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Synthesis, reactions and biological activity of 3-arylidene-5-(4-methylphenyl)-2(3*H*)-furanones≠

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Abstract: 3-Arylidene-5-(4-methylphenyl)-2(3*H*)-furanones **2a**–**m** were prepared from 3-(4-methyl-benzoyl)propanoic acid **1** and several aromatic aldehydes. Some of the selected furanones were reacted with ammonia gas and benzylamine to give corresponding 3-arylidene-1,3-dihydro-5-(4-methylphenyl)-2*H*-pyrrol-2-ones **3a**–**h** and 3-arylidene-1-benzyl-1,3-dihydro-5-(4-methylphenyl)-2*H*--pyrrol-2-ones **4a**–**f**, respectively, which were characterized on the basis of IR, ^{1}H-NMR, mass spectral data and elemental analysis results. These compounds were tested for their anti-inflammatory and antibacterial activities. The compounds, which showed significant anti-inflammatory activity, were further screened for their analgesic and ulcerogenic activities. Three new compounds (**2e**, **2h** and **4d**), out of twenty-seven 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. The antibacterial activity is expressed as the corresponding *MIC* values.

Keywords: furanone; pyrrolone; anti-inflammatory; analgesic; antibacterial activity.

INTRODUCTION

The chemistry of furanones has attracted more attention in the last few decades due to their reactivity and novel biological activities. Butenolides, a family of α,β-unsaturated lactones, also known as furanones, are ubiquitous chemical moieties found in many natural products. The furanone system, as present in many natural compounds, is associated with important biological actions.[1] Even the simpler butyrolactone, 3,3-diethylbutyrolactone, shows anticonvulsant activity.[2] While the furanones exhibit antibiotic activity,[3] they have been reported[4–8] to also have anti-inflammatory, analgesic, anthelmintic, antiviral and anticancer properties. The reactivity of the γ-lactone ring present in furanone derivatives has

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been further exploited for the synthesis of nitrogen heterocycles of potential pharmacological interest.[9,10]

Herein, the syntheses and reactions of 3-arylidene-5-(4-methylphenyl)-2(3*H*)--furanones following the literature procedure[10,11] with a slight modification and a study of biological activities of the resulting products are reported. Previously, the anti-inflammatory activity of a number of 2-arylidene-4-substituted phenyl--but-3-en-4-olides was studied and the results were encouraging.[8,12]

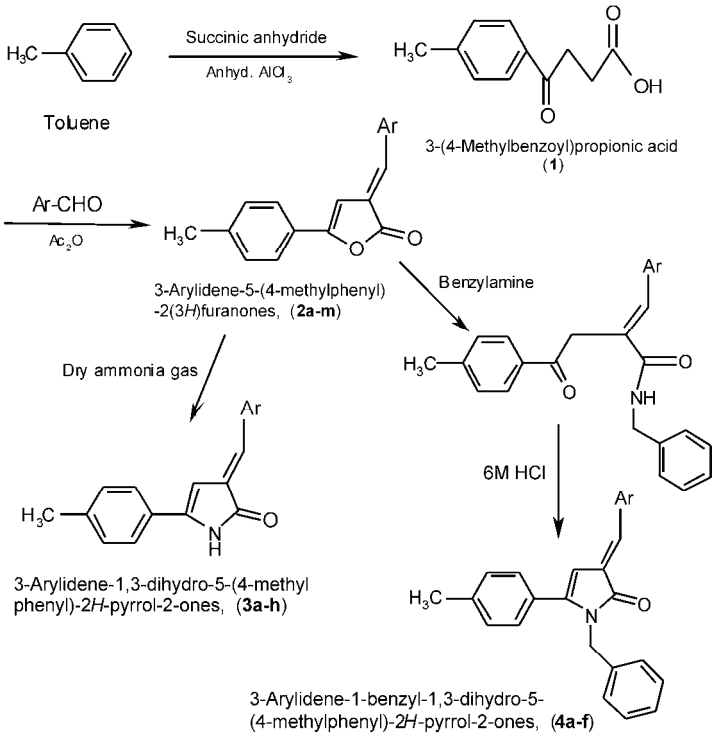
3-(4-Methylbenzoyl)propanoic acid **1** is an example of the aroylpropanoic acid class of non-steroidal anti-inflammatory drugs (NSAIDs). Aroylpropanoic acids are good anti-inflammatory agents; however, they have been reported[13–15] to have gastrointestinal side effects, as do other commonly used NSAIDs. In view of these observations, it was therefore considered worthwhile to study various furanone derivatives of 3-(4-methylbenzoyl)propanoic acid for their anti-inflammatory, analgesic and ulcerogenic actions. These furanones were further exploited for the synthesis of nitrogen heterocycles (pyrrolone and benzylpyrrolone). In view of the reported antimicrobial activity of furanones and pyrrolones, these compounds were also screened for their antibacterial activity with encouraging results.

RESULTS AND DISCUSSION

Chemistry

Overall, twenty-seven new compounds (**2a**–**m**, **3a**–**h** and **4a**–**f**) were prepared as outlined in Scheme 1. The 3-arylidene-5-(4-methylphenyl)-2(3*H*)-furanones **2a**–**m** were synthesized from 3-(4-methylbenzoyl)propanoic acid **1** by reacting with aromatic aldehydes in the presence of triethylamine in acetic anhydride following modified Perkin reaction conditions. The required 3-(4-methylbenzoyl)propanoic acid was prepared by condensing dry toluene with succinic anhydride in presence of anhydrous aluminum chloride, following Friedel-Crafts acylation reaction conditions. 3-arylidene-1,3-dihydro-5-(4-methylphenyl)-2*H*-pyrrol-2-ones **3a**–**h** were prepared by reacting the furanones with ammonia gas in absolute ethanol. The 3-arylidene-1-benzyl-1,3-dihydro-5-(4-methylphenyl)-2*H*-pyrrol-2-ones **4a**–**f** were synthesized by reacting the appropriate furanone with benzylamine in dry benzene to give *N*-benzyl-γ-ketoamides, which were then cyclized in 6 M HCl to give the corresponding benzylpyrrolones. Calculations of the δ values using incremental parameters for the hydrogen (semicyclic double bond) seems to suggest the (*E*)-configuration. The structures assigned to the compounds are supported by the IR, ^{1}H-NMR and mass spectral data and elemental analysis results given below.

