Eur. J. Med. Chem. 35 (2000) 359–364
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S0223523400001173/FLA

Laboratory note

Synthesis and preliminary evaluation of new 5-pyrazolinone derivatives as analgesic agents

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Received 16 March 1999; revised 19 August 1999; accepted 9 September 1999

Abstract – New 4-(aroyloxyalkanoyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones (**5**) were cyclized to 4-(2-aryl-5-unsubstituted/substituted oxazol-4-yl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones (**6**) employing the Davidson procedure. Preliminary evaluation of analgesic activity revealed that the effect of 4-(2-phenyl-5-ethyloxazol-4-yl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 4-[2-(4-chlorophenyl)-5-ethyloxazol-4-yl]-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one on acetic acid induced writhing was superior to that of antypyrine and aminopyrine. 4-[2-(4-Chlorophenyl)-5-methyloxazol-4-yl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 4-[2-(4-methoxyphenyl)-5-ethyloxazol-4-yl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one were more potent than aminopyrine, whereas 4-(2-phenyl-5-methyloxazol-4-yl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 4-[2-(4-methoxyphenyl)-5-methyl-oxazol-4-yl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one were not as active (modified Koster's Test; 0.19–0.21 mmol.kg^{-1}). None of the selected entries showed inhibition of formaldehyde-induced paw oedema. © 2000 Éditions scientifiques et médicales Elsevier SAS

pyrazolin-5-one / oxazole / synthesis / analgesic activity

1. Introduction

Antipyrine, 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, was the first pyrazolone derivative used in the management of pain and inflammation. Research devoted to the development of new analgesic agents of this series led to the discovery of aminopyrine and dipyrone. Reports of fatal agranulocytosis diminished interest in these agents, however. In an effort to increase analgesic properties and decrease adverse effects pyrazolidinedione derivatives, phenylbutazone and its potent metabolite oxyphenbutazone, were synthesized. Studies on biochemical properties of these structures bearing the pyrazole nucleus revealed their ability to uncouple oxidative phosphorylation, stabilize lysosomal membranes, inhibit biosynthesis of various mucopolysaccharides, and perhaps most importantly, also inhibit prostaglandin biosynthesis at the cyclo-oxygenase stage, which primarily accounts for their anti-inflammatory and analgesic effects [1]. Intense research has also been focused on oxazole derivatives [2, 3] after the discovery of the anti-inflammatory agent oxaprozin, 4,5-diphenyloxazole-2-propanoic acid. In a previous work we reported on the analgesic effect of 4-(2-phenyloxazol-4-yl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [4]. Based on this result and a recent report on the analgesic activity of 3-pyrazolin-5-one derivatives [5], we have designed and synthesized structural homologues of 4-(2-phenyloxazol-4-yl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one in an attempt to enhance its analgesic properties.

2. Chemistry

The synthetic routes followed for obtaining compounds **2–6** are outlined in *figure 1*. Thus, Friedel-Crafts acylation of 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**1**), with appropriate α-halogenated acyl halides, afforded the respective adducts **2–4** [6], which yielded the requisite oxazole precursors **5** on reaction with sodium benzoate or substituted sodium benzoates [7]. Exposure of **5**

