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Short communication

Design, synthesis and antiinflammatory activity of some 1,3,4-oxadiazole derivatives

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Summary — A series of substituted 1,3,4-oxadiazole derivatives **19–34** were synthesized as antiinflammatory agents. The target compounds were obtained by cyclodesulfurization of the corresponding thiosemicarbazides **3–18** using either dicyclohexylcarbodiimide DCC, or I_2/NaOH. Intermediates **3–18** are readily accessible through conversion of the carboxylic acids **1a–d** to the respective hydrazides **2a–d** followed by treatment with appropriate isothiocyanate derivatives. The structures of the synthesized compounds were confirmed by elemental as well as spectroscopic analyses. The antiinflammatory activity was investigated by determination of the inhibitory effects of the oxadiazole derivatives **19–34** on histamine-induced edema in rat abdomen. Compounds **19a**, **21a**, **23b**, **28c** and **32d** proved to be more potent antiinflammatory agents at 200 mg/kg po than ibuprofen, the standard reference drug. Other compounds such as **20a**, **25b**, **27c**, **29c**, and **33d** showed significant antiinflammatory activity but less than ibuprofen at the same dose level. The low toxicity of the most potent compounds was reflected by their higher LD_{50} value, ranging from ~1000 to 1500 mg/kg, as well as the lower ulcerogenic liability at 200 mg/kg po. Furthermore, some of the newly synthesized derivatives were better analgesics than the reference drug as observed from the percentage writhing inhibition in the *p*-benzoquinone (PBQ)-induced writhing test in mice.

1,3,4-oxadiazole / antiinflammatory activity / analgesic effect / acute toxicity / ulcerogenic liability

Introduction

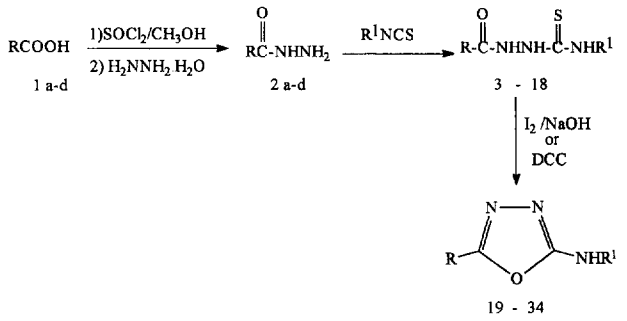
Non-steroidal antiinflammatory drugs (NSAIDs) are widely used in the treatment of rheumatoid arthritis and inflammatory diseases. However, long-term NSAID use has been associated with gastrointestinal (GI) ulceration, bleeding and nephrotoxicity [1]. The tendency of many acidic drugs to accumulate in stomach walls soon after oral absorption, as evidenced by radioautography, has been considered as a contributing factor to GI irritation [2]. In addition, cyclooxygenase (CO) inhibition, which is the principle mechanism for analgesic and antiinflammatory properties of NSAIDs [3], has also been associated with nephrotoxicity and GI side effects [4].

It has been reported that many non-acidic antiinflammatory agents with comparable potency to indomethacin have better GI-tolerance in animal models [5]. Meanwhile, the replacement of the carboxylic acid functionality of some NSAIDs, eg, flufenamic and meclofenamic acids, with a tetrazole group not only retained CO inhibitory activity of the parent drug, but also introduced 5-lipooxygenase (5-LO) inhibition [6]. Several other heterocyclic compounds, including di-*tert*-butylphenyloxazoles, thiazoles or imidazoles [7] and substituted oxadiazole and thiadiazole derivatives [6, 8–11] have been studied and proved to be potent CO/5-LO inhibitors. This novel dual inhibitory activity of the enzyme pathways holds promise as antiinflammatory agents with an improved efficacy and safety profile.

Encouraged by these findings, we replaced the carboxylic acid group of ibuprofen and some other heterocyclic carboxylic acids (nicotinic, isonicotinic and quinoline-6-carboxylic acid) with a substituted amino-1,3,4-oxadiazole nucleus in a trial of obtaining additional inhibitors of cellular arachidonate metabolism. The basic substituent on the oxadiazole nucleus counteracts any tendency for accumulation in stomach walls affording an additional safety factor.