*3-(4-Methylbenzoyl)propanoic acid (**1**).*Yield: 65 %; m.p. 106 °C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.37 (3H, *s*, CH_3), 2.65 and 3.26 (*t*, each 2×CH_2), 7.27 and 7.85 (*d*, each A_2B_2, *p*-substituted phenyl).



Scheme 1. Protocol for synthesis of furanones (**2a-m**), pyrrolones (**3a-h**) and benzylpyrrolones (**4a-f**).

*3-Benzylidene-5-(4-methylphenyl)-2(3*H*)-furanone (**2a**)*. Yield: 72 %; m.p. 90 °C. Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.35; H, 5.34. IR (KBr, cm^{-1}): 1772 (lactone C=O), 1611 (ArC=C), 821 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.34 (3H, *s*, CH_3), 6.59 (1H, *s*, furanone ring), 7.28 (1H, *s*, olefinic H), 7.3 and 7.56 (*d*, each A_2B_2, tolyl ring), 7.42 (3H, *m*, H-3,4,5, phenyl), 7.61 (2H, *m*, H-2,6, phenyl). MS (*m*/*z*): 262 (M^+), 119, 91.

*3-(2-Methoxybenzylidene)-5-(4-methylphenyl)-2(3*H*)-furanone (**2b**)*. Yield: 74 %; m.p. 132–134 °C. Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.88; H, 5.46. IR (KBr, cm^{-1}): 1762 (lactone C=O), 1604 (ArC=C), 812 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.35 (3H, *s*, CH_3), 3.85 (3H, *s*, OCH_3), 6.83 (1H, *s*, furanone ring), 6.94 (1H, *m*, H-3, arylidene ring), 7.29 (1H, *s*, olefinic H), 7.11 and 7.53 (*d*, each A_2B_2, tolyl ring), 7.39 (2H, *m*, H-4,5, arylidene ring), 7.67 (1H, *dd*, H-6, arylidene ring). MS (*m*/*z*): 292 (M^+), 119, 91.

*3-(3-Methoxybenzylidene)-5-(4-methylphenyl)-2(3*H*)-furanone (**2c**)*. Yield: 71 %; m.p. 140–142 °C. Anal Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.75; H, 5.44. IR (KBr, cm^{-1}): 1771 (lactone C=O), 1617 (ArC=C), 822 (ArC–H). ^{1}H-NMR ($CDCl_3$, ppm): 2.37 (3H, *s*, CH_3), 3.88 (3H, *s*, OCH_3), 6.88 (1H, *s*, furanone ring), 7.13 (1H, *m*, H-4, arylidene ring), 7.49 (3H, *m*, H-2,5,6 arylidene

ring), 7.63 (1H, *s*, olefinic H), 7.26 and 7.59 (*d*, each A_2B_2, tolyl ring). MS (*m*/*z*): 292 (M^+), 119, 107, 91.

*3-(4-Methylbenzylidene)-5-(4-methylphenyl)-2(3*H*)-furanone (**2d**)*. Yield: 68 %; m.p. 122 °C. Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.36; H, 5.78. IR (KBr, cm^{-1}): 1720 (lactone C=O), 1601 (ArC=C), 806 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.37 and 2.44 (*s*, each 2×CH_3), 6.71 (1H, *s*, furanone ring), 6.97 and 7.25 (*d*, each A_2B_2, tolyl ring), 7.35 (1H, *s*, olefinic H), 7.56 (4H, *m*, H-2,3,5,6 arylidene ring). MS (*m*/*z*): 276 (M^+), 119, 91.

*5-(4-Methylphenyl)-3-(2,3,4-trimethoxybenzylidene)-2(3*H*)-furanone (**2e**)*. Yield: 65 %; m.p. 168–170 °C. Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.43; H, 5.75. IR (KBr, cm^{-1}): 1766 (lactone C=O), 1611 (ArC=C), 817 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.41 (*s*, CH_3), 3.94 (*s*, 3×OCH_3), 6.71 (1H, *s*, furanone ring), 7.16 and 7.62 (*d*, each A_2B_2, tolyl ring), 7.35 (1H, *s*, olefinic H), 7.69 (2H, *m*, H-5,6 arylidene ring). MS (*m*/*z*): 352 (M^+), 119, 91.

*3-(4-Acetoxybenzylidene)-5-(4-methylphenyl)-2(3*H*)-furanone (**2f**)*. Yield: 69 %; m.p. 156–158 °C. Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.10; H, 5.12. IR (KBr, cm^{-1}): 1729 (lactone C=O), 1612 (ArC=C), 819 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.14 (3H, *s*, $OCOCH_3$), 2.31 (3H, *s*, CH_3), 6.98 (1H, *s*, furanone ring), 7.02 (2H, *m*, H-2,6 arylidene ring), 7.28 (1H, *s*, olefinic H), 7.11 and 7.56 (*d*, each A_2B_2, tolyl ring), 7.42 and 7.63 (*d*, each A_2B_2, arylidene ring). MS (*m*/*z*): 320 (M^+), 119, 91, 77.

