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Synthesis and Some Pharmacological Studies of New Benzenesulfonamide Derivatives

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Summary. New benzenesulfonamide derivatives containing pyrazole and oxadiazole moieties were prepared starting from sodium saccharin. The structures of the novel compounds were characterized by elemental analyses and spectroscopic methods. The new compounds are structurally related to the COX-2 inhibitor celecoxib (Celebrex®). A pharmacological study of the pyrazoles revealed that several compounds possess higher analgesic and antiinflammatory activities than celecoxib, particularly **11** and **17**. Most of the pyrazoles showed a significant increase in the sleeping time of thiopentone anaesthesized mice and also protected mice against the convulsive and lethal effects of pentylenetetrazole. Moreover, the ulcerogenic activity of those compounds showing a pronounced antiinflammatory effect was also studied.

Keywords. Sodium saccharin; Benzenesulfonamide derivatives; Pyrazoles; Analgesic; Antiinflammatory.

Introduction

Several pyrazole and oxadiazole derivatives have been reported to exhibit analgesic and antiinflammatory activity [1–3]. Moreover, many drugs containing the pyrazole moiety are still used clinically as analgesic and antiinflammatory agents, *e.g.* antipyrine and aminopyrine [1, 2]. Recently, the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib [4–6], a benzenesulfonamide derivative carrying a pyrazole moiety, has been introduced into medicine as an analgesic and antiinflammatory agent. The use of celecoxib for treatment of inflammation and pain avoided many side effects of the nonsteroidal antiinflammatory drugs because of its selectivity as COX-2 inhibitor [7, 8]. In this article, new benzenesulfonamide derivatives containing a pyrazole moiety were designed and synthesized which are structurally related to celecoxib in order to produce potent analgesic and

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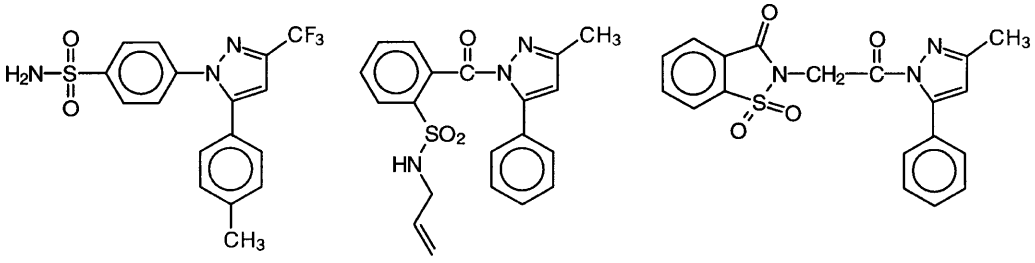
antiinflammatory agents with no or less tendency to evoke gastric ulceration. In addition, new benzenesulfonamide derivatives containing an oxadiazole moiety were prepared.