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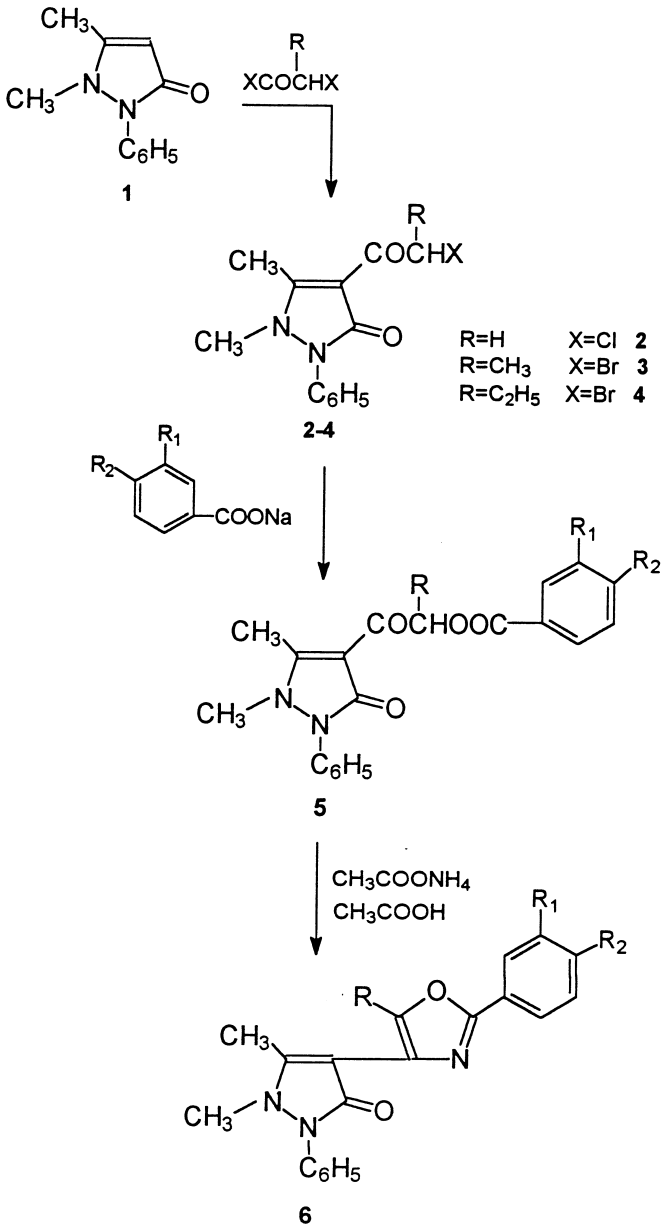

Figure 1. Synthetic routes to compounds **2–6.**

to an excess of NH_4Ac in AcOH at reflux, according to the Davidson procedure, provided **6** [8]. It is hypothesized that the cyclization reaction involves the formation of a labile imine intermediate from the reaction of NH_3 formed in the medium and **5** which undergoes cyclodehydration to the oxazole. The structures of **5** and **6** were established on the basis of analytical (C, H, N) and spectral (UV, IR,^{1}H-NMR, EIMS) data (*table I*).

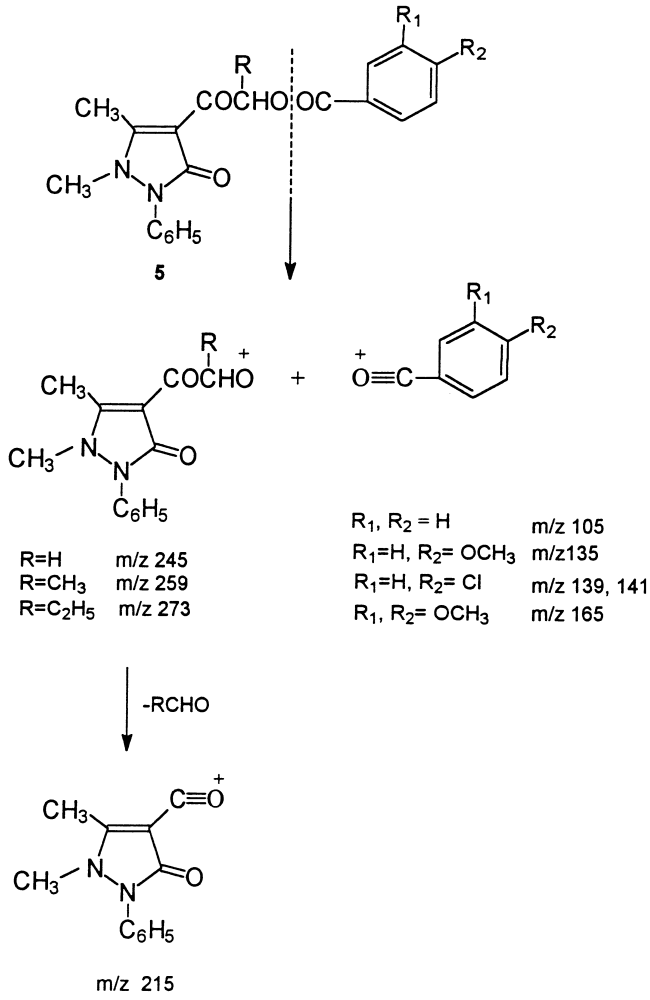

Figure 2 Major fragments in the EIMS of **5.**

The IR spectra of **5** showed the ester C=O absorption at about 1 725–1 707 cm^{-1}. The amide and the ketone C=O functions were observed in the 1 672–1 652 cm^{-1} region separately or as a single band [7].