*3-(3-Acetoxybenzylidene)-5-(4-methylphenyl)-2(3*H*)-furanone (**2g**)*. Yield: 73 %; m.p. 144–146 °C. Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.86; H, 5.06. IR (KBr, cm^{-1}): 1733 (lactone C=O), 1609 (ArC=C), 827 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.15 (3H, *s*, $OCOCH_3$), 2.35 (3H, *s*, CH_3), 6.98 (1H, *s*, furanone ring), 7.11 (1H, *m*, H-4, arylidene ring), 7.53 (3H, *m*, H-2,5,6, arylidene ring), 7.48 (1H, *s*, olefinic H), 7.26 and 7.60 (*d*, each A_2B_2, tolyl ring). MS (*m*/*z*): 320 (M^+), 119, 91.

*3-(4-Acetoxy-3-ethoxybenzylidene)-5-(4-methylphenyl)-2(3*H*)-furanone (**2h**)*. Yield: 66 %; m.p. 132–134 °C. Anal. Calcd. for $C_{22}H_{20}O_5$: C, 72.52; H, 5.53. Found: C, 72.26; H, 5.38. IR (KBr, cm^{-1}): 1748 (lactone C=O), 1618 (ArC=C), 808 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.45 (3H, *t*, $OCH_2C\mathbf{H}_3$), 2.34 (3H, *s*, $OCOCH_3$), 2.37 (3H, *s*, CH_3), 4.08 (2H, *q*, $OC\mathbf{H}_2CH_3$), 6.94 (1H, *s*, furanone ring), 7.19 (2H, *m*, H-5,6 arylidene ring), 7.31 (1H, *m*, H-2 arylidene ring), 7.46 (1H, *s*, olefinic H), 7.17 and 7.66 (*d*, each A_2B_2, tolyl ring). MS (*m*/*z*): 364 (M^+), 119, 91.

*3-(2-Furanylmethylene)-5-(4-methylphenyl)-2(3*H*)-furanone (**2i**)*. Yield: 63 %; m.p. 160–162 °C. Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 75.93; H, 4.66. IR (KBr, cm^{-1}): 1779 (lactone C=O), 1635 (ArC=C), 820 (ArC–H). ^{1}H-NMR ($CDCl_3$ δ, ppm): 2.41 (3H, *s*, CH_3), 7.04 (1H, *s*, furanone ring), 7.43

(3H, *m*, furylidene ring), 7.61 (1H, *s*, olefinic H), 7.18 and 7.72 (*d*, each A_2B_2, tolyl ring). MS (*m*/*z*): 252 (M^+), 119, 91.

*3-(3,4-Methylenedioxybenzylidene)-5-(4-methylphenyl)-2(3*H*)-furanone* (***2j***). Yield: 67 %; m.p. 174–176 °C. Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61. Found: C, 74.38; H, 4.50. IR (KBr, cm^{-1}): 1755 (lactone C=O), 1616 (ArC=C), 814 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.35 (3H, *s*, CH_3), 4.08 (2H, *s*, OCH_2O), 6.93 (1H, *s*, furanone ring), 7.16 (2H, *m*, H-5,6 arylidene ring), 7.33 (1H, *m*, H-2 arylidene ring), 7.51 (1H, *s*, olefinic H), 7.12 and 7.67 (*d*, each A_2B_2, tolyl ring). MS (*m*/*z*): 306 (M^+), 121, 119, 91.

*3-(9-Anthrylmethylene)-5-(4-methylphenyl)-2(3*H*)-furanone* (***2k***). Yield: 72 %; m.p. 166 °C. Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.17; H, 5.01. Found: C, 85.91; H, 4.96. IR (KBr, cm^{-1}): 1778 (lactone C=O), 1611 (ArC=C), 818 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.32 (3H, *s*, CH_3), 6.67 (1H, *s*, furanone ring), 7.24 (1H, *s*, olefinic H), 7.35 and 7.66 (*d*, each A_2B_2, tolyl ring), 7.53 (4H, *m*, H-2,3,6,7, anthryl), 8.05 (4H, *m*, H-1,4,5,8, anthryl), 8.24 (1H, *s*, H-10, anthryl). MS (*m*/*z*): 362 (M^+), 181, 119.

*3-[4-(Diethylamino)benzylidene]-5-(4-methylphenyl)-2(3*H*)-furanone* (***2l***). Yield: 68 %; m.p. 126–128 °C; Anal. Calcd. for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.18; H, 7.02; N, 4.16. IR (KBr, cm^{-1}): 1751 (lactone C=O), 1608 (ArC=C), 820 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.33 (3H, *s*, CH_3), 3.35 (6H, *s*, 2×–$CH_2C\mathbf{H}_3$), 3.78 (4H, *s*, 2×–$C\mathbf{H}_2CH_3$), 7.23 (1H, *s*, furanone ring), 7.21 and 7.63 (*d*, each A_2B_2, tolyl ring), 7.32 and 7.56 (*d*, each A_2B_2, arylidene ring), 7.72 (1H, *s*, olefinic H). MS (*m*/*z*): 333 (M^+), 119, 91, 77.

*3-(Cinnamoylmethylene)-5-(4-methylphenyl)-2(3*H*)-furanone* (***2m***). Yield: 70 %; m.p. 158 °C. Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.16; H, 5.45. IR (KBr, cm^{-1}): 1782 (lactone C=O), 1618 (ArC=C), 819 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.36 (3H, *s*, CH_3), 6.70 (1H, *s*, furanone ring), 7.31 and 7.57 (*d*, each A_2B_2, tolyl ring), 7.64–7.82 (7H, *m*, arylidene ring + 2 olefinic protons). MS (*m*/*z*): 288 (M^+), 119, 91.