Celecoxib **11** **17**

Results and Discussion

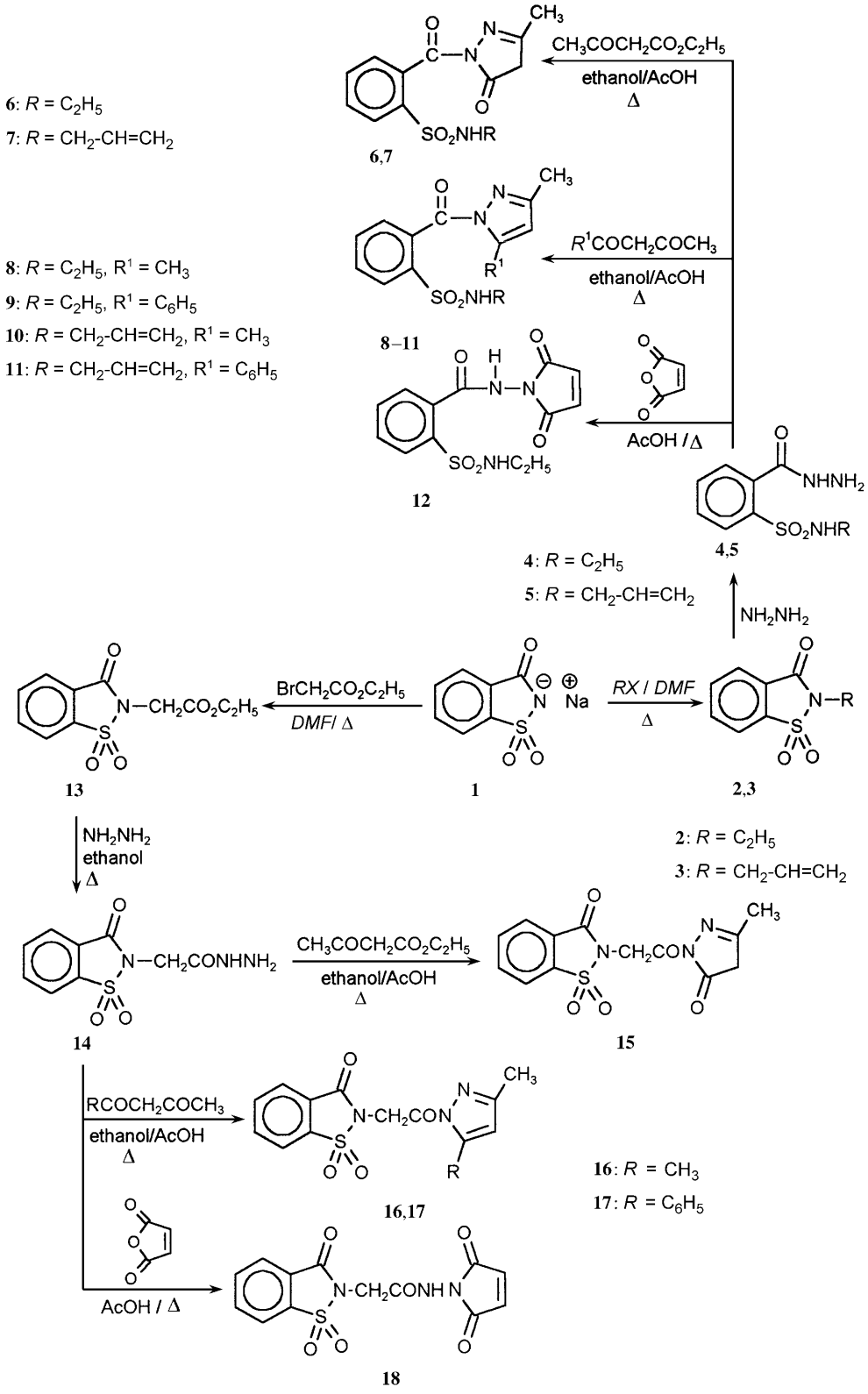
Chemistry

The preparation of the new compounds is outlined in Scheme 1. N-Alkyl saccharins (**2**, **3**, and **13**) were prepared *via* the reaction of ethyl iodide [9, 10], allyl bromide [11–13], or ethyl bromoacetate [11] with sodium saccharin by heating the reactants in *DMF* for 2 h according to a reported procedure [9]. The hydrazide key intermediates **4**, **5**, and **14** were prepared either by stirring **2** or **3** with excess hydrazine hydrate at room temperature for 10–20 min [9] (**4**, **5**) or by heating equimolar amounts of **13** and hydrazine hydrate in ethanol under reflux for 1 h (**14**). The hydrazides were cyclized [14] with β-diketones such as ethyl acetoacetate, acetylacetone, or benzoylacetone by heating equimolar amounts of the reactants under reflux in ethanol containing 2 cm^3 acetic acid for 12 h to afford the novel antiinflammatory pyrazole derivatives **6**–**11** and **15**–**17** in high yields. Moreover, the hydrazides **4** and **14** were condensed with maleic anhydride by heating the reactants in glacial acetic acid for 8 h to give the novel maleimido derivatives **12** and **18**.