Compounds **5b–i** are chiral molecules. Thus the ^{1}H-NMR spectra of **5b–e** displayed the CH_3 protons attached to the chiral centre as a doublet (δ 1.63–1.65 ppm), whereas the $\underline{CH_2}CH_3$ protons of compounds **5f–i** resonated as two separate multiplets (δ 2.15–2.10 ppm and δ 1.92–1.84 ppm) due to magnetic non-equivalance. The CH proton on the chiral carbon absorbed as a quartet in **5b–e** (δ 6.28–6.27 ppm) and as a doublet of doublets in **5f–i** (δ 6.11–6.08 ppm) again due to magnetic non-equivalance resulting from molecular asymmetry. The corresponding CH_2 protons of the unsubstituted derivative **5a** resonated as a singlet at δ 5.32 ppm.

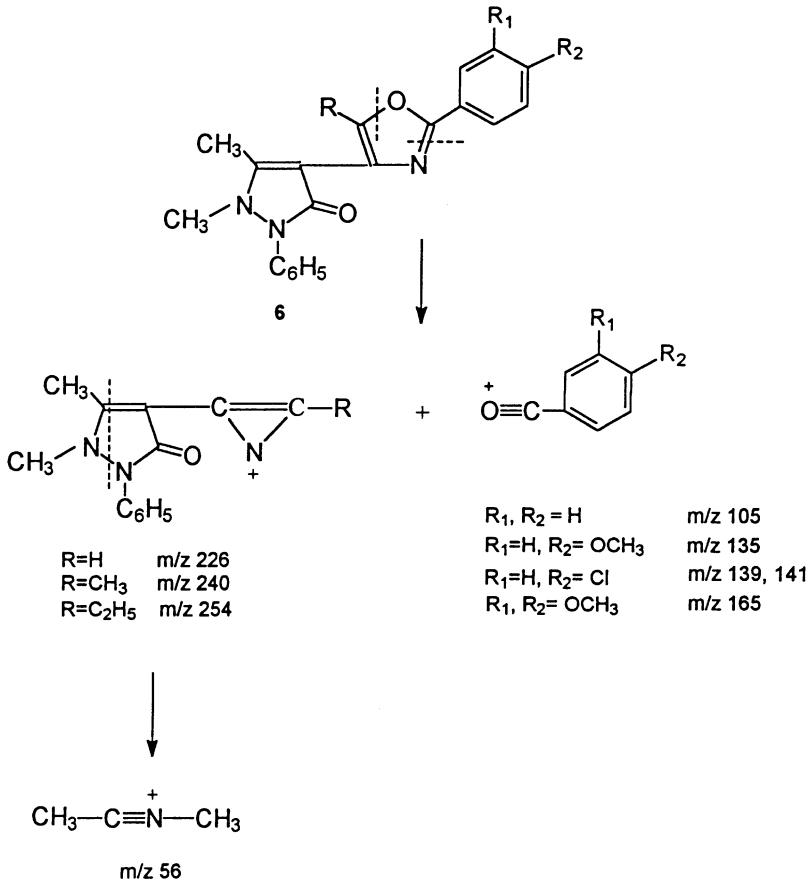

Figure 3 Major fragments in the EIMS of **6.**

Molecular ions observed in the EIMS confirmed the molecular weights of **5**. The major fragmentation route involved the cleavage of the ester function with subsequent loss of RCHO, which led to the base peak at m/z 215 (*figure 2*).

Cyclization to **6** was confirmed by the IR spectra which showed a single C=O band (1 675–1 653 cm^{-1}) assigned to the amide function.

Absence of the O–C<u>H</u>–R resonance and downfield shifts observed in the absorption positions of R (R = H, δ 8.32 ppm; R = CH_3, δ 2.58–2.52 ppm; R = CH_2CH_3, δ 2.98–2.95 ppm and δ 1.32 ppm) in the ^{1}H-NMR spectra provided further support for ring formation [7].

6 displayed abundant molecular ions in the EIMS which provided conclusive evidence for the anticipated structures. A common fragmentation pattern which involved the cleavage of the 2–3 and 1–5 bonds of the oxazole moiety has been proposed and outlined in *figure 3*. Further spectral details are presented in the experimental protocols.