Chemistry

The acid hydrazides **2a–d**, which are key intermediates for synthesis of the oxadiazoles **19–34** (scheme 1), were prepared according to reported methods [12–14]. Treatment of **2a–d** with the appropriate isothiocyanate rapidly gave the corresponding thiosemicarbazide derivatives **3–18** in quantitative yields (table I). Cyclodesulfurization of the thiosemicarbazide derivatives to afford 2,5-disubstituted 1,3,4-oxadiazole deri-



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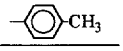
	$-CH_2CH_3$			
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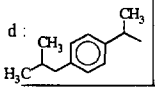
d: 	15 31	16 32	17 33	18 34

Scheme 1. Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles.

Table I. Physical constants, yields and elemental analyses of the thiosemicarbazides **3–18**.

Compound	*Yield (%)*	*Mp (°C) (solvent)*	*Molecular formula (mol wt)*
3a	93	178–180 (Et)	$C_9H_{12}N_4OS$ (224.27)
4a	95	187–188 (Et)	$C_{13}H_{18}N_4OS$ (278.36)
5a	93	181–182 (Et)	$C_{13}H_{12}N_4OS$ (272.31)
6a	90	164–166 (Et)	$C_{14}H_{14}N_4OS$ (286.34)
7b	96	212–215 (aq DMF)	$C_9H_{12}N_4OS$ (224.27)
8b	97	208–210 (Et)	$C_{13}H_{18}N_4OS$ (278.36)
9b	97	182–184 (Et)	$C_{13}H_{12}N_4OS$ (272.31)
10b	98	185–186 (Et)	$C_{14}H_{14}N_4OS$ (286.34)
11c	93	187–188 (Et)	$C_{13}H_{14}N_4OS$ (274.33)
12c	96	196–198 (Et)	$C_{17}H_{20}N_4OS$ (328.42)
13c	97	128–130 (Et)	$C_{17}H_{14}N_4OS$ (322.37)
14c	96	154–156 (Et)	$C_{18}H_{16}N_4OS$ (336.40)
15d	95	150–152 (aq Et)	$C_{16}H_{25}N_3OS$ (307.44)
16d	98	163–165 (Et)	$C_{20}H_{31}N_3OS$ (361.53)
17d	98	178–180[a] (Et)	$C_{20}H_{25}N_3OS$ (355.48)
18d	96	165–167 (aq Et)	$C_{21}H_{27}N_3OS$ (369.51)

Crystallization solvent: Et = ethanol; aq Et = aqueous ethanol; aq DMF = aqueous dimethylformamide; [a]reported 180–181 °C [14].

vatives **19–34** (table II) was carried out in analogy to reported methods for related compounds using either dicyclohexylcarbodiimide (DCC) (*Method A*) [15] or I_2/NaOH (*Method B*) [11]. The purity of the products was the principle factor in selection of the cyclodesulfurization method. The problem of separation of the resulting dicyclohexylurea (DCU) limits the application of *Method A* as a general method for synthesis. Alternatively, cyclodesulfurization with I_2/NaOH is a simple, rapid method and afforded pure products as evidenced by TLC (chloroform/acetone/triethyl amine 5:4:0.5). All compounds of the substituted thiosemicarbazides **3–18** and the oxadiazoles **19–34** were characterized by elemental and spectral analysis (tables I–III).

The assignment of the chemical shifts in the ^{1}H-NMR spectra to the respective protons (table III) was achieved with reference to reported data for analogous compounds [15, 16]. The protons of the thiosemicarbazide moiety $CON^1HN^2HCSN^4HR^1$ appeared mostly as three signals for the NH-groups. The N^4-proton was found to be resonating at different chemical shifts depending on the nature of the substituent R^1. In the aliphatic series (R^1 = ethyl or cyclohexyl) it appeared as a split signal at 7.4–7.8 ppm, while in case of the aromatic analogues (R^1 = phenyl or *p*-tolyl) it is downfield shifted to 10.7 ppm. This pattern is also

Table II. Physical constants, yields and elemental analyses of 2,5-disubstituted-1,3,4-oxadiazoles **19–34**.