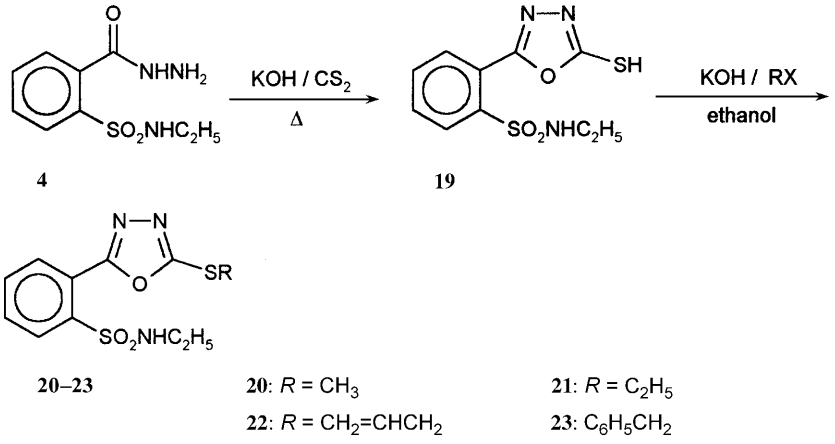
The novel benzenesulfonamide derivatives containing an oxadiazole moiety were prepared as shown in Scheme 2. 2-(5-Mercapto-1,3,4-oxadiazol-2-yl)-N-ethylbenzenesulfonamide (**19**) was obtained in high yield according to *Young* and *Wood* [15] by refluxing **4** with carbon disulfide in aqueous ethanol in the presence of potassium hydroxide. **19** was allowed to react with different alkyl or aralkyl halides in ethanol containing potassium hydroxide at room temperature to afford 2-(5-substituted-thio-1,3,4-oxadiazol-2-yl)-N-ethylbenzenesulfonamides **20**–**23**.

Pharmacology

The novel compounds **6**–**12** and **17** were tested for their analgesic and antiinflammatory activities using celecoxib for comparison. In addition, the effects of these compounds on the sleeping time of thiopentone anaesthesized mice and their anticonvulsant activities were studied.


6: R = C2H5
7: R = CH2-CH=CH2
8: R = C2H5, R1 = CH3
9: R = C2H5, R1 = C6H5
10: R = CH2-CH=CH2, R1 = CH3
11: R = CH2-CH=CH2, R1 = C6H5
CH3COCH2CO2C2H5
ethanol/AcOH
Δ
6,7
R1COCH2COCH3
ethanol/AcOH
Δ
8–11
AcOH /Δ
12
4,5
4: R = C2H5
5: R = CH2-CH=CH2
NH2NH2
BrCH2CO2C2H5
DMF/ Δ
13
1
RX / DMF
Δ
2,3
2: R = C2H5
3: R = CH2-CH=CH2
NH2NH2
ethanol
Δ
14
CH3COCH2CO2C2H5
ethanol/AcOH
Δ
15
RCOCH2COCH3
ethanol/AcOH
Δ
16,17
16: R = CH3
17: R = C6H5
AcOH / Δ
18

Scheme 1



Scheme 2

The results presented in Table 1 illustrate the analgesic activity [16] of the test compounds following their intraperitoneal (i.p.) injection at a dose level of 1.7 mg/kg body weight of mice. Obviously, **7** and **12** have no significant analgesic effect. Compounds **6**, **8**, **9**, **10**, **11** and **17** show analgesic activity as they increase the reaction time. The effect decreases in the order **17** > **11** > **9** > celecoxib > **8** > **6** > **10**.

The intradermal injection of carrageenin (10%) at a dose of 0.1 cm^3 in the rat paw of the hind limb [17] significantly increased its thickness after 1, 2, 3 and 4 hours after injection. Likewise, the i.p. injection of the test compounds at a dose of 18 mg/kg body weight of rat significantly decreased the thickness of rat paw after two hours till the end of the experiment as shown in Table 2. The antiinflammatory effect decreases in the order **17** > **11** > **9** > **12** > **8** > celecoxib > **10** > **7** > **6**.

