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Original scientific paper

Synthesis of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-ones as safer anti-inflammatory and analgesic agents

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Abstract: A novel series of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-one was synthesized by reaction of 3-(4-phenoxybenzoyl)propionic acid with several aryl acid hydrazides in phosphorus oxychloride. The structures of the compounds were supported by IR, ¹H- and ¹³C-NMR, MS data and elemental analysis results. These compounds were tested for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation actions. A few compounds were found to have very good anti-inflammatory activity in the carrageenan-induced rat paw edema test, while a fair number of the compounds showed significant analgesic activity in the acetic acid-induced writhing test. These new compounds showed very low ulcerogenic action with reduced malondialdehyde content (MDA), which is one of the by-products of lipid peroxidation.

Keywords: 1,3,4-oxadiazole; anti-inflammatory; analgesic; ulcerogenic; lipid peroxidation.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are used for the treatment of pain, fever and inflammation, particularly arthritis;^{1,2} they are the most commonly prescribed medications in the world. The most prevalent side effects of the use of non-steroidal anti-inflammatory drugs are the occurrence of gastrointestinal side effects³ (gastric upset, irritation and ulceration). The search for safer NSAIDs continues with the failure of the anticipated “ideal” anti-inflammatory agents, the coxibs, on long-term usage.^{4,5} 3-(4-Phenoxybenzoyl)propionic acid is an example of the well known aroylpropionic acid class of anti-inflammatory drugs.⁶ Aroylpropionic acids are good anti-inflammatory agents but suffer from inducing gastrointestinal side effects.^{6,7} It is well known that structural modifica-

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tions can improve the pharmacological profile of an active molecule. Synthetic approaches based on chemical modification have been taken with the aim of improving the safety profile of NSAIDs.^{7–12} These studies showed that derivatization of the carboxylate function of some NSAIDs resulted in an increased anti-inflammatory activity with a reduced ulcerogenic effect.

During recent years, there has been extensive investigation of different classes of oxadiazole compounds, many of which were found to possess a wide spectrum of biological activities. In particular, compounds having 1,3,4-oxadiazole nucleus are known to exhibit good anti-edema and anti-inflammatory activity.^{13–15} Differently substituted oxadiazole moieties have also been found to have other interesting activities, such as analgesic, antibacterial, bactericidal, antifungal, anticonvulsant, anticancer, *etc.*^{16–20}

In our attempt to discover safer agents for the treatment of inflammatory conditions, the carboxylic acid group of 3-(4-phenoxybenzoyl)propionic acid was replaced with an additional heterocycle, *i.e.*, 1,3,4-oxadiazole, which was found to possess potential anti-inflammatory and analgesic activity with significant reduction in their ulcerogenic effect.

RESULTS AND DISCUSSION

Chemistry

The 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-ones **4a–I** described in this study are shown in Table I and the reaction sequence for their preparation is outlined in Scheme 1. The required 3-(4-phenoxybenzoyl)propionic acid **3** was prepared by condensing diphenyl ether with succinic anhydride in the presence of anhydrous aluminum chloride, following the Friedel–Crafts acylation reaction conditions. The reaction between 3-(4-phenoxybenzoyl)propionic acid **3** and aryl acid hydrazides **2a–I** in phosphorous oxychloride (the reaction time varied from 2 to 5 h) afforded the title compounds **4a–I** in 48–66 % yield after recrystallization from methanol. The purity of compounds was controlled by TLC and elemental analysis. Both the analytical and spectral data (¹H-NMR, IR and mass spectra) of the synthesized compounds were in full agreement with the proposed structures.

1-(4-Phenoxyphenyl)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-1-one (4a). Yield: 62 %, m.p. 142 °C; IR (KBr, cm⁻¹): 3050, 1650, 1420, 780; ¹H-NMR (CDCl₃, δ, ppm): 2.51 and 3.47 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 7.47 (6H, *m*, H-3,4,5, 2×phenyl), 7.63 (4H, *m*, H-2,6, 2×phenyl), 7.67 and 8.13 (each *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.8 (C₁), 34.3 (C₂), 191.8 (C₃), 161.7 (C_{2''}), 164.2 (C_{5''}), 129.8 (C₄), 130 (C_{5,9}), 118.3 (C_{6,8}), 155.8 (C₇), 155.1 (C₁₀), 119.7 (C_{11,15}), 133.1 (C_{12,14}), 124.2 (C₁₃), 130.2 (C_{1'}), 127.1 (C_{2',6'}), 129.1 (C_{3',5'}), 131.3 (C_{4'}); MS (*m/z*): 370 (M⁺), 197, 170, 78, 77.