*3-Benzylidene-1,3-dihydro-5-(4-methylphenyl)-2*H*-pyrrol-2-one* (***3a***). Yield: 65 %; m.p. 128–130 °C. Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.61; H, 5.66; N, 5.23. IR (KBr, cm^{-1}): 3384 (N–H), 1756 (C=O), 1616 (ArC=C), 799 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.41 (3H, *s*, CH_3), 6.44 (1H, *s*, pyrrolone ring), 7.33 (1H, *s*, olefinic H), 7.27 and 7.43 (*d*, each A_2B_2, tolyl ring), 7.46 (3H, *m*, H-3,4,5, arylidene ring), 7.62 (2H, *m*, H-2,6, arylidene ring), 7.97 (1H, *s*, NH). MS (*m*/*z*): 261 (M^+), 118, 91, 77.

*1,3-Dihydro-3-(2-methoxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one* (***3b***). Yield: 68 %; m.p. 174 °C. Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.08; H, 5.56; N, 4.85; IR (KBr, cm^{-1}): 3445 (N–H), 1699 (C=O), 1509 (ArC=C), 809 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.32 (3H, *s*, CH_3), 3.77 (3H, *s*, OCH_3), 6.92 (1H, *s*, pyrrolone ring), 7.09 (1H, *m*, H-3,

arylidene ring), 7.27 and 7.54 (*d*, each A_2B_2, tolyl ring), 7.45 (2H, *m*, H-4,5, arylidene ring), 7.68 (1H, *s*, olefinic H), 7.71 (1H, *dd*, H-6, arylidene ring), 8.11 (1H, *s*, NH). MS (*m*/*z*): 291 (M^+), 118, 91.

*1,3-Dihydro-3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one* (***3c***). Yield: 65 %; m.p. 188 °C. Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.16; H, 5.53; N, 4.78. IR (KBr, cm^{-1}): 3462 (N–H), 1697 (C=O), 1613 (ArC=C), 817 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.39 (3H, *s*, CH_3), 3.83 (3H, *s*, OCH_3), 6.86 (1H, *s*, pyrrolone ring), 7.19 (1H, *m*, H-4, arylidene ring), 7.31 and 7.74 (*d*, each A_2B_2, tolyl ring), 7.53 (3H, *m*, H-2,5,6, arylidene ring), 7.65 (1H, *s*, olefinic H), 7.95 (1H, *s*, NH). MS (*m*/*z*): 291 (M^+), 118, 91.

*1,3-Dihydro-3-(4-methoxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one* (***3d***). Yield: 62 %; m.p. 156–158 °C. Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.50; H, 6.25; N, 4.88. IR (KBr, cm^{-1}): 3471 (N–H), 1725 (C=O), 1616 (ArC=C), 801 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.37 and 2.43 (*s*, each 2×CH_3), 6.72 (1H, *s*, pyrrolone ring), 7.07 and 7.51 (*d*, each A_2B_2, tolyl ring), 7.62 (1H, *s*, olefinic H), 7.68 (4H, *m*, H-2,3,5,6 arylidene ring), 8.11 (1H, *s*, NH). MS (*m*/*z*): 275 (M^+), 118, 91.

*1,3-Dihydro-5-(4-methylphenyl)-3-(2,3,4-trimethoxybenzylidene)-2*H*-pyrrol-2-one* (***3e***). Yield: 64 %. m.p. 172–174 °C. Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.56; H, 5.83; N, 4.12. IR (KBr, cm^{-1}): 3458 (N–H), 1708 (C=O), 1631 (ArC=C), 813 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.34 (*s*, CH_3), 3.91 (*s*, 3×OCH_3), 7.41 (1H, *s*, pyrrolone ring), 7.16 and 7.86 (*d*, each A_2B_2, tolyl ring), 7.51 (1H, *s*, olefinic H), 7.75 (2H, *m*, H-5,6 arylidene ring), 8.19 (1H, *s*, NH). MS (*m*/*z*): 351 (M^+), 118, 91.

*1,3-Dihydro-3-(4-hydroxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one* (***3f***). Yield: 61 %; m.p. 152–154 °C. Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.78; H, 5.24; N, 5.12. IR (KBr, cm^{-1}): 3424 (N–H), 1713 (C=O), 1596 (ArC=C), 830 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.41 (3H, *s*, CH_3), 6.94 (1H, *s*, pyrrolone ring), 7.64 (1H, *s*, olefinic H), 7.23 and 7.51 (*d*, each, A_2B_2, tolyl ring), 7.37 and 7.68 (*d*, each, A_2B_2, arylidene ring), 8.18 (*s*, 1H, NH). MS (*m*/*z*): 277 (M^+), 118, 91, 77.

*1,3-Dihydro-3-(3-hydroxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one* (***3g***). Yield: 58 %; m.p. 146–148 °C. Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.82; H, 5.31; N, 5.16. IR (KBr, cm^{-1}): 3419 (N–H), 1745 (C=O), 1616 (ArC=C), 821 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.28 (*s*, 3H, CH_3), 6.92 (*s*, 1H, pyrrolone ring), 7.21 (*m*, 1H, H-5, arylidene ring), 7.22 and 7.61 (*d*, each, A_2B_2, tolyl ring), 7.73 (*s*, 1H, olefinic H), 8.03 (*m*, 1H, H-4, arylidene ring), 8.15 (*d*, 1H, H-2, arylidene ring), 8.58 (*s*, 1H, NH). MS (*m*/*z*): 277 (M^+), 118, 91.