The results presented in Table 3 reveal that the i.p. injection of the test compounds at a dose level of 1.7 mg/kg body weight significantly prolonged the

Table 1. Analgesic activity evaluation of the test compounds **6**–**12** and **17** administered i.p. in a dose of 1.7 mg/kg to mice ($n = 6$)

	Reaction time in seconds after					
	10 min	20 min	30 min	60 min	90 min	120 min
Control	12.1 ± 0.47	12.33 ± 0.46	13.2 ± 0.54	13.72 ± 0.75	14.2 ± 0.73	15.11 ± 0.81
Celecoxib	23 ± 2.2^{c}	32 ± 2.5^{c}	35 ± 2.6^{c}	36 ± 2.1^{c}	33 ± 2^{c}	31.6 ± 2.2^{c}
6	22 ± 3.1^{b}	26 ± 2.8^{c}	26 ± 2.7^{c}	28 ± 2.2^{c}	23 ± 1.5^{b}	21 ± 0.58^{b}
7	12 ± 0.34	14 ± 0.22	14 ± 0.38	14 ± 0.32	15 ± 0.82	15 ± 0.78
8	15 ± 0.49^{b}	28 ± 3.1^{c}	33 ± 3.2^{c}	35 ± 4.1^{c}	35 ± 3.8^{c}	29 ± 3.3^{c}
9	22 ± 2.3^{b}	35 ± 2.6^{c}	41 ± 2.7^{c}	50 ± 2.3^{c}	53 ± 2.4^{c}	55 ± 2.82^{c}
10	15 ± 0.32^{b}	15.3 ± 0.38^{b}	17 ± 0.55^{b}	18 ± 0.91^{a}	19 ± 1.0^{a}	18.2 ± 0.87
11	42 ± 2.3^{c}	48 ± 3.2^{c}	67 ± 3.4^{c}	70 ± 3.3^{c}	57 ± 2.8^{c}	53 ± 2.2^{c}
12	13 ± 0.58	16.3 ± 0.95^{a}	17 ± 1.2	18.2 ± 1.4	18 ± 1.2	17.3 ± 1.1
17	33 ± 1.9^{c}	45 ± 2.1^{c}	65 ± 3.2^{c}	69 ± 3.1^{c}	68 ± 3.2^{c}	67 ± 2.1^{c}

[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$ (P: probability level)

Table 2. Antiinflammatory activity evaluation of the test compounds **6**–**12** and **17** administered i.p. in a dose of 18 mg/kg to mature rats ($n = 6$)

	Initial volume	Thickness of paw skin in mm after			
	(zero time)	1 hour	2 hours	3 hours	4 hours
Control (Carrageenin 10%, 0.1 cm^3)	0.4 ± 0.02	0.71 ± 0.06	1.32 ± 0.074	1.56 ± 0.08	1.68 ± 0.073
Celecoxib	0.41 ± 0.06	0.52 ± 0.068	0.59 ± 0.088[a]	0.72 ± 0.071[a]	0.72 ± 0.041[a]
6	0.43 ± 0.07	0.6 ± 0.033	0.73 ± 0.043[a]	0.78 ± 0.049[a]	0.82 ± 0.048[a]
7	0.42 ± 0.033	0.67 ± 0.03	0.71 ± 0.069[a]	0.76 ± 0.025[a]	0.81 ± 0.072[a]
8	0.42 ± 0.063	0.51 ± 0.032	0.57 ± 0.055[a]	0.70 ± 0.04[a]	0.70 ± 0.073[a]
9	0.43 ± 0.05	0.51 ± 0.078	0.55 ± 0.079[a]	0.68 ± 0.068[a]	0.69 ± 0.044[a]
10	0.44 ± 0.06	0.49 ± 0.067	0.56 ± 0.076[a]	0.71 ± 0.033[a]	0.75 ± 0.059[a]
11	0.41 ± 0.06	0.46 ± 0.029	0.49 ± 0.085[a]	0.53 ± 0.06[a]	0.58 ± 0.038[a]
12	0.40 ± 0.033	0.49 ± 0.086	0.55 ± 0.070[a]	0.69 ± 0.067[a]	0.70 ± 0.058[a]
17	0.42 ± 0.07	0.43 ± 0.087	0.45 ± 0.034[a]	0.45 ± 0.075[a]	0.51 ± 0.043[a]