TABLE I. Anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activity of the compounds **4a–l**

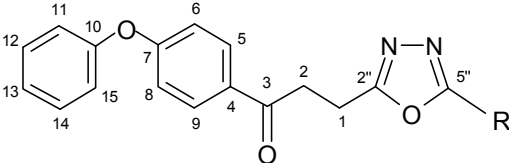
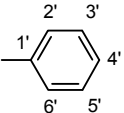
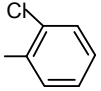
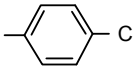
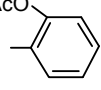
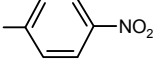
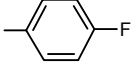
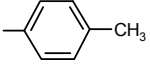
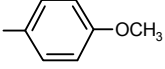
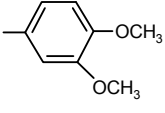
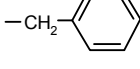
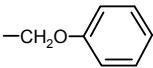
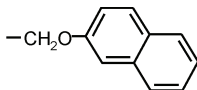
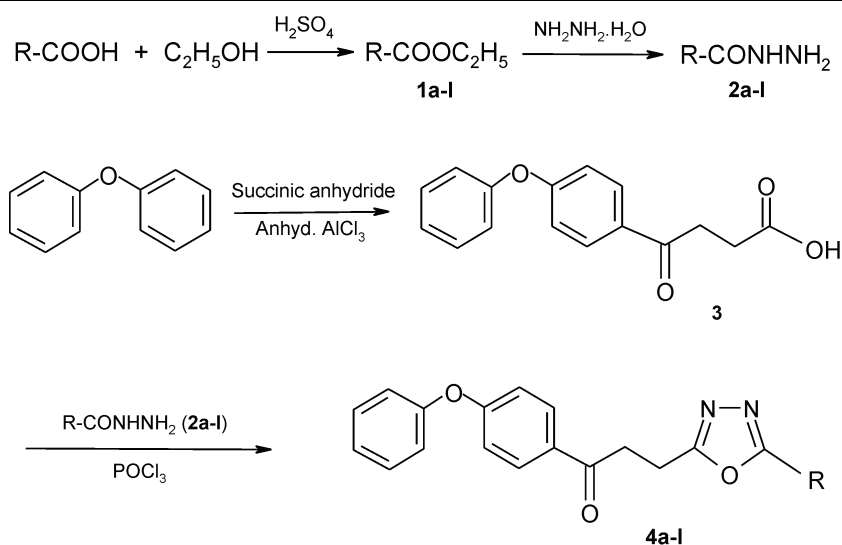
					
Compd.	R	Anti-inflam- matory activity, % inhibition	Analgesic activity, % protection	Ulcerogenic activity (seve- rity index)	Lipid peroxida- tion (nmol MDA content/100 mg tissue)
4a		40.63	41.12	0.454	4.425
4b		43.75	56.35	0.523	5.733
4c		46.87	61.86	0.581	5.813
4d		65.63	76.33	0.666	5.808
4e		50.00	38.80	0.525	4.715
4f		53.13	58.52	0.581	4.830
4g		37.50	41.12	0.525	5.054
4h		56.25	54.31	0.523	6.115
4i		62.50	67.83	0.581	4.973
4j		46.87	50.12	0.666	5.018

TABLE I. Continued

4k		50.00	55.80	0.525	5.433
4l		53.13	58.57	0.581	5.834
3	—	43.75	46.36	1.553	6.651
Indomethacin		68.75	72.44	2.332	8.133



R=C₆H₅-, 2-Cl-C₆H₄-, 4-Cl-C₆H₄-, 2-OAc-C₆H₄-, 4-NO₂-C₆H₄-, 4-F-C₆H₄-, 4-CH₃-C₆H₄-,
 -4-OCH₃-C₆H₄-, 3,4-(OCH₃)₂-C₆H₃-, C₆H₅CH₂-, C₆H₅-OCH₂-, 2-C₁₀H₇-OCH₂-

Scheme 1.

