Asian Journal of Chemistry Vol. 17, No. 1 (2005), 576–580

Synthesis and Antiinflammatory Activity of Some Analogues of 4-Substituted-2-phenyl imidazolin-5(4H)-one Derivatives

V.S. SARAVANAN, S.P. VINOTH KUMAR, BIPLAB DE† and JAYANTA KUMAR GUPTA*
Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700 032, India
E-mail: jkgjupt@yahoo.co.in

A series of imidazolinone derivatives were synthesized from the respective oxazolinones followed by treatment with benzaldehyde to form their Schiff bases. The chemical structures of such seven synthesized compounds were confirmed by spectral analysis. The synthesized compounds on screening for antiinflammatory activity exhibited significant activity.

Key Words: Synthesis, Antiinflammatory agent, Oxazolones, Imidazolin-5-ones.

INTRODUCTION

Although there are many non-steroidal anti-inflammatory drugs (NSAIDs) in the market, many of these are with serious side effects such as gastrointestinal irritation, kidney damage, etc. Thus, the investigation on ideal anti-inflammatory agents is still a challenge. The therapeutic importance of imidazolinones has been reported[1–7]. On the basis of all these, it was thought worth while to synthesize a few 4-substituted-2-phenyl imidazolin-5(4H)-ones and to evaluate them for their anti-inflammatory activity. The chemical structures of the synthesized compounds were confirmed by ^{1}H-NMR, IR spectral data and elemental analysis. The synthesized compounds were tested for their anti-inflammatory activity by carrageenan induced rat paw edema method[8].

EXPERIMENTAL

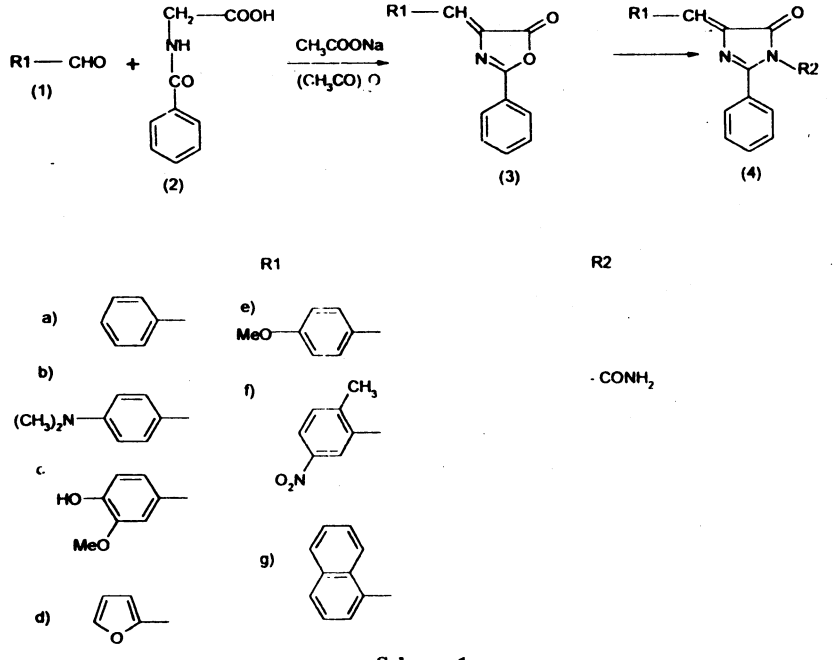
The melting points of synthesized compounds were taken in open capillary tubes on an ADCO melting point apparatus and are uncorrected. The IR spectra of the compounds were recorded in the 4000–400 cm^{-1} range using KBr disks on a Perkin-Elmer 297 spectrophotometer. The ^{1}H-NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer in $CDCl_3$. Microanalyses for C, H, N were performed in Heraeus CHN rapid analyzer and the compounds gave satisfactory chemical analyses (±0.4%).

General Procedure for the Synthesis of Oxazolones (3)

4-Substituted-2-phenyloxazol-5(4H)-ones were prepared by refluxing benzoylglycine[9] (hippuric acid) (0.25 mol) and appropriate aldehydes (0.25 mol) in acetic anhydride (0.75 mol) with freshly fused sodium acetate (0.25 mol) for 2 h (Erlenmeyer oxazolone condensation). After cooling ethanol (10 mL) was

†Regional Institute of Pharmaceutical Science and Technology, Agartala, Tripura-799 005, India.

added and kept overnight at 5°C, the solid obtained was filtered, washed with alcohol, dried in vacuum and recrystallized from benzene.