Compound	*Yield (%)*	*Mp (°C) (solvent)*	*Molecular formula (mol wt)*
19a	77 (B)	180–182 (Et)	$C_{15}H_{13}N_7O_8$ (419.31)
20a	75 (B)	165–167 (Et)	$C_{19}H_{19}N_7O_8$ (473.40)
21a	60 (A)	225–227 (Et)	$C_{13}H_{10}N_4O$ (238.25)
22a	65 (A)	254–256 (Et)	$C_{14}H_{12}N_4O$ (252.28)
23b	75 (B)	220–222 (Et)	$C_{15}H_{13}N_7O_8$ (419.31)
24b	79 (B)	229–230 (Et)	$C_{13}H_{16}N_4O$ (244.30)
25b	73 (B)	218–220[a] (Et)	$C_{13}H_{10}N_4O$ (238.25)
26b	72 (B)	240–242 (Et)	$C_{14}H_{12}N_4O$ (252.28)
27c	66 (A)	175–176 (aq Et)	$C_{13}H_{12}N_4O$ (240.27)
28c	74 (B)	210–213 (aq Et)	$C_{23}H_{21}N_7O_8$ (523.46)
29c	64 (A)	225–226 (Et)	$C_{17}H_{12}N_4O$ (288.31)
30c	66 (A)	258–259 (aq DMF)	$C_{18}H_{14}N_4O$ (302.34)
31d	70 (B)	163–165 (aq Et)	$C_{22}H_{26}N_6O_8$ (502.48)
32d	75 (B)	161–163 (aq Et)	$C_{20}H_{29}N_3O$ (327.47)
33d	75 (B)	147–148 (aq Et)	$C_{20}H_{23}N_3O$ (321.42)
34d	77 (B)	148–150 (aq Et)	$C_{21}H_{25}N_3O$ (335.43)

Cyclodesulfurization A: DCC; B: I_2/NaOH. Compounds **19a**, **20a**, **23b**, **28c** and **31d** separated as picrate; [a]reported 222 °C [21].

Table III. ^{1}H-NMR data of the thiosemicarbazides **3–18** and the substituted oxadiazoles **19–34**.