*1,3-Dihydro-3-(4-hydroxy-3-ethoxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one* (***3h***). Yield: 60 %; m.p. 182–184 °C. Anal. Calcd. for $C_{20}H_{19}NO_3$: C,

74.75; H, 5.96; N, 4.36. Found: C, 74.60; H, 5.72; N, 4.24. IR (KBr, cm^{-1}): 3396(N–H), 1738 (C=O), 1629 (ArC=C), 827 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.44 (3H, *t*, $OCH_2C\mathbf{H}_3$), 2.35 (3H, *s*, $OCOCH_3$), 2.39 (3H, *s*, CH_3), 4.08 (2H, *q*, $OC\mathbf{H}_2CH_3$), 6.95 (1H, *s*, pyrrolone ring), 7.31(2H, *m*, H-5,6 arylidene ring), 7.43 (1H, *m*, H-2 arylidene ring), 7.18 and 7.88 (*d*, each A_2B_2, tolyl ring), 7.64 (1H, *s*, olefinic H), 8.05 (1H, *s*, NH). MS (*m*/*z*): 321 (M^+), 118, 91.

*1-Benzyl-3-benzylidene-1,3-dihydro-5-(4-methylphenyl)-2*H*-pyrrol-2-one (**4a**)*. Yield: 65 %; m.p. 122–124 °C. Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.38; H, 5.90; N, 4.12. IR (KBr, cm^{-1}): 1750 (C=O), 1616 (ArC=C), 799 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.34 (3H, *s*, CH_3), 4.85 (2H, *s*, CH_2), 6.16 (1H, *s*, pyrrolone ring), 6.97 and 7.63 (*d*, each A_2B_2, tolyl ring), 7.3 (6H, *m*, 2×H-3,4,5 benzyl + phenyl), 7.43 (1H, *s*, olefinic H), 7.27 and 7.43 (*d*, each A_2B_2, tolyl ring), 7.5 (4H, *m*, 2×H-2,6 benzyl + phenyl). MS (*m*/*z*): 351 (M^+), 260, 118, 91, 77.

*1-Benzyl-1,3-dihydro-3-(3-methoxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one (**4b**)*. Yield: 67 %; m.p. 132–134 °C. Anal. Calcd. for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.65; H, 6.15; N, 3.73; IR (KBr, cm^{-1}): 1729 (C=O), 1598 (ArC=C), 817 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.39 (3H, *s*, CH_3), 3.83 (3H, *s*, OCH_3), 6.86 (1H, *s*, pyrrolone ring), 7.19 (1H, *m*, H-4 arylidene ring), 7.31 and 7.74 (*d*, each A_2B_2, tolyl ring), 7.53 (3H, *m*, H-2,5,6 arylidene ring), 7.65 (1H, *s*, olefinic H), 7.95 (1H, *s*, NH). MS (*m*/*z*): 381 (M^+), 118, 91.

*1-Benzyl-1,3-dihydro-3-(4-methoxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one (**4c**)*. Yield: 61 %; m.p. 118–120 °C. Anal. Calcd. for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83. Found: C, 85.41; H, 6.22; N, 4.02. IR (KBr, cm^{-1}): 1737 (C=O), 1616 (ArC=C), 793 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.34 (3H, *s*, CH_3), 4.85 (2H, *s*, CH_2), 6.16 (1H, *s*, pyrrolone ring), 6.97 and 7.63 (*d*, each A_2B_2, tolyl ring), 7.3 (6H, *m*, 2×H-3,4,5 benzyl + phenyl), 7.43 (1H, *s*, olefinic H), 7.27 and 7.43 (*d*, each A_2B_2, tolyl ring), 7.5 (4H, *m*, 2×H-2,6 benzyl + phenyl). MS (*m*/*z*): 365 (M^+), 274, 118, 91, 77.

*1-Benzyl-1,3-dihydro-5-(4-methylphenyl)-3-(2,3,4-trimethoxybenzylidene)-2*H*-pyrrol-2-one (**4d**)*. Yield: 58 %; m.p. 138–140 °C. Anal. Calcd. for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 75.94; H, 6.12; N, 3.10. IR (KBr, cm^{-1}): 1716 (C=O), 1606 (ArC=C), 819 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.34 (3H, *s*, CH_3), 3.68 (*s*, 3×OCH_3), 4.82 (2H, *s*, CH_2), 6.45 (1H, *s*, pyrrolone ring), 6.97 and 7.62 (*d*, each A_2B_2, tolyl ring), 7.24 (3H, *m*, H-3,4,5 benzyl), 7.41 (1H, *s*, olefinic H), 7.52 (2H, *m*, H-2,6 benzyl), 7.73 (2H, *m*, H-5,6 arylidene ring). MS (*m*/*z*): 441 (M^+), 118, 91, 77.

*1-Benzyl-1,3-dihydro-3-(3,4-methylenedioxybenzylidene)-5-(4-methylphenyl)-2*H*-pyrrol-2-one (**4e**)*. Yield: 61 %; m.p. 182–184 °C. Anal. Calcd. for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.51. Found: C, 78.83; H, 5.31; N, 3.48. IR (KBr, cm^{-1}): 1749 (C=O), 1610 (ArC=C), 815 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ,

ppm) 4.85 (2H, *s*, CH_2), 6.01 (2H, *s*, –OCH_2O–), 6.52 (1H, *s*, pyrrolone ring), 6.95 (1H, *d*, H-5 arylidene ring), 7.12 and 7.76 (*d*, each A_2B_2, tolyl, ring) 7.17 (7H, *m*, 5H phenyl + H-2,6 arylidene), 7.25 (5H, *m*, benzyl), 7.66 (1H, *s*, olefinic H). MS (*m*/*z*): 395 (M^+), 304, 91, 77.