3-[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (4b). Yield: 56 %, m.p. 154–156 °C; IR (KBr, cm⁻¹): 3100, 1655, 1435, 820; ¹H-NMR (CDCl₃, δ, ppm): 2.55 and 3.43 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 7.29 (4H, *m*, H-3,4,5,6, *o*-chlorophenyl), 7.58 (5H, *m*, phenyl), 7.73 and 7.84 (each *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃ δ, ppm): 27.4 (C₁), 34.3 (C₂), 192.5 (C₃), 159.8 (C_{2'}), 164.1 (C_{5'}), 129.7 (C₄), 130.6 (C_{5,9}), 117.6 (C_{6,8}), 155.6 (C₇), 155.2 (C₁₀), 119.8 (C_{11,15}), 132.6 (C_{12,14}), 124.1 (C₁₃), 127.4 (C_{1'}), 135.2 (C_{2'}), 128.7 (C_{3'}), 130.2 (C_{4',6'}), 127.8 (C_{5'}); MS (*m/z*): 404 (M⁺), 197, 169, 77.

3-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (4c). Yield: 60 %, m.p. 142 °C; IR (KBr, cm⁻¹): 3080, 1655, 1430, 810; ¹H-NMR (CDCl₃, δ, ppm): 2.51 and 3.57 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 7.33

(3H, *m*, H-3,4,5, phenyl), 7.38 (2H, *m*, H-2,6, phenyl), 7.46 and 7.65 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl; phenoxyphenyl), 7.15 and 7.83 (each, *d*, *J* = 8.4 Hz, 2×A₂B₂, *p*-chlorophenyl); ¹³C-NMR (CDCl₃, δ, ppm): 27.3 (C₁), 34.3 (C₂), 193.1 (C₃), 159.2 (C₂''), 164.1 (C₅''), 129.2 (C_{4,1'}), 131.2 (C_{5,9}), 118.7 (C_{6,8}), 155.4 (C₇), 155.2 (C₁₀), 119.6 (C_{11,15}), 131.3 (C_{12,14}), 124.1 (C₁₃), 126.7 (C_{2',6'}), 129.9 (C_{3',5'}), 136.6 (C_{4'}); MS (*m/z*): 404 (M⁺), 197, 169.

3-[5-(2-Acetoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (**4d**). Yield: 66 %, m.p. 136–138 °C; IR (KBr, cm⁻¹): 3100, 1660, 1425, 800; ¹H-NMR (CDCl₃, δ, ppm): 2.43 (3H, *s*, OCOCH₃), 2.61 and 3.54 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 7.46 (3H, *m*, H-3,4,5, phenyl), 7.67 (2H, *m*, H-2,6, phenyl), 7.25 (4H, *m*, H-3,4,5,6, *o*-disubstituted phenyl), 7.77 and 7.84 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.9 (C₁), 34.1 (C₂), 191.7 (C₃), 160.6 (C₂''), 165.5 (C₅''), 130 (C₄), 129.8 (C_{5,9}), 122.4 (C_{6,8,3'}), 156.1 (C₇), 155.8 (C₁₀), 119.8 (C_{11,15}), 127.2 (C_{12,14}), 123.5 (C₁₃), 113.9 (C_{1'}), 147.2 (C_{2'}), 133.8 (C_{4'}), 124.3 (C_{5'}), 125.6 (C_{6'}), 168.3 (C=O), 20.7 (–OAc); MS (*m/z*): M⁺ not observed, 197, 169, 92, 78, 77.

3-[5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (**4e**). Yield: 54 %, m.p. 152 °C; IR (KBr, cm⁻¹): 3080, 1665, 1433, 815. ¹H-NMR (CDCl₃, δ, ppm): 2.63 and 3.57 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 7.44 (3H, *m*, H-3,4,5, phenyl), 7.66 (2H, *m*, H-2,6, phenyl), 7.73 and 7.85 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl), 7.77 and 7.98 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.8 (C₁), 34.3 (C₂), 192.3 (C₃), 158.8 (C₂''), 164.3 (C₅''), 129.6 (C₄), 129.8 (C_{5,9}), 123.5 (C_{6,8}), 157.3 (C₇), 155.1 (C₁₀), 118.4 (C_{11,15}), 128.6 (C_{12,14,1'}), 123.9 (C₁₃), 126.9 (C_{2',6'}), 119.6 (C_{3',5'}), 135.7 (C_{4'}). MS (*m/z*): 415 (M⁺), 197, 169.