[a] $P < 0.001$

Table 3. Effect of the test compounds **6**–**12** and **17** on the sleeping time of thiopentone anaesthesized mice administered i.p. in a dose of 1.7 mg/kg body weight ($n = 6$)

	Sleeping time/min
Control (Thiopentone-Na, 20 mg/kg)	16 ± 1.33
Celecoxib + Thiopentone-Na	94 ± 5.3[a]
6 + Thiopentone-Na	80 ± 3.2[a]
7 + Thiopentone-Na	120 ± 6.1[a]
8 + Thiopentone-Na	92 ± 4.3[a]
9 + Thiopentone-Na	70 ± 2.1[a]
10 + Thiopentone-Na	67 ± 1.5[a]
11 + Thiopentone-Na	145 ± 6.2[a]
12 + Thiopentone-Na	127 ± 5.4[a]
17 + Thiopentone-Na	105 ± 3.4[a]

[a] $P < 0.001$

sleeping time of thiopentone anesthesized mice [18] decreasing in the order **11** > **12** > **7** > **17** > celecoxib > **8** > **6** > **9** > **10**.

It is evident from Table 4 that the i.p. injection of the test compounds at a dose level of 1.7 mg/kg body weight significantly prolonged the time of onset of convulsion and time of death of mice when compared with the control group [19] in the order **17** > celecoxib > **7** > **8** > **6** > **11** > **10** > **9** > **12**.

The pyrazoles showing the highest antiinflammatory activity (**8**, **9**, **10**, **11**, **17**, and celecoxib) were tested for their ulcerogenic activity [20, 21]; indomethacin was used as reference drug. The results presented in Table 5 show that the order of potency of ulcerogenic activity is indomethacin > **11** > **9** > **17** > **10** > **8** > celecoxib.

Table 4. Effect of the test compounds **6–12** and **17** administered i.p. in a dose of 1.7 mg/kg on pentylenetetrazole-induced convulsions in mice ($n = 6$)

	Time of onset/min	Time of death/min
Control (Pentylenetetrazole, 10 mg/kg)	1.20 ± 0.08	3.5 ± 0.21
Celecoxib + Pentylenetetrazole	3.23 ± 0.32[a]	121 ± 4.3[a]
6 + Pentylenetetrazole	2.58 ± 0.22[a]	26 ± 1.5[a]
7 + Pentylenetetrazole	2.2 ± 0.11[a]	113 ± 4.2[a]
8 + Pentylenetetrazole	3.1 ± 0.41[a]	102 ± 5.1[a]
9 + Pentylenetetrazole	2.3 ± 0.16[a]	12.5 ± 0.35[a]
10 + Pentylenetetrazole	3.11 ± 0.24[a]	23 ± 1.2[a]
11 + Pentylenetetrazole	2.1 ± 0.50[a]	23.6 ± 2.1[a]
12 + Pentylenetetrazole	2.51 ± 0.18[a]	9.66 ± 0.44[a]
17 + Pentylenetetrazole	3.54 ± 0.23[a]	149 ± 8.3[a]

[a] $P < 0.001$

Table 5. Ulcerogenic activity of the test compounds **8–11**, **17**, and celecoxib ($n = 6$)

	Incidence of gastric ulceration	Mean ulcer score	Ulcer index
Control	0.00	0.00	0.00
Indomethacin	100%	4.75 ± 0.25	475
Celecoxib	100%	1.25 ± 0.25	125
8	100%	1.30 ± 0.30[b]	130
9	100%	1.80 ± 0.20[b]	180
10	100%	1.50 ± 0.15[b]	150
11	100%	3.66 ± 0.34[a]	366
17	100%	1.66 ± 0.20[b]	166