*3-(9-Anthrylmethylene)-1-benzyl-1,3-dihydro-5-(4-methylphenyl)-2*H*-pyrrol--2-one (**4f**)*. Yield: 69 %; m.p. 146–148 °C. Anal. Calcd. for $C_{33}H_{25}NO$: C, 87.78; H, 5.58; N, 3.10. Found: C, 87.61; H, 5.50; N, 3.14. IR (KBr, cm^{-1}): 1756 (C=O), 1614 (ArC=C), 821 (ArC–H). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.31 (3H, *s*, CH_3), 6.61 (1H, *s*, pyrrolone ring), 7.31 and 7.76 (*d*, each A_2B_2, tolyl ring), 7.24 (1H, *s*, olefinic H), 7.54 (4H, *m*, H-2,3,6,7 anthryl), 8.03 (4H, *m*, H-1,4,5,8 anthryl), 8.23 (1H, *s*, H-10, anthryl). MS (*m*/*z*): 451 (M^+), 119, 91.

In general, the infrared spectral data of the furanones **2a**–**m** revealed bands at 1782–1720 (lactone C=O), 1635–1601 (ArC=C) and 827–806 (ArC–H). The pyrrolones **3a**–**h** showed bands at 3471–3384 (pyrrolone N–H), 1745–1697 (C=O), 1631–1596 (ArC=C) and 830–799 (ArC–H). The benzylpyrrolones **4a**–**f** revealed bands at 1756–1716 (lactam C=O), 1616–1598 (ArC=C) and 821–793 (ArC–H). In the ^{1}H-NMR spectral data, all the compounds showed a singlet of three protons at around δ 2.3 ppm, accounted for by the methyl group of the tolyl ring. Two singlets of one proton each were present at around δ 6.5 and 7.4 ppm, which could be assigned to the ring β H and the olefinic hydrogen of the arylidene substituent. Other peaks were observed at the appropriate positions. Some points could be made regarding the fragmentation pattern observed in the electron impact mass spectrum. The 3-arylidene-5-(4-methylphenyl)-2(3*H*)-furanones **2a**–**m** gave an M^+ peak in reasonable intensities. The major fragment appears to be CH_3–C_6H_4–C≡O^+ (*m*/*z* 119), arising from the heterocyclic oxygen and γ-carbon with its substituent. Subsequently, it loses CO to give $(C_7H_7)^+$ (*m*/*z* 91). A peak at *m*/*z* 77, corresponding to $(C_6H_5)^+$, appeared. Occasionally, the aryl ring of the arylidene moiety also appeared as Ar^+. In the case of pyrrolones **3a**–**h**, the major fragmentation is through CH_3–C_6H_4–C≡N^+H (*m*/*z* 118), which is followed by loss of HCN to give $(C_7H_7)^+$ (*m*/*z* 91). In case of benzylpyrrolones **4a**–**f**, loss of 91 mass units, corresponding to the benzyl moiety from the molecular ion, was observed together with peaks at *m*/*z* 91, 77. The other pathway is *via* CH_3–C_6H_4––C≡N^+H (*m*/*z* 118), arising from C-2 and its substituent, which appears to be novel. This also loses HCN to give $(C_7H_7)^+$ (*m*/*z* 91).

Biological evaluation

Anti-inflammatory activity. The anti-inflammatory activity test showed that compound **2h** exhibited the maximum anti-inflammatory activity (69.05 % inhibition), two compounds, **2e** and **4d**, also showed good activity with 61.90 and 64.28 % inhibition, respectively. The standard drug diclofenac exhibited 78.57 % inhibition. Compound **2b**, **2f**, **4b**, **4c** and **4f** showed significant activity ranging from 40.47–54.76 %. The results are presented in Table I.

The structure activity relationship showed that substitution of the oxygen atom of the furanone ring with NH (pyrrolones) resulted in a marked decrease in the anti-inflammatory activity, while substitution of the oxygen atom with the benzylamine moiety (benzylpyrrolones) markedly increased the activity. Compounds having trimethoxyl functions at the 2,3,4-position of the arylidene moiety were found to have better anti-inflammatory activity than those having one or no methoxyl function.

TABLE I. Biological data of the synthesized compounds

Compd.	Anti-inflammatory activity[a]		Analgesic activity[a]		Ulcerogenic activity[a] (severity index)
	Change in edema volume[b], mL	Inhibition %	No. of writhing episodes[b]	Protection %	
2b	0.22±0.01	47.62	16.3±0.42	27.87	0.50±0.18
2d	0.28±0.02	33.33	nt	–	nt
2e	0.16±0.02	61.90	7.6±0.36	66.37	0.75±0.11
2f	0.20±0.01	52.38	12.6±0.22	44.24	0.583±0.08
2h	0.13±0.02	69.05	6.3±0.33	72.27	0.666±0.11
2k	0.27±0.01	35.72	nt[c]	–	nt
2l	0.26±0.02	38.10	nt	–	nt
3b	0.34±0.02	19.05	nt	–	nt
3d	0.36±0.02	14.28	nt	–	nt
3e	0.31±0.01	26.19	nt	–	nt
3f	0.29±0.01	30.95	nt	–	nt
4b	0.19±0.02	54.76	8.3±0.33	63.28	0.75±0.17
4c	0.24±0.01	42.86	14.5±0.42	35.84	0.416±0.15
4d	0.15±0.01	64.28	6.6±0.33	70.79	0.833±0.16
4f	0.25±0.02	40.47	17.3±0.33	23.31	0.583±0.20
Control	0.42±0.02	–	22.6±0.42	–	0.00
Diclofenac	0.09±0.03	78.57	7.3±0.42	67.69	2.33±0.21

[a]Number of animals in each group was 6; [b]values as ±S.E.M.; [c]nt = not tested

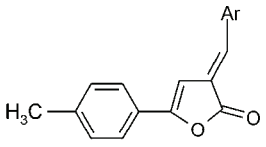
Analgesic activity. The analgesic activity as evaluated by the acetic acid-induced writhing test in albino mice showed that compound **2h** exhibited the maximum analgesic activity (72.27 %) while the standard drug diclofenac showed 67.69 % activity. Compound **2e**, **4b** and **4d** also showed good analgesic activity, ranging from 63.28–70.79 % (Table I).