Compound	*δ (ppm)*
4a	1.5 (m, 11H, cyclohexyl); 7.4 (m, 2H, pyr-H5; -CSN*H*-); 8.2 (m, 1H, pyr-H4); 8.8 (dd, 1H, pyr-H6); 9.1 (d, 1H, pyr-H2); 9.2 (s, 1H, -NHCS-); 10.4 (bs, 1H,CONH)
5a	7.5 (m, 6H, phenyl; pyr-H5); 8.3 (m, 1H, pyr-H4); 8.8 (dd, J = 6.5, 2 Hz, 1H, pyr-H6); 9.1 (d, J = 2 Hz, 1H, pyr-H2); 9.8 (s, 1H, -NHCS-); 9.9 (s, 1H, -CONH-) 10.5 (s, 1H, -CSNH)
7b	1.2 (t, 3H, J = 7 Hz, -CH_3); 3.5 (q, 2H, J = 7 Hz, -CH_2-); 7.9 (bd, 3H, pyr H3, H5 + CSNH-); 8.8 (d, 2H, J = 6 Hz, pyr-H2, H6); 9.2 (bs, 1H, -NHCS-); 10.5 (bs, 1H, -CONH-)
8b	1.5 (m, 11H, cyclohexyl); 7.8 (m, 3H, pyr-H3, H5, -CSNH-); 8.75 (d, J = 6 Hz, pyr-H2, H6); 9.2 (bs, 1H, -NHCS-); 10.5 (s, 1H, -CONH)
9b	7.3 (m, 5H, phenyl); 7.8 (d, J = 6.5 Hz, 2H, pyr-H3, H5); 8.8 (d, J = 6.5 Hz, 2H, pyr-H2, H6); 9.8 (bs, 1H, -NHCS-); 10.7 (bs, 2H, -CSNH- + -CONH-)
10b	2.3 (s, 3H, CH_3); 7.2 (d, J = 9 Hz, 2H, phenyl-H3, H5); 7.4 (d, J = 9 Hz, 2H, phenyl H2, H6); 7.8 (d, J = 6 Hz, 2H, pyr-H3, H5); 8.8 (d, J = 6 Hz, 2H, pyr-H2, H6); 9.9 (s, 1H, -NHCS-); 10.7 (bs, 2H, -CSNH- + -CONH-)
12c	1.5 (m, 11H cyclohexyl); 7.7 (m, 3H, quinol-H3, H8, -CSNH-); 8.2 (dd, J = 6, 2Hz, 1H, quinol-H4); 8.5 (m, 2H, quinol-H5, H7); 9.0 (d, J = 2 Hz, 1H, quinol-H2); 9.2 (bs, 1H, -NHCS); 10.6 (bs, 1H,-CONH)
13c	7.4–8.3 (m, 8H, phenyl, quinol-H3, H4, H8); 8.5 (m, 2H, quinol-H5, H7); 9.0 (d, J = 3 Hz, quinol-H2); 9.9 (s, 1H, NHCS-); 10.6 (bs, 2H, -CSNH, -CONH)
16d	0.9 (d, J = 7 Hz, 6H, 2CH_3), 1.4 (bm, 15H, -CH_3, -CH, cyclohexyl), 2.4 (d, J = 7 Hz, 2H, -CH_2); 3.7 (q, J = 7 Hz, 1H, -CHCO-); 6.6 (d, J = 8 Hz, 1H, -CSNH-); 7.2 (d, J = 8 Hz, 4H, phenyl); 9.1 (bs, 1H, -NHCS-); 9.9 (bs, 1H, -CONH-)
17d	0.9 (d, 6H, 2CH_3); 1.4 (d, J = 6 Hz, 3H, -CH_3); 1.8 (m, 1H, -CH); 2.5 (d, J = 7 Hz, 2H, CH_2); 3.7 (q, J = 7.5, 1H, -CHCO); 7.3 (m, 9H, phenyl); 9.4 (bs, 1H,-NHCS-); 9.6 (bs, 1H, -CONH); 10.1 (bs, 1H, -CSNH-)
22a	2.3 (s, 3H, CH_3); 7.2 (d, J = 9 Hz, 2H, phenyl H3, H5); 7.6 (d, J = 9 Hz, 2H, phenyl H2, H6); 7.8 (m, 1H, pyr-H5); 8.2 (m, 1H, pyr-H4); 8.8 (dd, J = 4.5, 2 Hz, 1H, pyr-H6); 9.1 (d, J = 1.5 Hz, 1H, pyr-H2)
25b	7.4 (m, 5H, phenyl); 7.9 (d, J = 7 Hz, 2H, pyr-H3, H5); 8.8 (d, J = 7 Hz, 2H, pyr-H2, H6); 10.9 (s, 1H, -NH-)
26b	2.3 (s, 3H, -CH_3); 7.2 (d, J = 9 Hz, 2H, phenyl-H3, H5); 7.5 (d, J = 9 Hz, 2H, phenyl-H2, H6); 7.9 (d, J = 6.5 Hz, 2H, pyr-H3, H5); 8.8 (d, J = 6.5 Hz, 2H, pyr-H2, H6)
29c	7.5–8.3 (m, 8H, phenyl, quinol-H3, H4, H8); 8.6 (m, 2H, quinol-H5, H7); 8.7 (d, J = 3 Hz, 1H, quinol-H2)
32d	0.9 (d, J = 7 Hz, 6H, 2CH_3); 1.5 (bm, 15H, -CH_3, -CH, cyclohexyl); 2.5 (d, J = 7 Hz, 2H, -CH_2); 4.2 (q, J = 7 Hz, 1H, -CHCO-); 5.55 (d, J = 8 Hz, 1H, -NH) 7.1 (s, 4H, phenyl)
33d	1.0 (d, 6H, 2CH_3); 1.8 (d, J = 7 Hz, 3H, -CH_3); 2.2 (m, 1H, -CH); 2.6 (d, J = 7 Hz, 2H, -CH_2); 4.3 (q, J = 6.6 Hz, 1H, -CHCO); 7.3 (m, 9H, phenyl); 8.0 (bs, 1H, -NH)
34d	1.0 (d, J = 7 Hz, 6H, 2CH_3); 1.8 (m, 4H, -CH + -CH_3); 2.35 (s, 3H, CH_3); 2.5 (d, J = 7 Hz, 2H, -CH_2); 4.2 (q, J = 7 Hz, 1H, -CH); 7.2 (m, 8H, arom) 7.7 (bs, 1H, NH)

Chemical shifts in δ ppm; solvent: d_6-DMSO; compounds **16d**, **32d–34d** in $CDCl_3$; bs: broad singlet

observed in the oxadiazole series **19–34**; the corresponding chemical shifts are 5.55 and 7.77 ppm, respectively.