[a] Compared with indomethacin, $P < 0.05$; [b] $P < 0.001$

Conclusions

The main objective of this study was to develop effective analgesic and anti-inflammatory agents. To achieve this goal, several structural changes on the potent and selective cyclooxygenase-2 inhibitor celecoxib which is commercially used were performed. Our investigation resulted in the following observations: replacement of triflouromethyl by methyl did not affect the activity; five-membered ring such as pyrazole or its isostere maintain the activity as observed for compound **12** (Table 2); a phenyl ring attached to the pyrazole at position 5 enhances the activity; a sulfonamido group at the *ortho* position is as active as at the *para* position of the phenyl ring (Tables 1, 2); cyclic sulfonamides (**17**) have higher analgesic/antiinflammatory effects than celecoxib (Tables 1, 2) and possess a weak ulcerogenic activity (Table 5); compound **8** has nearly the same antiinflammatory and ulcerogenic activity as celecoxib (Tables 2, 5).

Most of the novel benzenesulfonamide derivatives containing a pyrazole moiety showed potent analgesic and antiinflammatory activities. The compounds are structurally related to the selective COX-2 inhibitor celecoxib, and some of them are more active than celecoxib as analgesic and antiinflammatory agents. Moreover, some of the pyrazoles with the highest antiinflammatory properties showed lower ulcerogenic activity as compared to indomethacin. Further studies are required to investigate their binding at COX-2 and to determine their selectivity.

Experimental

General

Melting points were determined with a Gallenkamp Digital melting point apparatus in open capillaries and are uncorrected. IR spectra (KBr) were recorded using a Testscan Shimadzu FTIR 8000 spectrophotometer. ^{1}H NMR spectra were determined on Varian EM-390, Bruker AC 250, and Varian Mercury 300 NMR spectrometers using *TMS* as internal standard (chemical shifts in δ (ppm)). Mass spectra were measured on a Hewlett Packard MS-5988 mass spectrometer at 70 eV. Elemental analyses were performed at the microanalytical center, Faculty of Science, Cairo University, Cairo, Egypt. Their results corresponded to the calculated values within experimental error. TLC was performed on silica gel G (Merck), and spots were visualized by iodine vapour or by irradiation with UV light (254 nm). Compounds **2**, **3**, **4**, and **13** were prepared according to reported procedures [9, 13].

2-Hydrazinocarbonyl-N-allylbenzenesulfonamide (**5**; $C_{10}H_{13}N_3O_3S$)

A mixture of N-allyl-saccharin (**3**; 10 mmol) and hydrazine hydrate (30 mmol) was stirred at room temperature for 20 min. The separated product was filtered, washed with H_2O, dried, and recrystallized from EtOH.

Yield: 90%; m.p.: 99–100°C; IR: $\nu = 3355$ (NH_2), 3200 (NH), 3088 (CH, aromatic), 2971 (CH, aliphatic), 1655 (C=O), 1615 (C=C), 1327 (SO_2) cm^{-1}; ^{1}H NMR (250 MHz, δ, *DMSO*-d_6): 3.28–3.48 (m, 2H, CH_2), 4.1 (s, 2H, NH_2, exch.), 4.85–5.00 (m, 2H, $=CH_2$), 5.35 (t, 1H, NH, exch.), 5.49–5.58 (m, 1H, C=CH), 7.20–7.89 (m, 4H, ArH), 9.03 (s, 1H, NH, exch.) ppm; MS: m/z (rel. int.) = 255 (M^+, 0.36), 224 (45.61), 198 (99.74), 184 (34.58), 76 (100).