3. Results and discussion

Selected entries from the oxazole series (**6**) were evaluated for analgesic and anti-inflammatory activity against acetic acid induced writhing (modified Koster's test) and formaldehyde-induced paw oedema, respectively [9, 10]. Antipyrine and aminopyrine were used as the standards in both tests. The results summarized in *table II* demonstrate that the presence of an ethyl residue at position 5- of the oxazole ring enhances analgesic activity significantly. Thus 5-ethyl substituted derivatives were more active than 5-methyl substituted compounds. Among 5-methyl substituted compounds only **6d** was more active than aminopyrine, whereas the analgesic effect of two of the entries from the 5-ethyl substituted

Table I. Physicochemical data of **5** and **6.**

Compound	R	R_1	R_2	Yield (%)	M.p. (°C)	Formula (M.W.)
5a	H	OCH_3	OCH_3	85	178–179	$C_{22}H_{22}N_2O_6$ (410.43)
5b	CH_3	H	H	87	135–137	$C_{21}H_{20}N_2O_4$ (364.40)
5c	CH_3	H	OCH_3	80	144–147	$C_{22}H_{22}N_2O_5$ (394.43)
5d	CH_3	H	Cl	94	202–205	$C_{21}H_{19}ClN_2O_4$ (398.84)
5e	CH_3	OCH_3	OCH_3	92	181–182	$C_{23}H_{24}N_2O_6$ (424.45)
5f	C_2H_5	H	H	87	152–154	$C_{22}H_{22}N_2O_4$ (378.43)
5g	C_2H_5	H	OCH_3	84	157–159	$C_{22}H_{24}N_2O_5$ (408.45)
5h	C_2H_5	H	Cl	92	163–165	$C_{23}H_{21}ClN_2O_5$ (412.87)
5i	C_2H_5	OCH_3	OCH_3	88	164–165	$C_{24}H_{26}N_2O_6$ (438.48)
6a	H	OCH_3	OCH_3	82	164–165	$C_{22}H_{21}N_3O_4$ (391.43)
6b	CH_3	H	H	84	163–165	$C_{21}H_{19}N_3O_2$ (345.40)
6c	CH_3	H	OCH_3	79	186–188	$C_{22}H_{21}N_3O_3$ (375.43)
6d	CH_3	H	Cl	76	141–143	$C_{21}H_{18}ClN_3O_2$ (379.84)
6e	CH_3	OCH_3	OCH_3	84	181–182	$C_{21}H_{23}N_3O_4$ (405.45)
6f	C_2H_5	H	H	82	123–125	$C_{22}H_{21}N_3O_4$ (359.43)
6g	C_2H_5	H	OCH_3	76	135–137	$C_{23}H_{23}N_3O_3$ (389.45)
6h	C_2H_5	H	Cl	82	171–174	$C_{22}H_{20}ClN_3O_2$ (393.87)
6i	C_2H_5	OCH_3	OCH_3	80	152–153	$C_{24}H_{25}N_3O_2$ (419.48)

compounds (**6f** and **6h**) was superior to that of the standards. The increase observed in the analgesic activity that parallels the elongation of the side chain may be attributed to the change in the overall lipophilicity of **6** which in turn improves the pharmacokinetic parameters of the molecule.

None of the tested compounds reduced formaldehyde-induced paw oedema.

4. Experimental protocols

4.1. Chemistry

Melting points were determined on a Gallenkemp melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer Model 240 elemental analyzer and were within ± 0.4% of the theoretical values. UV, IR, ^{1}H-NMR spectra were run on Shimadzu UV-260, Shimadzu 435 and Bruker AC 200 or 300 (200/300 MHz) instruments, respectively. EIMS were recorded at the Pennsylvania State University. Starting materials were either commercially available or synthesized according to the indicated literature methods.

4.1.1. Synthesis of substituted sodium benzoates [7]

Equimolar amounts of substituted benzoic acids and NaOH solution were mixed and the resulting solutions were evaporated to dryness to afford substituted sodium benzoates which were used without further purification.

*4.1.2. Synthesis of 4-(Aroyloxyalkanoyl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones (**5**)*

A mixture of **2**–**4** (1 mmol) and an appropriate sodium benzoate (1.1 mmol) was refluxed in DMF (10 mL) for 60–90 min, cooled and poured onto ice-water. The precipitate thus formed was filtered, dried and recrystallized from C_2H_5OH to afford **5**.