Pharmacological results and discussion

Antiinflammatory activity

The antiinflammatory activity of the synthesized 1,3,4-oxadiazole derivatives **19–34** (at 200 mg/kg, po) was evaluated using Golikov's method [17]. Intradermally injected histamine was used as the phlogogenic substance and trypan blue (iv) as indicator. The increase in the time elapsed until the appearance of the blue colour at the site of injection of histamine vs control was taken as a measure of the antiinflammatory activity of the tested compounds and the reference standard drug (ibuprofen). This antiinflammatory in vivo model is simple and easily to test as compared with the other common methods for determination of antiinflammatory activity. In addition, the accuracy in time measurement is easily and precisely controlled by the appearance of the blue colour of the indicator used.

The results are expressed as the mean time (min) ± standard error (fig 1), and the significance of the values of compounds treated and control groups was evaluated using the Student's *t*-test (table IV). The difference in results was considered significant when $P < 0.05$ [18]. It was observed that 13 compounds of the tested oxadiazole derivatives showed significant ($P < 0.05$) inhibition against histamine-induced inflammation in rats as compared with the control. Among the significantly active compounds, the oxadiazoles **19a**, **21a**, **23b**, **28c** and **32d** were the most potent and exhibited higher antiinflammatory activity than ibuprofen, the standard reference drug. On the other hand oxadiazole derivatives with a *p*-tolyl substituent, **22a**, **26b**, **30c** and **34d** were inactive under the antiinflammatory test conditions.

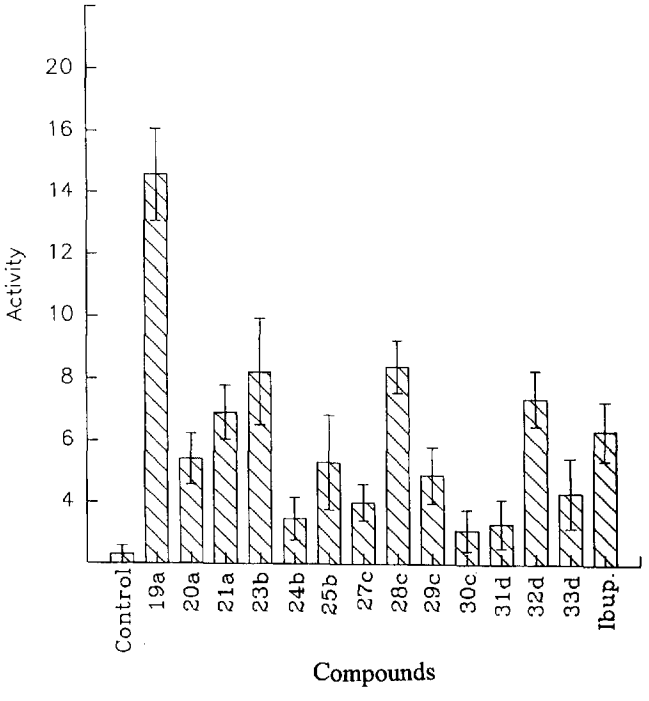


Fig 1. Antiinflammatory activity (mean time ± SE) of the oxadiazole derivatives and ibuprofen at 200 mg/kg po.

Analgesic activity

The oxadiazole derivatives were tested for analgesic activity at 200 mg/kg po in *p*-benzoquinone-induced writhing test [19]. The vehicle (5% gum acacia) used for suspension of the tested compounds exhibited no protection (control group) against PBQ-induced writhing. The reference drug (ibuprofen) resulted in 90% reduction of induced writhing. Oxadiazoles derived from nicotinic acid (**21a**) and quinoline-6-carboxylic acid (**28c**, **29c**) were found to be the most active derivatives, exhibiting 100% inhibition of the induced writhing 30 min after injection of PBQ. Other derivatives showed inhibition values ranging from 30–80%.

Acute toxicity

The 24 h intraperitoneal LD_{50} of the most active compounds was determined using Pershin's mathematical method [20]. In this method six dose levels were used beginning with the dose which produces 0% mortality and ending with the dose which causes 100% mortality. The dose interval between each two succesive doses was kept the same and the LD_{50} values were calculated according to the formula indicated in the *Experimental protocols*. The results (table IV) reveal that, among the oxadiazole derivatives tested, compounds **19a**, **21a**, **31d** and **32d** showed higher LD_{50} than the standard reference drug, while compounds **23b**, **28c** and **33d** showed higher toxicity.