Acute ulcerogenesis. The tested compounds tested a significant reduction in ulcerogenic activity, ranging from 0.416 to 0.833, whereas the standard drug diclofenac showed a high severity index (2.33). The results indicate that compounds are almost devoid of ulcerogenic action (Table I).

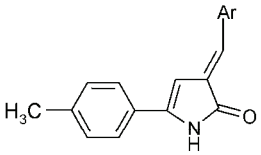
Antibacterial activity. Compounds **2h**, **3e** and **3h** showed significant activity against *S. aureus* with *MIC* values of 12.5 (**2h** and **3e**) and 6.5 μg/ml (**3h**) (Table II). Of these compounds, compound **3e** also showed good activity against *E. coli* with *MIC* value of 15 μg/ml. Compounds **2f**, **2l**, **3b**, **3c**, **3f**, and **4d** exhibited

appreciable antibacterial activity against both the bacterial strains with *MIC* values ranging from 20–50 μg/ml. Analyses of the results indicate that the introduction of a NH in place of the oxygen atom in the furanone ring (pyrrolones) enhanced the antibacterial action whereas the benzylpyrrolones were weak in their antibacterial action.

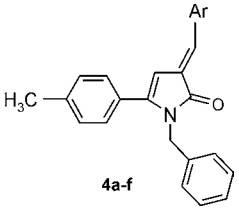
TABLE II. Physical data and *in vitro* antibacterial screening of the synthesized compounds



2a-m



3a-h



4a-f

Compd.	Ar	M.p. °C	Mol. formula/M_r	*MIC* / μg mL^{-1}	
				S. aureus	*E. coli*
2a	Phenyl-	90	$C_{18}H_{14}O_2$/262.31	–[a]	–
2b	2-Methoxyphenyl-	132–134	$C_{19}H_{16}O_3$/292.33	>100	–
2c	3-Methoxyphenyl-	140–142	$C_{19}H_{16}O_3$/292.33	>100	>100
2d	4-Methylphenyl-	122	$C_{19}H_{16}O_2$/276.33	–	–
2e	2,3,4-Trimethoxyphenyl-	168–170	$C_{21}H_{20}O_5$/352.38	50	>100
2f	4-Acetoxyphenyl-	156–158	$C_{20}H_{16}O_4$/320.34	50	50
2g	3-Acetoxyphenyl-	144–146	$C_{20}H_{16}O_4$/320.34	100	50
2h	4-Acetoxy-3-ethoxyphenyl-	132–134	$C_{22}H_{20}O_5$/364.39	12.5	25
2i	2-Furyl-	160–162	$C_{16}H_{12}O_3$/252.27	–	–
2j	3,4-Methylenedioxyphenyl-	174–176	$C_{19}H_{14}O_4$/306.32	>100	>100
2k	9-anthryl-	166	$C_{26}H_{18}O_2$/362.43		–
2l	4-(Diethylamino)phenyl-	126–128	$C_{22}H_{23}NO_2$/333.43	20	25
2m	Cinnamoyl-	158	$C_{20}H_{16}O_2$/288.34	–	–
3a	Phenyl-	128–130	$C_{18}H_{15}NO$/261.32	50	>100
3b	2-Methoxyphenyl-	174	$C_{19}H_{17}NO_2$/291.35	50	50
3c	3-Methoxyphenyl-	188	$C_{19}H_{17}NO_2$/291.35	25	50
3d	4-Methylphenyl-	156–158	$C_{19}H_{17}NO$/275.35	>100	–
3e	2,3,4-Trimethoxyphenyl-	172–174	$C_{21}H_{21}NO_4$/351.4	12.5	15
3f	4-Hydroxyphenyl-	152–154	$C_{18}H_{15}NO_2$/277.32	50	25
3g	3-Hydroxphenyl-	146–148	$C_{18}H_{15}NO_2$/277.32	>100	>100
3h	4-Hydroxy-3-ethoxyphenyl-	182–184	$C_{20}H_{19}NO_3$/321.37	6.5	25
4a	Phenyl-	122–124	$C_{25}H_{21}NO$/351.44	–	–
4b	3-Methoxyphenyl-	132–134	$C_{26}H_{23}NO_2$/381.47	>100	–
4c	4-Methylphenyl-	118–120	$C_{26}H_{23}NO$/365.47	–	–
4d	2,3,4-Trimethoxyphenyl-	138–140	$C_{28}H_{27}NO_4$/441.52	25	25
4e	3,4-Methylenedioxyphenyl-	182–184	$C_{26}H_{21}NO_3$/395.46	50	>100
4f	9-Anthryl-	146–148	$C_{33}H_{25}NO$/451.56	–	–
Nitrofurazone		–	–	12.5	6.5

[a]Insignificant antibacterial activity

EXPERIMENTAL

Chemistry

Melting points were taken in open capillary tubes and are uncorrected. Microanalysis of the compounds was performed on a Perkin-Elmer model 240 analyzer and the values were found to be within ±0.4 % of the theoretical values. The ^{1}H-NMR spectra were recorded on a Varian E-360 MHz or a Bruker spectropsin DPX-300 MHz; The chemical shifts, δ, are reported in ppm downfield from tetramethylsilane (TMS), which was used as the internal standard. The mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. The progress of the reactions was monitored by TLC, which was performed on silica gel (Merck No. 5554).