5a: UV (EtOH): λ_{max} (log ε) 294 (4.37), 265 (4.25), 220 (4.56) nm. IR (KBr): ν 1 707, 1 657 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz/DMSO-d_6): δ 7.68–7.38 (7H, m, ar), 7.10 (1H, d *J* = 8.50 Hz, ar), 5.32 (2H, s, O–CH_2), 3.85, 3.81 (6H, 2s, 2 OCH_3), 3.36 (3H, s, N–CH_3), 2.59 (3H, s, C–CH_3) ppm. EIMS m/z (%): 410 (M^+, 12), 245 (71), 215 (100), 182 (31), 165 (42), 77 (35), 69 (53), 56 (32), 44 (50).

Table II. Analgesic activity of **6b**–**d** and **6f**–**h.**

Treatment	Mean stretching number	Analgesic activity (%)
6b	21.75 ± 9.16	37.9
6c	28.0 ± 7.34	20.0
6d	14.75 ± 9.60	57.9
6f	6.40 ± 3.56	81.7
6g	13.0 ± 8.42	62.9
6h	8.00 ± 2.90	77.1
Antipyrine	11.4 ± 7.12	67.4
Aminopyrine	18.83 ± 6.53	47.6
Control	5 ± 8.60	–

5b: UV (EtOH): λ_{max} (log ε) 294 (4.17), 228 (4.49), 205 (4.39) nm. IR (KBr): ν 1 714, 1 672, 1 655 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 8.11 (2H, d *J* = 8.53 Hz, ar), 7.54–7.30 (8H, m, ar), 6.28 (1H, q *J* = 6.29 Hz, O–C<u>H</u>–CH_3), 3.36 (3H, s, N–CH_3), 2.68 (3H, s, C–CH_3), 1.65 (3H, d *J* = 6.93 Hz, O–CHC<u>H</u>$_3$) ppm. EIMS m/z (%): 364 (M^+, 3), 259 (41), 215 (100), 189 (5), 147 (3), 135 (1), 122 (1), 105 (16), 91 (3), 77 (17), 56 (14), 28 (2).

5d: UV (EtOH): λ_{max} (log ε) 294 (4.19), 235 (4.45), 207 (4.43) nm. IR (KBr): ν 1 725, 1 670, 1 664 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 8.04 (2H, d *J* = 8.74 Hz, ar), 7.39 (2H, d *J* = 8.58, ar), 7.57–7.30 (5H, m, ar), 6.27 (1H, q *J* = 6.85 Hz, O–CH–CH_3) 3.36 (3H, s, N–CH_3), 2.68 (3H, s, C–CH_3), 1.63 (3H, d *J* = 6.93 Hz, O–CHC<u>H</u>$_3$) ppm. EIMS m/z (%): 398 (M^+, 3), 259 (73), 215 (100), 189 (5), 141, 139 (4, 14), 113, 111 (3, 9), 91 (4), 77 (5), 67 (5), 56 (26), 43 (3), 28 (2).

5f: UV (EtOH): λ_{max} (log ε) 294 (4.28), 229 (4.57), 207 (4.44) nm. IR (KBr): ν 1 708, 1 672, 1 652 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 8.13 (2H, d *J* = 8.30 Hz, ar), 7.53–7.30 (8H, m, ar), 6.11 (1H, dd *J* = 9.00 Hz, 3.00 Hz, O–C<u>H</u>–CH_2CH_3), 3.35 (3H, s, N–CH_3), 2.68 (3H, s, C–CH_3), 2.15, 1.92 (2H, 2m, O–CH–C<u>H</u>$_2$$CH_3$), 1.16 (3H, t *J* = 7.30 Hz, O–CH–CH_2C<u>H</u>$_3$) ppm. EIMS m/z (%): 378 (M^+, 1), 291 (2), 273 (35), 257 (2), 215 (100), 200 (3), 189 (7), 147 (4), 130 (1), 115 (2), 105 (32), 91 (5), 77 (10), 67 (10), 56 (36), 43 (2), 28 (2).