Scheme-1

4-Benzylidene-2-phenyl-oxazol-5(4H)one (3a): Yield = 97.05%; m.p. = 166-167°C; ^{1}H-NMR ($CDCl_3$) δ: 6.5–6.9 (m, 10H; $(C_6H_5)_2$, 5.8 (s, 1H; CH=C). IR (KBr) cm^{-1}: 1652 ν(C=O), 1628 ν(C=N), 1592 ν(C=C), 1127 ν(C—O—C). Calcd. for $C_{16}H_{11}NO_2$: 249.26; Anal.: Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.49; N, 5.61%. Found: C, 76.58; H, 4.78; N, 5.48%.

4-(4-Dimethylamino benzylidine)-2-phenyl-oxazol-5(4H)one (3b): Yield = 62.06%; m.p. = 216–217°C. ^{1}H-NMR ($CDCl_3$) δ: 6.3–6.9 (m, 9H; Ar—H), 5.7 (s, 1H; CH=C), 2.8 (s, 6H; —$N(CH_3)_2$). IR (KBr) cm^{-1}: 1660 ν(C= O), 1618 ν(C=N), 1612 ν(C=C), 1136 ν(C—O—C). Calcd. for $C_{18}H_{16}N_2O_2$: 292.3). Anal.: Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.51; N, 9.58%. Found: C, 73.26; H, 5.72; N, 9.12%.

4-{4′-Hydroxy-3′-methoxy benzylidine-2-phenyl-oxazol-5(4H)one (3c): Yield = 95.08%; m.p. = 192–193°C. ^{1}H-NMR ($CDCl_3$) δ: 9.7 (s, 1H; Ar—OH), 6.8–7.8 (m, 8H; Ar—H), 6.1 (s, 1H; CH=C), 4.1 (s, 3H; OCH_3). IR (KBr) cm^{-1}: 3680 ν(OH), 1674 ν(C=O), 1622 ν(C=N), 1596 ν(C=C), 1120 ν(C—O—C). Calcd. for $C_{17}H_{13}NO_4$: 295.29. Anal.: Calcd. for $C_{17}H_{13}NO_4C$, : 69.14; H, 4.43; N, 4.74. Found: C, 68.76; H, 4.12; N, 4.92.

4-(Furfur-2-yl)-2-phenyl-oxazol-5(4H)one (3d): Yield = 78.62%; m.p. =

168–169°C. ^{1}H-NMR ($CDCl_3$) δ: 6.3–6.8 (m, 8H; Ar—H), 5.7 (s, 1H; CH=C). IR (KBr) cm^{-1}: 1660 ν(C=O), 1620 ν(C=N), 1590 ν(C=C), 1132 ν(C—O—C). Calcd. for $C_{14}H_{10}NO_3$: 239.23. Anal.: Calcd. for $C_{14}H_{10}NO_3$: C, 70.29; H, 3.79; N, 5.85. Found: C, 70.02; H, 3.12; N, 5.24.

4-(4′-Methoxy benzylidine)-2-phenyl oxazol-5(4H)one (3e): Yield = 75.09%; m.p. 154–155°C. ^{1}H-NMR ($CDCl_3$) δ: 6.72–6.75 (m, 4H; Ar—H), 6.24–6.42 (m, 5H; C_6H_5), 2.24–2.4 (s, 3H; OCH_3). IR (KBr) cm^{-1}: 1722 ν(C=O), 1627 ν(Aro—CH), 1052 ν(C—O—C). Calcd. for $C_{17}H_{13}NO_3$: 279.29). Anal.: Calcd. for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.04. Found: C, 73.02; H, 4.58; N, 4.92.

4-(5′-Nitro-2′-methyl phenyl)-2-phenyl oxazol-5(4H)one (3f): Yield = 58.68%; m.p. = 198–199°C. ^{1}H-NMR (CDC_{13}) δ: 6.3–6.8 (m, 3H; C_6H_3), 5.7 (s, 1H; CH=C). IR (KBr) cm^{-1}: 1660 ν(C=O), 1513 ν(CH_3). Calcd. for $C_{17}H_{12}N_2O_4$: 308.29). Anal.: Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H. 3.92; N, 9.08. Found: C, 66.14; H, 3.78; N, 9.02.