3-[5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (**4f**). Yield: 65 %, m.p. 146–148 °C; IR (KBr, cm⁻¹): 3020, 1655, 1430, 760; ¹H-NMR (CDCl₃, δ, ppm): 2.55 and 3.52 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 7.47 (3H, *m*, H-3,4,5, phenyl), 7.68 (2H, *m*, H-2,6, phenyl), 7.44 and 7.56 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl), 7.05 and 7.87 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.9 (C₁), 34.5 (C₂), 192.7 (C₃), 159.1 (C₂''), 164.5 (C₅''), 131.1 (C₄), 132.9 (C_{5,9}), 124.4 (C_{6,8,13}), 157.1 (C₇), 155.3 (C₁₀), 119.8 (C_{11,15}), 129.4 (C_{12,14,1'}), 127.3 (C₁₃), 127.3 (C_{2',6'}), 129.4 (C_{3',5'}), 143.6 (C_{4'}); MS (*m/z*): 388 (M⁺), 197, 169, 77.

3-[5-(4-Methylphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (**4g**). Yield: 57 %, m.p. 146 °C; IR (KBr, cm⁻¹): 3030, 1665, 1428, 805; ¹H-NMR (CDCl₃, δ, ppm): 2.13 (3H, *s*, CH₃), 2.55 and 3.49 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 6.68 and 7.77 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, phenyl), 7.43 (5H, *m*, phenyl), 6.91 and 7.64 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-methylphenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.7 (C₁), 34.1 (C₂), 193.1 (C₃), 158.7 (C₂''), 163.9 (C₅''), 130.8 (C_{4,1'}), 133.7 (C_{5,9}), 124.3 (C_{6,8}), 157.6 (C₇), 156.2 (C₁₀), 118.4 (C_{11,15}), 129.9

(C_{12,14}), 126.6 (C₁₃), 127.1 (C_{2',6'}), 128.3 (C_{3',5'}), 133.7 (C_{4'}), 22.4 (CH₃); MS (*m/z*): 384 (M⁺), 197, 169, 91.

3-[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (4h). Yield: 58 %, m.p. 164–166 °C; IR (KBr, cm⁻¹): 3020, 1655, 1433, 780; ¹H-NMR (CDCl₃, δ, ppm): 3.84 (3H, *s*, OCH₃), 2.60 and 3.19 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 6.78 and 7.87 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, phenyl), 7.55 (5H, *m*, phenyl), 7.13 and 7.73 (each, *d*, *J* = 8.4 Hz, 2×A₂B₂, *p*-methoxy phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.1 (C₁), 34.3 (C₂), 194.4 (C₃), 158.9 (C_{2''}), 164.2 (C_{5''}), 130.8 (C₄), 132.4 (C_{5,9}), 123.3 (C_{6,8}), 157.8 (C₇), 156.6 (C₁₀), 118.1 (C_{11,15}), 130.2 (C_{12,14}), 125.8 (C₁₃), 126.5 (C_{1'}), 125.1 (C_{2',6'}), 129.4 (C_{3',5'}), 141.7 (C_{4'}), 52.6 (OCH₃). MS (*m/z*): 400 (M⁺), 197, 169.

3-[5-(3,4-Dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (4i). Yield: 62 %, m.p. 162 °C; IR (KBr, cm⁻¹): 3100, 1660, 1420, 810; ¹H-NMR (CDCl₃, δ, ppm): 3.96 (6H, two closely spaced singlets, 2×OCH₃), 2.58 and 3.44 (each, *t*, *J* = 6.6 Hz, 2×CH₂), 6.99 (1H, *d*, *J* = 7.8 Hz, H-5, dimethoxyphenyl), 7.15 (1H, *d*, *J* = 2 Hz, H-2, dimethoxy phenyl), 7.37 (1H, *dd*, *J* = 7.8 Hz, H-6, dimethoxyphenyl), 7.46 (3H, *m*, H-3,4,5, phenyl), 7.66 (2H, *m*, H-2,6, phenyl), 7.71 and 8.17 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.4 (C₁), 34.8 (C₂), 192.8 (C₃), 158.5 (C_{2''}), 164.1 (C_{5''}), 129.6 (C₄), 131.8 (C_{5,9}), 121.3 (C_{6,8}), 159.1 (C₇), 157.2 (C₁₀), 118.5 (C_{11,15}), 130.1 (C_{12,14}), 124.3 (C₁₃), 127.1 (C_{1'}), 119.8 (C_{2',5'}), 146.2 (C_{3'}), 143.7 (C_{4'}), 107.6 (C_{6'}), 54.7 (OCH₃); MS (*m/z*): 430 (M⁺), 197, 169, 77.

