carried out by acetic acid induced writhing method [20] in swiss albino mice (25–30 g) of either sex. A 1% aqueous acetic acid solution (i.p. injection in a volume of 0.1 ml) was used as writhing induced agent. In each group six mice were kept. Mice were kept individually in the test cage, before acetic acid injection and habituated for 30 min. Screening of analgesic activity was performed after p.o. administration of test drugs at a dose of 20 mg/kg. The compounds, which exhibited good anti-inflammatory activity comparable to that of indomethacin, were screened for analgesic activity. All compounds were dissolved in 1% CMC solution. One group was kept as control and received p.o. administration of 1% CMC. Ibuprofen was used as reference drug. After 1 h of drug administration 0.10 ml of 1% acetic acid solution was given to mice intraperitoneally. Stretching movements consisting of arching of the back, elongation of body and extension of hind limbs were counted for 5–15 min of acetic acid injection. The analgesic activity was expressed in terms of % inhibition. % Analgesic activity = (n – n'/n) × 100 where n = mean number of writhes of control group and n' = mean number of writhes of test group. Statistical analysis was done using Student's t-test. The percent protection in mice brought about by administration of the drugs is shown in Table 2.

4.2.3. Acute ulcerogenesis

Acute ulcerogenesis test was done according to Cioli et al. [21]. Albino rats (150–200 g) were divided into different groups consisting of six animals in each group. Ulcerogenic

activity evaluated after p.o. administration of test compounds or ibuprofen at the dose of 50 mg/kg. Control rats received p.o. administration of vehicle (suspension of 1% methyl cellulose). Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The gastric mucosa of the rats was examined by means of a 4× binocular magnifier. The lesions were counted and divided into large (greater than 2 mm in diameter), small (1–2 mm) and punctiform (less than 1 mm). For each stomach the severity of mucosal damage was assessed according to the following scoring system: 0—no lesions or upto five punctiform lesions; 1—more than five punctiform lesions; 2—one to five small ulcers; 3—more than five small ulcers or one large ulcer; 4—more than one large ulcer.

The mean score of each treated group minus the mean score of the control group was considered the 'severity index' of gastric damage.

4.2.4. Antimicrobial activity

The bacterial strains gram positive (*S. aureus*; NCTC-6571), gram negative (*E. coli*; ATCC-25922) and yeast (*C. albicans*) were used. The test was carried out according to the turbidity method [22]. A solution of the compounds was prepared in dimethylformamide (DMF) 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 37° for 24 h and examined for turbidity. The tube with highest dilution showing no turbidity was MIC.

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