4-(l-Naphthyl-2-phenyl-oxazol-5(4H)one (3g): Yield = 51.25%; m.p. = 164–165°C. ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.2 (m, 12H; Ar—H), 5.8 (s, 1H; CH=C), IR (KBr) cm^{-1}: 1634 ν(C=N), 1610 ν(C=C), 1142 ν(C—O—C). Calcd. for $C_{20}H_{13}NO_2$: 299.32). Anal.: Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.37; N, 4.67. Found: C, 79.56; H, 4.02; N, 4.68.

General procedure for the synthesis of 1,4-disubstituted imidazolones (4)

The respective 4-substituted oxazolones (0.1 mol) were refluxed with equimolar quantity (0.1 mol) of ethylenediamine in dioxan (10 mL) in a water bath for 6 h, N,N-dimethylamino benzene in dioxan (10 mL) in a water bath for 6 h and urea in pyridine (10 mL) in an oil bath at 150°C for 6 h separately to yield the respective 1-substituted imidazolones. The excess of solvent was distilled off from the reaction mixture in vacuum. The mixture was cooled and poured into crushed ice. The solid obtained was filtered and recrystallized from rectified spirit (**4a–g**).

1-Carboxamido-2-phenyl-4-benzylidene imidazole-5(4H)one (4a): Yield = 96.21%; m.p. = 272–273°C. ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.1 (m, 10H; Ar—H), 6.3 (s, 2H; $CONH_2$), 5.3 (s, 1H; CH—C). IR (KBr) cm^{-1}: 3226 ν(NH), 1655 ν(C=O), 1635 ν(C=N), 1580 ν(C=C). Calcd. for $C_{17}H_{13}N_3O_2$: 291.30. Anal.: Calcd. for $C_{17}H_{13}N_3O_2$: C, 71.80; H, 4.49; N, 14.42. Found: C, 71.62; H, 4.34; N, 14.28.

1-Carboxamido-2-phenyl-4-(4-dimethylaminobenzylidene)-imidazole-5(4H)one (4b): Yield = 47.31%; m.p. 265–266°C. ^{1}H-NMR ($CDCl_3$) δ: 6.8–7.1 (m, 9H; Ar—H), 6.1 (s, 2H; $CONH_2$), 5.5 (s, 1H; CH=C), 2.98 (s, 4H; $N(CH_3)_2$). IR (KBr) cm^{-1}: 1655 ν(CO), 1620 ν(C=N), 1610 ν(C=C). (Calcd. for $C_{19}H_{18}N_4O_2$: 334.37. Anal.: Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.42; N, 16.75. Found: C, 68.02; H, 5.12; N, 17.06.

1-Carboxamido-2-phenyl-4′-hydroxy-3′-methoxybenzylidene)-imidazole-5

(4H)one (4c): Yield = 95.23%; m.p. = 198–199°C. ^{1}H-NMR ($CDCl_3$) δ: 9.5 (s, 1H; Ar—H), 7.3–8.2 (m, 8H; Ar—H), 6.2 (s, 2H; $CONH_2$), 3.8 (s, 3H; OCH_3). IR (KBr) cm^{-1}: 3782 ν(OH), 1645 ν(C=O), 1610 ν(C=N), 1595 ν(C=C). Calcd. for $C_{18}H_{15}N_3O_4$: 337.33. Anal.: Calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.45. Found: C, 63.82; H, 4.52; N, 12.18.

1-Carboxamido-2-phenyl-4-(furfur-2-yl)-imidazole-5(4H)one (4d): Yield = 81.85%; m.p. 258–259°C. ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.1 (m, 8H; Ar—H), 6.1 (s, 2H; $CONH_2$), 5.3 (s, 1H; CH=C). IR (KBr) cm^{-1}: 1665 ν(C=O), 1622 ν(C=N), 1592 ν(C=C). Calcd. for $C_{15}H_{11}N_3O_3$: 281.27. Anal.: Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.93. Found: C, 64.28; H, 3.64; N, 14.28.

1-Carboxamido-2-phenyl-4-(4′-methoxy phenyl) imidazole-5(4H)-one (4e): Yield= 67.48%; m.p.= 181–182°C; ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.1 (m, 8H; Ar—H), 6.2 (s, 2H; $CONH_2$), 5.3 (s, 1H; CH=C), 3.9 (s, 3H; OCH_3). IR (KBr) cm^{-1}: 1665 ν(C=O), 1622 ν(C=N), 1592 ν(C=C). Calcd. for $C_{18}H_{15}N_3O_3$: 321.33. Anal. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.35; H, 4.70; N, 13.07. Found: C, 63.87; H, 4.46; N, 12.78.