3-[5-(5-Benzyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (4j). Yield: 54 %, m.p. 155 °C; IR (KBr, cm⁻¹): 3080, 1655, 1435, 805; ¹H-NMR (CDCl₃, δ, ppm): 2.37 and 3.58 (each 2H, *t*, *J* = 6.6 Hz, 2 x CH₂), 4.14 (3H, *s*, CH₂), 7.39 (6H, *m*, H-3,4,5, 2×phenyl), 7.61 (4H, *m*, H-2,6, 2×phenyl), 7.66 and 7.81 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 27.1 (C₁), 35.3 (C₂), 192.6 (C₃), 160.5 (C_{2''}), 159.8 (C_{5''}), 131.4 (C₄), 132.2 (C_{5,9}), 120.6 (C_{6,8}), 157.1 (C₇), 156.6 (C₁₀), 118.7 (C_{11,15}), 130.1 (C_{12,14}), 123.2 (C₁₃), 132.2 (C_{1'}), 128.6 (C_{2',6'}), 127.7 (C_{3',5'}), 127.5 (C_{4'}), 32.3 (CH₂); MS (*m/z*): 384 (M⁺), 197, 169, 91, 77.

3-[5-(Phenoxymethyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (4k). Yield: 64 %, m.p. 162 °C; IR (KBr, cm⁻¹): 3090, 1653, 1422, 790; ¹H-NMR (CDCl₃, δ, ppm): 2.52 and 3.48 (each 2H, *t*, *J* = 6.6 Hz, 2×CH₂), 4.56 (3H, *s*, OCH₂), 7.47 (6H, *m*, H-3,4,5, 2×phenyl), 7.65 (4H, *m*, H-2,6, 2×phenyl), 7.73 and 7.85 (each, *d*, *J* = 8.1 Hz, 2×A₂B₂, *p*-disubstituted phenyl); ¹³C-NMR (CDCl₃, δ, ppm): 26.3 (C₁), 35.8 (C₂), 191.1 (C₃), 161.3 (C_{2''}), 157.1 (C_{5''}), 131.9 (C₄), 131.7 (C_{5,9}), 122.5 (C_{6,8}), 157.8 (C₇), 156.2 (C₁₀), 117.1 (C_{11,15}), 128.4 (C_{12,14}), 121.8 (C₁₃), 141.9 (C_{1'}), 121.5 (C_{2',6'}), 129.3 (C_{3',5'}), 123.6 (C_{4'}), 60.3 (OCH₂); MS (*m/z*): 400 (M⁺), 197, 169, 135.

3-[5-(2-Naphthyloxymethyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one (**4l**). Yield: 48 %, m.p. 174 °C; IR (KBr, cm^{-1}): 3085, 1655, 1435, 785.; $^1\text{H-NMR}$ (CDCl_3 , δ , ppm): 2.54 and 3.48 (each 2H, *t*, $J = 6.6$ Hz, $2\times\text{CH}_2$), 4.89 (3H, *s*, OCH_2), 7.21 (2H, *m*, H-1,3, naphthoxy), 7.47 (3H, *m*, H-3,4,5, phenyl), 7.67 (2H, *m*, H-2,6, phenyl), 7.76 and 8.13 (each, $J = 8.1$ Hz, $2\times\text{A}_2\text{B}_2$, *p*-disubstituted phenyl), 7.97 (5H, *m*, H-4,5,6,7,8, naphthoxy); $^{13}\text{C-NMR}$ (CDCl_3 , δ , ppm): 26.8 (C_1), 36.1 (C_2), 192.3 (C_3), 160.7 (C_2''), 156.3 (C_5''), 130.9 (C_4), 132.3 ($\text{C}_{5,9}$), 121.8 ($\text{C}_{6,8}$), 156.1 (C_7), 155.8 (C_{10}), 118.2 ($\text{C}_{11,15}$), 128.7 ($\text{C}_{12,14}$), 122.8 (C_{13}), 144.2 ($\text{C}_{1'}$), 108.9 (C_2'), 135.3 ($\text{C}_{3'}$), 126.1 ($\text{C}_{4',5',6',7'}$), 129.3 ($\text{C}_{8',9'}$), 119.8 ($\text{C}_{10'}$), 61.6 (OCH_2); MS (m/z): 450 (M^+), 197, 169, 128.