Ulcerogenic liability

Oxadiazole derivatives **19a**, **28c** and **32d** with best overall profile in animal efficacy model were evaluated for gastric ulcerogenic potential in rat stress model (table IV). Compared with ibuprofen, compounds **19a** and **32d** did not cause any significant gastric ulceration in this model at oral dose of 200 mg/kg for 4 days. Scanning of stomach specimens using electron microscopy revealed that in rats treated with these two compounds there is no injury observed in stomach mucosa. As illustrated in figure 2, specimens B and D

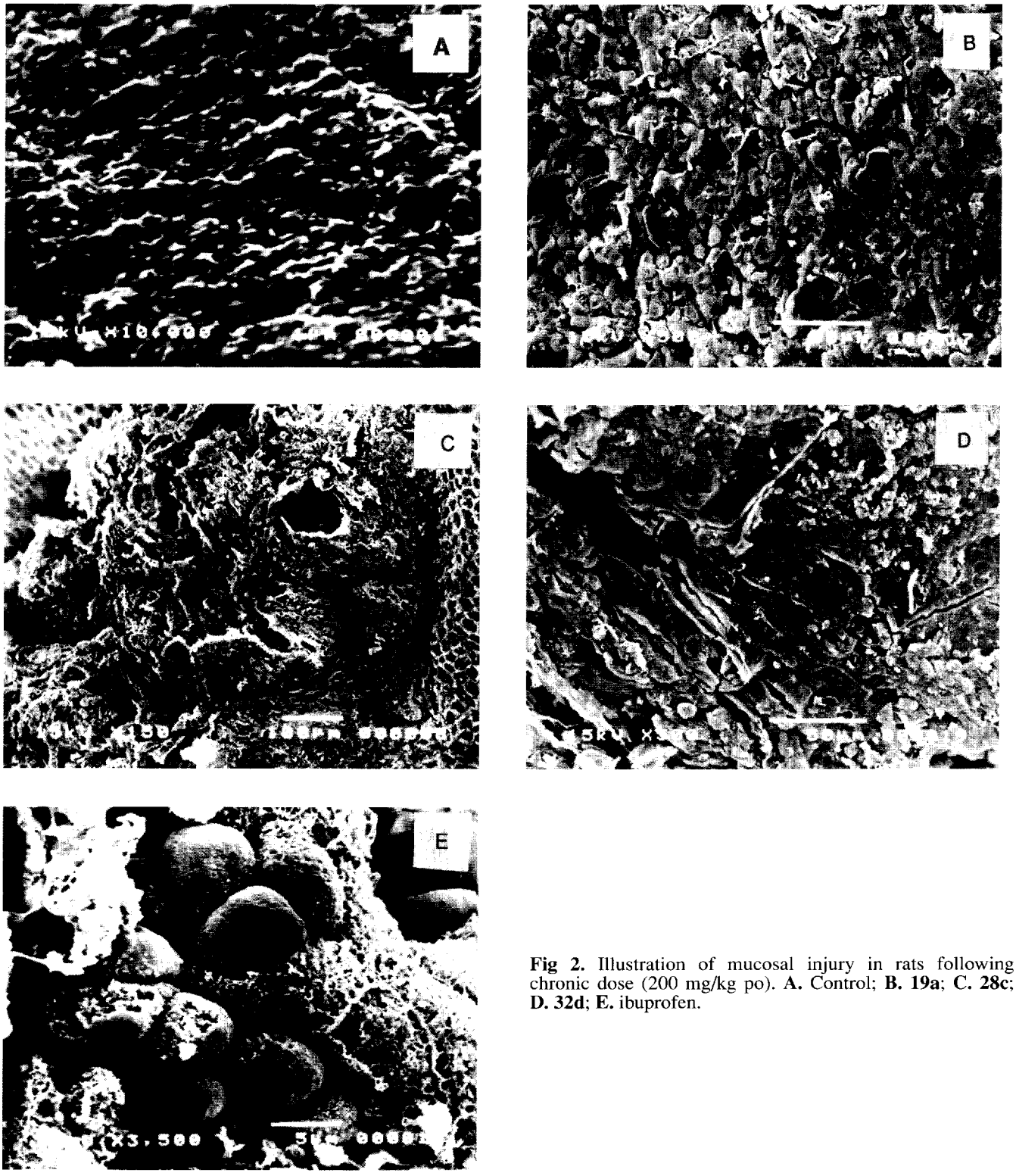


Fig 2. Illustration of mucosal injury in rats following chronic dose (200 mg/kg po). **A.** Control; **B. 19a**; **C. 28c**; **D. 32d**; **E.** ibuprofen.