1-Carboxamido-2-phenyl-4-(5′-nitro-2′-methyl phenyl) imidazole-5(4H)-one (4f): Yield = 52.26%; m.p. = 218–219°C. ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.1 (m, 8H; Ar—H), 6.1 (s, 2H; $CONH_2$), 5.8 (s, 1H; CH=C), 2.6 (s, 3H; CH_3). IR (KBr) cm^{-1}: 1642 ν(C=O), 1630 ν(C=N), 1594 ν(C=C). Calcd. for $C_{18}H_{24}N_4O_4$: 350.33. Anal.: Calcd. for $C_{18}H_{24}N_4O_4$: C, 61.71; H, 4.02; N, 15.99. Found: C, 61.28; H, 3.94; N, 15.28.

1-Carboxamido-2-phenyl-4-(1-naphthyl) imidazole-5(4H)one (4g): Yield = 62.48%; m.p. = 148–149°C. ^{1}H-NMR ($CDCl_3$) δ: 6.7–7.1 (m, 12H; Ar—H), 6.1 (s, 2H; $CONH_2$), 5.3 (s, 1H; CH=C). IR (KBr) cm^{-1}: 1665 ν(C=O), 1632 ν(C=N), 1612 ν(C=C). Calcd. for $C_{21}H_{15}N_3O_2$: 341.36. Anal.: Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.42; N, 12.30. Found: C, 73.14; H, 4.12; N, 11.88.

Pharmacological Studies

The synthesized compounds were screened for anti-inflammatory activity by carrageenan-induced paw edema test in rats[8]. Indomethacin 10 mg/kg was administered as standard drug for comparison. The test compounds were administered at 100 mg/kg dose levels. The paw volumes were measured using the mercury displacement technique with the help of a plethysmograph immediately before and 30 min, 1, 2, 3 and 4 h after carrageenan injection. The per cent inhibition of paw edema was calculated by using the following formula:

$$\text{Per cent inhibition } I = 100[1 - (a - x)/(b - y)]$$

where x = the mean paw volume of rats before the administration of carrageenan and test compounds or standard compound, a stands for mean paw volume of rats after the administration of carrageenan in the control group, b is the mean paw volume of rats before the administration of carrageenan in the control group, y is the mean paw volume of rats after the administration of carrageenan in the control group.

TABLE-1
ANTI-INFLAMMATORY ACTIVITY (CARRAGEENAN-INDUCED RAT PAW EDEMA METHOD)

Compd. No.	Dose (mg/kg)	Per cent inhibition				
		30 min	1 h	2 h	3 h	4 h
4a	100	51.3 ± 0.04†	58.8 ± 0.09†	69.4± 0.05†	40.5± 0.02†	33.6± 0.12†
4b	100	49.4 ± 0.02†	50.5 ± 0.06†	56.1 ± 0.04†	40.5± 0.04†	31.8± 0.02†
4c	100	51.2 ± 0.02†	53.7 ± 0.06†	59.4 ± 0.05†	37.8± 0.50†	32.5± 0.02†
4d	100	37.4 ± 0.06†	40.7 ± 0.04†	45.3 ± 0.06†	37.8± 0.06†	30.2± 0.03†
4e	100	45.1 ± 0.08†	54.3 ± 0.02†	57.2 ± 0.04†	41.7± 0.02†	34.3± 0.10†
4f	100	52.7 ± 0.02†	59.1 ± 0.08†	67.1 ± 0.06†	42.3± 0.02†	35.4± 0.14†
4g	100	47.1 ± 0.10†	49.6 ± 0.02†	56.7 ± 0.03†	41.3± 0.14†	33.5± 0.02†
Control	100	4.19 ± 0.46	3.31 ± 0.27	2.47 ± 0.40	3.39± 0.51	2.91± 0.42
Indomethacin	10	42.44 ± 0.28‡	49.18 ± 0.80‡	36.19± 0.86*	31.17± 0.12*	27.92± 0.13*

Significance levels: * p = 0.05, † p = 0.01 and ‡ p = 0.001.

RESULTS AND DISCUSSION

It has been observed that all the compounds tested showed significant anti-inflammatory activity when compared with indomethacin. Three compounds, namely, **4a, 4b** and **4d** having a phenyl, a dimethylaminophenyl and a furfur-2-yl substitution respectively at 4 positions of the imidazolone ring had shown anti-inflammatory activity almost comparable to that of indomethacin. However, the most active compound of the series was found to be **4d** where the onset of action and the duration of action both were quite remarkable.

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(*Received*: 14 June 2004; *Accepted*: 12 September 2004) AJC-3572