5g: UV (EtOH): λ_{max} (log ε) 291 (4.33), 257 (4.45), 209 (4.57) nm. IR (KBr): ν 1 715, 1 664, 1 655 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 8.07 (2H, d *J* = 9.05 Hz, ar), 7.52–7.30 (5H, m, ar), 6.91 (2H, d *J* = 9.05 Hz, ar), 6.08 (1H, dd *J* = 9.00 Hz, 3.00 Hz, O–C<u>H</u>–CH_2CH_3), 3.85 (3H, s, OCH_3), 3.35 (3H, s, N–CH_3), 2.68 (3H, s, C–CH_3), 2.10, 1.84 (2H, 2m, O–CH–C<u>H</u>$_2$$CH_3$), 1.15 (3H, t *J* = 7.30 Hz, O–CH–CH_2C<u>H</u>$_3$) ppm. EIMS m/z (%): 408 (1), 321 (1), 273 (30), 215 (100), 189 (4), 147 (2), 135 (22).

5h: UV (EtOH): λ_{max} (log ε) 294 (4.43), 234 (4.69), 207 (4.68) nm. IR (KBr): ν 1 725, 1 672, 1 664 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 8.04 (2H, d *J* = 8.39 Hz, ar), 7.55–7.26 (7H, m, ar), 6.11 (1H, dd *J* = 9.00 Hz, 3.00 Hz, O–C<u>H</u>–CH_2CH_3), 3.34 (3H, s, N–CH_3), 2.66 (3H, s, C–CH_3), 2.15, 1.90 (2H, 2m, O–CH–C<u>H</u>$_2$$CH_3$), 1.14 (3H, t *J* = 7.30 Hz, O–CH–CH_2C<u>H</u>$_3$) ppm. EIMS m/z (%): 412 (M^+, 2), 325 (1), 273 (79), 257 (3), 241 (2), 215 (100), 189 (6), 156 (1), 141 (4), 139 (13), 113 (2), 111 (7), 91, 77 (4), 67 (5), 56 (14), 43 (1), 28 (1).

*4.1.3. Synthesis of 4-(2-aryl-5-unsubstituted/substituted oxazol-4-yl)-2,3-dimethyl-1-phenyl-3-pyrazolin-5-ones (***6***)*

A mixture of **5** (1 mmol) and CH_3COONH_4 (10 mmol) was refluxed in CH_3COOH (10 mL) for 5 h. The reaction mixture was poured onto ice water and the pH was adjusted to 6–6.5 with NH_4OH. The precipitate thus obtained was filtered, washed with H_2O and recrystallized from CH_3COCH_3:H_2O to afford **6**.

6a: UV (EtOH): λ_{max} (log ε) 307 (4.32), 210 (4.45) nm. IR (KBr): ν 1 675 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz/DMSO-d_6): δ 8.32 (1H, s, oxazole C5-H), 7.62–7.34 (7H, m, ar), 7.11 (1H, d *J* = 8.50 Hz, ar), 3.86, 3.83 (6H, 2s, 2OCH_3), 3.18 (3H, s, N–CH_3), 2.77 (3H, s, C–CH_3) ppm. EIMS m/z (%): 391 (M^+, 100), 362 (3), 226 (34), 209 (2), 198 (23), 185 (6), 165 (85), 137 (2), 119 (4), 108 (8), 94 (5), 91 (5), 81 (5), 80 (7), 77 (19), 66 (17), 56 (63), 44 (11), 32 (54), 31 (71), 29 (43), 28 (38).

6b: UV (EtOH): λ_{max} (log ε) 289 (4.48), 243 (4.37), 207 (4.54) nm. IR (KBr): ν 1 653 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 8.06–8.00 (2H, m, ar), 7.47–7.29 (8H, m, ar), 3.18 (3H, s, N–CH_3), 2.58 (3H, s, C–CH_3), 2.54 (3H, s, C–CH_3) ppm. EIMS m/z (%): 345 (M^+, 80), 330 (3), 316 (3), 302 (2), 268 (1), 253 (23), 240 (15), 225 (6), 213 (1), 198 (26), 172 (6), 118 (6), 105 (48), 94 (7), 91 (6), 77 (29), 66 (17), 56 (100), 51 (5), 43 (10), 28 (4).