In general, IR data revealed bands at 3100–3030 (C–H); 1650–1665 (C=O); 1440–1420 (C–N) and 750–830 cm^{-1} (aromatic). In the $^1\text{H-NMR}$ spectral data, the title compounds showed two triplets of two protons each at around δ 2.5 and 3.5, which could be assigned to the two methylene protons ($-\text{CH}_2-\text{CH}_2-$). Other peaks were observed at appropriate δ values. The mass spectra of the oxadiazoles showed acylium fragments containing phenoxyphenyl and aryl moieties as the major peaks, followed by peaks with the loss of CO, in addition to the molecular ion peaks in reasonable intensities. The elemental analysis results were within ± 0.4 % of the theoretical values.

Biological screening

Anti-inflammatory activity. The tested compounds showed anti-inflammatory activity ranging from 37.50 to 65.63 % (Table I). Two compounds, 3-[5-(2-acetoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one **4d** and 3-[5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one **4i** showed very good anti-inflammatory activity with 65.63 and 62.50 %, respectively. The activity of these compounds (**4d** and **4i**) was comparable with that of indomethacin (68.75 %) and higher than that of the parent compound **3** (43.75 %).

These data show that the presence of 2-acetoxyphenyl, 3,4-dimethoxyphenyl or 4-methoxyphenyl substitution at position 5 of the oxadiazole ring caused a remarkable improvement in the anti-inflammatory activity.

Analgesic activity. The newly synthesized compounds showed activity ranging from 38.80 to 76.33 % (Table I). The activity showed that compound, 3-[5-(2-acetoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one **4d**, exhibited maximum analgesic activity (76.33 %) and its activity was better than that of standard drug indomethacin (72.44 %).

Acute ulcerogenesis. The tested compounds showed a significant reduction in ulcerogenic activity, ranging from 0.454 to 0.666, whereas the standard drug indomethacin and the parent drug **3** exhibited a high severity index, 2.332 and 1.553, respectively (Table I). The results indicate that the newly synthesized compounds are almost devoid of ulcerogenic action.

Lipid peroxidation study. It is evident that compounds showing less ulcerogenic activity also show a reduced malondialdehyde (MDA) content, a byproduct of lipid peroxidation.²¹ Therefore, an attempt was made to correlate the low ulcerogenesis of the studied compounds with that of lipid peroxidation. Indomethacin and **3** (standard and parent compound) showed high lipid peroxidation, 8.133 and 6.842 nmol/100 mg of tissue, respectively, whereas the control group showed 3.788 nmol/100 mg of tissue (Table I). It was found that all the compounds showing low ulcerogenic activity also showed a reduction in lipid peroxidation. Therefore, the study indicated that these oxadiazole derivatives inhibited the induction of gastric mucosal lesions. The results further suggest that their protective effect might be related to the inhibition of lipid peroxidation in the gastric mucosa.

EXPERIMENTAL

Chemistry

Chemicals were procured from E. Merck (Germany & India) and S. D. Fine Chemicals (India). Melting points were determined in open capillary tubes and are uncorrected. Micro-analysis of the compounds was done on Perkin-Elmer model 240 analyzer and the found values were within ± 0.4 % of the theoretical values. ¹H- and ¹³C-NMR spectra were recorded on Bruker spectropspin DPX-300 MHz and Bruker 400 Ultra Shield™ instruments, with tetramethylsilane (TMS) as the internal standard. The splitting pattern abbreviations are as follows: *s*, singlet; *d*, doublet; *dd*, double doublet; *t*, triplet; *m*, multiplet. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. The spectral data are consistent with the assigned structures. The progress of the reactions was monitored on silica gel G plates using iodine vapor as the visualizing agent.