Table IV. Analgesic and antiinflammatory activities and acute toxicity of the oxadiazole derivatives (**19–34**) and ibuprofen.

Compound	*Antiinflammatory activity*	*Analgesic activity*	*Acute toxicity*	
	Mean time[a] *(min ± SE)*	*% Inhibition*[b]	*ALD_{50} ip (mg/kg)*	*Gastric ulcers*[c]
Control	2.29 ± 0.29	0.0		
19a	14.56 ± 1.5	60	1468	0%
20a	5.4 ± 0.83	40		
21a	6.91 ± 0.88	100	1146	
22a	N			
23b	8.2 ± 1.71	60	952	
24b	3.46 ± 0.69	60		
25b	5.29 ± 1.54	60	1014	
26b	N	30		
27c	4.0 ± 0.59	70		
28c	8.39 ± 0.84	100	920	100%
29c	4.88 ± 0.91	100		
30c	3.1 ± 0.67	80		
31d	3.31 ± 0.79		1346	
32d	7.37 ± 0.90	50	1501	0%
33d	4.3 ± 1.14	60	777	
34d	N	50		
Ibuprofen	6.33 ± 0.96	90	1009	80%

[a]200 mg/kg, po, mean ± standard error of estimate ($n = 5$); [b]200 mg/kg, po, percentage writhing inhibition in 30 min after PBQ administration, calculated by comparing with vehicle-treated control animals ($n = 10$); [c]gastric ulcerogenicity data are percent rats with ulcers, at 200 mg/kg, po; $n = 6$ animals per experimental group. N: statistically non-significant compared to control ($P \geq 0.05$).

are identical to that of the control (A). Although compound **28c** is more potent than ibuprofen in histamine-induced edema in rats, it also exhibits the greatest incidence of ulceration. Gross observation in rats treated with this compound showed a pale stomach with a paper-thin structure and volcano-like ulcers (fig 2C). The stomach of ibuprofen-treated rats is characterized by complete damage of the protective mucosal layer (fig 2E).

Experimental protocols

Chemistry

Melting points were determined on capillary melting point apparatus (Stuart Scientific) and are uncorrected. Precoated silica-gel plates (Kiesel gel 60G F254 nm, Merk) were used for TLC. IR spectra were recorded on Shimadzu 200-91527 IR spectrophotometer using KBr disk method. The ^{1}H-NMR spectra were measured on Varian EM-360L NMR spectrometer (Varian, USA), TMS was used as internal standard and chemical shifts are given in ppm. Microanalyses were carried out on a Perkin-Elmer 240C elemental analyzer at Faculty of Science, Cairo University. All the determined values are within the accepted microanalytical limits of ±0.40%.

Stomach specimens were scanned in the electron microscope unit of Assiut university (Jeol JSM-5400LV scanning microscope).

Ibuprofen was purchased from Kahira Co for Drugs and Chemical Industries, Cairo, Egypt, histamine HCl from Aldrich Chemical Company, UK, and *p*-benzoquinone (PBQ) and Trypan blue from Chemapan, Prague. All other chemicals, reagents and solvents used in this study were of reagent grade. The acid hydrazides **2a–d** were prepared according to the usual methods, using the parent acids as the starting compounds. The resulting acid hydrazides were characterized and compared with the corresponding reported data.

Nicotinic acid hydrazide **2a**: mp 162–163 °C [12], yield 82%. Isonicotinic acid hydrazide **2b**: purchased from CID (Chemical Industrial Development Co), Assiut, Egypt. Quinoline-6-carboxylic acid hydrazide **2c**: mp 186–188 °C [13], yield 78%. 2-(4-Isobutylphenyl)propionic acid hydrazide **2d**: mp 75–76 °C reported as oil [14], yield 77%. IR, KBr (cm^{-1}): 3455, 3270 (NH_2, NH), 2950 (CH), 1695 (CONH-), 1636 (C=C); ^{1}H-NMR, $CDCl_3$, δ ppm: 1.25 (d, $J = 7$ Hz, 6H, $2CH_3$), 1.85 (d, $J = 7$ Hz, 3H, CH_3), 2.2 (m, 1H, CH), 2.8 (d, $J = 7$ Hz, 2H, CH_2), 3.85 (q, $J = 7$ Hz, 1H, CH-), 4.0 (s, 2H, NH_2), 7.5 (bs, 5H, C_6H_4- and NH-).