*Preparation of 3-(4-Methylbenzoyl)propanoic acid (**1**)*

To a mixture of succinic anhydride (0.10 mol) in dry toluene (50 mL) in a round bottom flask was added, in portions, anhydrous aluminum chloride (0.1125 mol). The reaction mixture was refluxed for two hours after which the excess toluene was removed by steam distillation. The residue was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The so obtained solid mass was filtered, washed with cold water, dried and crystallized from methanol to give fine crystals of **1**, which gave effervescence with sodium bicarbonate solution, confirming the presence of the carboxylic group.

*General procedure for the synthesis of 3-arylidene-5-(4-methylphenyl)-2(3*H*)-furanones (**2a**–**m**)*

A solution of 3-(4-methylbenzoyl)propanoic acid (0.71 g, 3.0 mmol) and the required aromatic aldehyde (equimolar, 3.0 mmol) in acetic anhydride (15 mL) with triethylamine (1–2 drops) was refluxed for 2–4 h under anhydrous conditions. After completion of the reaction, the contents were poured onto crushed ice in small portions under stirring. A colored solid mass separated out, which was filtered, washed with water and crystallized from a mixture of methanol:chloroform (1:1) to give **2a**–**m**.

*General procedure for the synthesis of 3-arylidene-1,3-dihydro-5-(4-methylphenyl)-2*H*-pyrrol--2-ones (**3a**–**h**)*

Dry ammonia gas was passed into an anhydrous ethanolic solution of the required furanone (1.0 g) for one hour at room temperature, the ethanol was distilled off under reduced pressure and the so obtained solid mass was crystallized from methanol/acetone to give **3a**–**h**.

*General procedure for the synthesis of 3-arylidene-1-benzyl-1,3-dihydro-5-(4-methylphenyl)--2*H*-pyrrol-2-ones (**4a**–**f**)*

Synthesis of these compounds involved the following two steps:

The synthesis of N*-benzyl-γ-ketoamides*. The required furanone (3.0 mmol) and benzylamine (4.0 mmol) were refluxed in dry benzene for two hours. On completion of the reaction, the excess benzene was distilled off and the solid mass so obtained was washed with petroleum ether and dried. The compounds obtained were used without crystallization.

Lactamization of the N*-benzyl-γ-ketoamides*. The required *N*-benzyl-γ-ketoamide (3.0 mmol) was refluxed in 6 M hydrochloric acid (20 ml) for one hour. The contents were then cooled and the so obtained solid mass was collected, washed with water and crystallized from methanol to give **4a**–**f**.

Biological evaluation

Anti-inflammatory activity. Some of the selected compounds were evaluated for their *in vivo* anti-inflammatory activity by the carrageenan induced rat paw edema method.[16] The pro-

tocol of the animal experiments was approved by the Institutional Animal Ethics Committee (IAEC). The compounds were tested at 20 mg/kg oral dose and were compared with the standard drug diclofenac (10 mg/kg). The foot volume of the rats was measured before and after 4 h of carrageenan injection by a plethysmograph. The percentage inhibition of inflammation was calculated according to the following formula: Anti-inflammatory activity (% inhibition) = 1 – – $V_t/V_c \times 100$, where V_t and V_c are the edema volumes in the drug-treated and the control groups, respectively.

Analgesic activity. The compounds which showed anti-inflammatory activity > 40 % were further tested for their analgesic activity. The analgesic activity of the synthesized compounds **2b**, **2e**, **2f**, **2h**, **4b**, **4c**, **4d** and **4f** was evaluated by the acetic acid induced writhing test[17] in albino mice. A 1.0 % aqueous acetic acid solution (*i.p*. injection; 0.10 ml) was used as the writhing induced agent. The compounds were tested at 20 mg/kg oral dose and were compared with the standard drug diclofenac (10 mg/kg). The analgesic activity was expressed in terms of % protection. Analgesic activity (%) = $(n - n'/n) \times 100$ where n = mean number of writhes of the control group and n' = mean number of writhes of the test group.

Acute ulcerogenesis. The compounds which were tested for analgesic activity were further screened for their ulcerogenic action. The test was performed according to Cioli *et al*.[14] The ulcerogenic activity was evaluated after *p.o*. administration of the test compounds or diclofenac at a dose of 60 mg/kg.

Antibacterial activity. The antibacterial studies were carried out on the synthesized compounds against the microorganism *viz. Staphylococcus aureus* and *Escherichia coli* in meat peptone agar medium at a concentration of 100 μg/ml by the 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.[18]

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И З В О Д

СИНТЕЗА, РЕАКЦИЈЕ И БИОЛОШКА АКТИВНОСТ 3-АРИЛИДЕН-5-(4-МЕТИЛФЕНИЛ)-2(3*H*)-ФУРАНОНА

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3-Арилиден-5-(4-метилфенил)-2(3*H*)-фуранони **2a**–**m** добијени су из 3-(4-метилбензоил)пропанске киселине **1** и неколико ароматичних алдехида. Одабрани фуранони реагују са амонијачним гасом и бензиламином градећи одговарајуће 3-арилиден-1,3-дихидро-5-(4-метилфенил)-2*H*-пирол-2-оне **3a**–**h**, односно 3-арилиден-1-бензил-1,3-дихидро-5-(4-метилфенил)--2*H*-пирол-2-оне **4a**–**f**, који су окарактерисани на основу IR, ^{1}H-NMR и MS података, као и елементалне анализе. Ова једињења су тестирана на анти-инфламаторну и анти-бактеријску активност. Једињења која су показала значајну анти-инфламаторну активност су затим даље тестирана на аналгетску и улцерогену активност. Три нова једињења, **2e**, **2h** и **4d**, од укупно 27, показала су врло добру анти-инфламаторну активност у карагеаном-индукованом тесту едема шапе пацова, уз изражену аналгетску активност у тесту грчења индукованог сир-

ћетном киселином, као и занемарљиву улцерогену активност. Антибактеријска активност изражена је помоћу одговарајућих *MIC* вредности.

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