Aryl acid ethyl esters and their hydrazides (**1a–l**, **2a–l**)

These compounds were obtained by the method reported in the literature.²²

3-(4-Phenoxy-benzoyl)propionic acid (**3**)

Compound **3** was prepared according to a literature method.⁸

General procedure for the synthesis of 1-(4-phenoxyphenyl)-3-[5-(substituted phenyl)-1,3,4-oxadiazol-2-yl]propan-1-ones (**4a–l**)

Compound **2a–l** (0.001 mol) was dissolved in phosphorus oxychloride (5 ml) and to it was added **3** (equimolar, 0.001 mol). The reaction mixture, after refluxing for 2–5 h, was cooled to room temperature and poured onto crushed ice. On neutralization of the contents with sodium bicarbonate solution (20 % w/v) a solid mass separated out which was filtered, washed with water, dried and recrystallized from methanol to give **4a–l**.

Biological screening

Anti-inflammatory activity. The newly synthesized compounds **4a–l** were evaluated for their *in vivo* anti-inflammatory activity by the carrageenan-induced rat paw edema method.²³ The protocol 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 indomethacin and **3** at the same oral dose. The foot volume of the rats was measured before and after 4 h of carrageenan injection using a plethysmograph. The percentage inhibition of inflammation was calculated by applying the Newbould formula.²⁴

Analgesic activity. The activity was carried out by acetic acid induced writhing method²⁵ on albino mice groups of six animals each. A 1.0 % aqueous acetic acid solution (i.p. injection, 0.10 ml) was used as writhing inducing agent. Test compounds and reference drugs (Indomethacin and compound **3**) were administered in the dose of 20 mg/kg as carboxymethylcellulose (CMC) suspension. One group was kept as control and received 1.0 % CMC. After 20 min of drug administration, 0.10 ml of 1.0 % acetic acid solution was given to mice intraperitoneally. The severity of writhing response was recorded for 20 min after administration of acetic acid solution. The analgesic activity was expressed in terms of percent protection $((n - n')/n) \times 100$, where n is the mean number of writhes of control group and n' is the mean number of writhes of test group).

Acute ulcerogenesis. The title compounds were screened for their ulcerogenic activity in albino rats according to the method of Cioli.²⁶ The ulcerogenic activity was evaluated after p.o. administration of the test compounds or Indomethacin or **3** at a dose of 30 mg/kg.

Lipid peroxidation study. Lipid peroxidation of the synthesized compounds, as well of indomethacin and **3** (standard and parent compound) was determined according to the method of Ohkawa.²⁷ The lipid peroxidation was measured as nmol of MDA/100 mg of tissue.

CONCLUSIONS

To summarize, a novel class of 3-(4-phenoxybenzoyl)propionic acid derivatives, as safer anti-inflammatory and analgesic agents, was synthesized. Cyclization of the terminal carboxylic group of 3-(4-phenoxybenzoyl)propionic acid into the oxadiazole nucleus resulted in increased anti-inflammatory and analgesic activity, with a significant decrease of ulcerogenic activity, which is a common side effect with commonly used non steroidal anti-inflammatory agents (NSAIDs). These results make the novel 1,3,4-oxadiazoles interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds holds promise towards the pursuit to discover safer anti-inflammatory and analgesic agents. Further studies to acquire more information about structure–activity relationships are in progress.

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ИЗВОД

СИНТЕЗА 1-(4-ФЕНОКСИФЕНИЛ)-3-5-(СУПСТИТУИСАНИ АРИЛ)-1,3,4-ОКСАДИАЗОЛ-2-ИЛ]ПРОПАН-1-ОНА КАО ПОГОДНИХ АНТИ-ИНФЛАМАТОРНИХ И АНАЛГЕТИЧКИХ АГЕНСА

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Реакцијом 3-(4-феноксibenзоил)пропионске киселине и низа хидразида ароматичних карбоксилних киселина у фосфороксихлориду синтетисана је серија нових 1-(4-феноксифенил)-3-5-(супституисани арил)-1,3,4-оксадиазол-2-ил]пропан-1-она. Структуре једињења по-

тврђене су одговарајућим IR, NMR (^1H и ^{13}C) и MS подацима, као и резултатима елементалне анализе. Синтетисана једињења подвргнута су тестовима анти-инфламаторног, аналгетичког и улцерогеног дејства, као и тесту изазивања липидне пероксидације. Неколико једињења показало је врло високо анти-инфламаторно дејство на едем шапе пацова изазван карагенаном. Мањи број синтетисаних једињења показао је значајну аналгетичку активност према грчевима изазваним сирћетном киселином. Новосинтетисана једињења показала су слабу улцерогену активност и довела до појаве ниског садржаја малондиалдехида (MDA), једног од споредних производа липидне пероксидације.

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