6d: UV (EtOH): λ_{max} (log ε) 292 (4.47), 248 (4.39), 207 (4.52) nm. IR (KBr): ν 1 660 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 7.96 (2H, d *J* = 8.64 Hz, ar), 7.41 (2H, d *J* = 8.70 Hz, ar), 7.48–7.30 (5H, m, ar), 3.18 (3H, s, N–CH_3), 2.57 (3H, s, C–CH_3), 2.52 (3H, s, C–CH_3) ppm. EIMS m/z (%): 381 ($(M + 2)^+$, 32), 379 (M^+, 95), 364 (5), 350 (4), 336 (2), 287 (23), 259 (10), 240 (23), 198 (36), 141, 139 (13, 40), 113 (2), 111 (9), 94 (9), 91 (6), 77 (18), 67 (18), 56 (100), 43 (8), 28 (12).

6f: UV (EtOH): λ_{max} (log ε) 289 (4.50), 222 (4.47), 207 (4.55) nm. IR (KBr): ν 1 659 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 8.04 (2H, dd *J* = 8.30, 2.2 Hz, ar), 7.48–7.30 (8H, m, ar), 3.17 (3H, s, N–CH_3), 2.98 (2H, q *J* = 7.41 Hz, C<u>H</u>$_2$$CH_3$), 2.53 (3H, s, C–$CH_3$), 1.32 (3H, t *J* = 7.42 Hz, CH_2C<u>H</u>$_3$) ppm. EIMS m/z (%): 359 (M^+, 47), 344 (100), 330 (10), 313 (5), 267 (5), 254 (8), 251 (13), 198 (8), 179 (13), 118 (1), 105 (37), 77 (20), 66 (5), 56 (62), 28 (3).

6g: UV (EtOH): λ_{max} (log ε) 290 (4.42), 209 (4.38) nm. IR (KBr): ν 1 666 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 7.97 (2H, d *J* = 9.00 Hz, ar), 7.48–7.30 (5H, m, ar), 6.95 (2H, d *J* = 9.00 Hz, ar), 3.86 (3H, s, OCH_3), 3.16 (3H, s, N–CH_3), 2.95 (2H, q *J* = 7.40 Hz, C<u>H</u>$_2$$CH_3$), 2.52 (3H, s, C–$CH_3$), 1.32 (3H, t *J* = 7.40 Hz, CH_2C<u>H</u>$_3$) ppm. EIMS m/z (%): 389 (M^+, 36), 374 (100), 360 (10), 343 (5), 297 (5), 281 (12), 254 (6), 242 (2), 227

(1), 211 (1), 194 (7), 135 (60), 119 (1), 108 (4), 94 (4), 77 (17), 66 (8), 56 (70), 28 (5).

6h: UV (EtOH): λ_{max} (log ε) 292 (4.36), 249 (4.26), 208 (4.39) nm. IR (KBr): ν 1 660 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz/$CDCl_3$): δ 7.97 (2H, d J = 8.70 Hz, ar), 7.48–7.30 (7H, m, ar), 3.18 (3H, s, N–CH_3), 2.97 (2H, q J = 7.60 Hz, C$\underline{H}_2$CH_3), 2.52 (3H, s, C–CH_3), 1.32 (3H, t J = 7.60 Hz, C$H_2\underline{CH}_3$) ppm. EIMS m/z (%): 395 ($(M + 2)^+$, 12), 393 (M^+, 35), 381, 378 (23, 70), 364 (2), 347 (3), 301 (3), 287, 285 (4, 12), 254 (10), 226 (1), 214 (1), 198 (10), 141, 139 (10, 30), 113 (2), 111 (8), 94 (5), 77 (18), 66 (12), 56 (100), 39 (1), 28 (3).

4.2. Pharmacology

4.2.1. Analgesic activity (modified Koster's test) [9]

Nine groups of albino mice, consisting of five animals of either sex, weighing 30–35 g received 0.5 mL solutions of the test compounds (**6b**–**6d**, **6f**–**6h**: 0.19–0.21 $mmol.kg^{-1}$, antipyrine 0.39 $mmol.kg^{-1}$ and aminopyrine 0.32 $mmol.kg^{-1}$) in DMSO through a stomach tube. The control group received only the vehicle (0.5 mL). One hour after the administration of the test compounds pain was induced by ip injection of 0.6% acetic acid solution (1 $mmol.kg^{-1}$). The number of nociceptive reactions (writhing and stretching) were recorded 5 min after the injection of acetic acid during a period of 10 min, and analgesic activity was calculated according to the following equation:

$$\% \text{ analgesic activity} = \frac{N - N'}{N} \times 100$$

Where N is the mean stretching number of the control group, and N′ is the mean stretching number of the experimental group.

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