*Substituted thiosemicarbazide derivatives **3–18***

To a solution of the acid hydrazide **2a–d** (4.4 mmol) in hot ethanol (40 mL) was added equivalent amount of the appropriate isothiocyanate in ethanol (10 mL) and the mixture was

refluxed with stirring for 30 min. The products, which either precipitated during reflux or after cooling to room temperature, were filtered and crystallized from the proper solvent. Yields and physical constants are listed in table I. ^{1}H-NMR data are presented in table III.

2,5-Disubstituted-1,3,4-oxadiazole derivatives ***19–34***

Method A. A solution of the respective thiosemicarbazide derivative (2.5 mmol) and DCC (3.7 mmol) in a mixture of absolute methanol/dry acetone (1:1 v/v) was refluxed with stirring for 5 h. After cooling to room temperature the products were filtered and crystallized from the appropriate solvent. Yields and physical constants are listed in table II. ^{1}H-NMR data are presented in table III.

Method B. To a stirred, cooled (0–5 °C) solution of the respective thiosemicarbazide derivative (5 mmol) in ethanol (30 mL), was added 2 N sodium hydroxide until the solution aquired pH 9. Iodine in potassium iodide solution (5%) was then added dropwise with stirring at room temperature until the yellow colour of iodine persisted. The solvent was removed under reduced pressure and the mixture cooled to precipitate the corresponding oxadiazole derivative. The products were then filtered, washed with water and carbon disulfide, dried and crystallized from the proper solvent (table II).

Pharmacology

Antiinflammatory activity

Groups of six rats (200–250 g) were used. The hair of the abdominal region of each rat was shaved and 1 mL suspension of the tested compounds and ibuprofen (reference drug) in 5% gum acacia solution were given orally. The control group received an equivalent amount of 5% gum acacia solution. After 30 min, trypan blue solution (0.5%) was intravenously injected in a dose of 2 mL/kg followed by intradermal injection of histamine HCl in the shaved region (0.02 mL of 1% solution). The antiinflammatory activity of the tested compounds and the reference drug was determined as the time in minutes taken until the appearance of the blue colour of the injected dye around the site of histamine injection. Student's *t*-test was performed and a value of $P < 0.05$ was considered significant.

Analgesic activity

Suspensions of the tested oxadiazole derivatives and ibuprofen (0.5 mL) in 5% gum acacia solution were administered orally to groups each of ten mice, weighing 18–22 g. *p*-Benzoquinone (0.025 mL of 0.02% solution) was injected ip 30 min after administration of the above compounds. The animals were immediately placed individually in a glass container and observed during the 30 min at which maximal writhing occurred in control animals. The number of writhes or abdominal constriction response displayed by each mouse was counted for 30 min after the administration of *p*-benzoquinone. The results are expressed as percentage inhibition of the induced writhing (table IV). Student's *t*-test was performed and a value of $P < 0.05$ was considered significant. Control animals receiving an equivalent oral dose (0.5 mL) of 5% gum acacia were used.

Acute toxicity

Groups of six albino mice weighing 18–22 g were fasted for 18 h prior to the administration of the tested compounds. The potent compounds (**19a**, **21a**, **23b**, **25b**, **28c** and **31d–33d**) and the reference drug were administered intraperitoneally in six dose levels ranging from 200 to 2000 mg/kg. The 24 h mortalities for each dose level were recorded to calculate the approximate LD_{50} values with the following formula:

$$LD_{50} = \Sigma(a + b)(m-n)/200$$

where a and b are any two successive doses; $(m-n)$ is the difference in mortalities of every two subsequent doses; the results are listed in table IV.

Gastric ulcerogenicity

Male rats (180–200 g) were fasted for 24 h and then subjected to a daily oral dose of 1 mL suspension of the tested compounds or ibuprofen in 0.5% methylcellulose for four successive days. The control rats were administered an equal volume of the dispersion medium. The rats were denied access to food throughout this period. At 24 h after the last dose the rats were sacrificed so that the stomach could be removed, opened along the greater curvature and cleaned gently by dipping in saline. The mucosal damage was examined grossly under binocular magnifier and specimen were prepared for scanning in electron microscope. Compounds were tested at a dose of 200 mg/kg po, with six animals per compound.

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