General procedure for the preparation of **6**–**11**

To a solution of the acid hydrazide **4** or **5** (10 mmol) in 30 cm^3 EtOH containing 2 cm^3 glacial acetic acid, an equimolar amount of ethyl acetoacetate or acetylacetone or benzoylacetone was added. The reaction mixture was heated under reflux for 12 h, concentrated to a small volume, cooled, and added to 30 cm^3 ice-cold water. The separated product was filtered, washed with H_2O, and recrystallized from the appropriate solvent.

2-(3-Methyl-5-oxo-1H-pyrazolin-1-ylcarbonyl)-N-ethylbenzenesulfonamide (**6**; $C_{13}H_{15}N_3O_4S$)

Yield: 85%; m.p.: 102–104°C (EtOH); IR: $\nu = 3440$ (NH), 3093 (CH, aromatic), 2977 (CH, aliphatic), 1735 (C=O), 1589 (C=N), 1458 (C=C), 1326 (SO_2) cm^{-1}; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 1.0 (t, 3H, CH_3), 2.0 (s, 3H, CH_3), 2.8–3.0 (m, 2H, CH_2), 4.2 (s, 2H, CH_2 of pyrazoline), 5.87 (t, 1H, NH, exch.), 7.25–8.0 (m, 4H, ArH) ppm; MS: m/z (rel. int.) = 309 (M^+, 2.84), 211 (15), 196 (100), 183 (4.17), 104 (30), 76 (39.2).

2-(3-Methyl-5-oxo-1H-pyrazolin-1-ylcarbonyl)-N-allylbenzenesulfonamide (**7**; $C_{14}H_{15}N_3O_4S$)

Yield: 80%; m.p.: 150–152°C (benzene/petroleum ether 60–80°C); IR: $\nu = 3340$ (NH), 3087 (CH, aromatic), 2940 (CH, aliphatic), 1720 (C=O), 1580 (C=N), 1455 (C=C), 1325 (SO_2) cm^{-1}; ^1H NMR (90 MHz, δ, $CDCl_3$): 2.00 (s, 3H, CH_3), 3.4–3.55 (m, 2H, CH_2), 4.3 (2H, s, CH_2 of pyrazoline), 5.0–5.18 (m, 2H, $=CH_2$), 5.51 (t, 1H, NH), 5.59–5.70 (m, 1H, C=CH), 7.3–8.0 (m, 4H, ArH) ppm.

2-(3,5-Dimethyl-1H-pyrazol-1-ylcarbonyl)-N-ethylbenzenesulfonamide (**8**; $C_{14}H_{17}N_3O_3S$)

Yield: 78%; m.p.: 152–154°C ($EtOH/H_2O$); IR: $\nu = 3320$ (NH), 3090 (CH, aromatic), 2920 (CH, aliphatic), 1630 (C=O), 1590 (C=N), 1470 (C=C), 1328 (SO_2) cm^{-1}; ^1H NMR (90 MHz, δ, $CDCl_3$): 1.0 (t, 3H, CH_3), 1.8 (s, 3H, CH_3), 1.9 (s, 3H, CH_3), 2.85–3.1 (m, 2H, CH_2), 5.3 (t, 1H, NH, exch.), 7.1–7.8 (m, 5H, ArH + CH of pyrazole) ppm.

2-(3-Methyl-5-phenyl-1H-pyrazol-1-ylcarbonyl)-N-ethylbenzenesulfonamide (**9**; $C_{19}H_{19}N_3O_3S$)

Yield: 80%; m.p.: 147–149°C (EtOH); IR: $\nu = 3310$ (NH), 3090 (CH, aromatic), 2930 (CH, aliphatic), 1640 (C=O), 1580 (C=N), 1490 (C=C), 1325 (SO_2) cm^{-1}; ^1H NMR (90 MHz, δ, $CDCl_3$): 1.0 (t, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.9–3.1 (m, 2H, CH_2), 5.6 (t, 1H, NH, exch.), 7.2–8.1 (m, 10H, ArH + CH of pyrazole) ppm.

2-(3,5-Dimethyl-1H-pyrazol-1-ylcarbonyl)-N-allylbenzenesulfonamide (**10**; $C_{15}H_{17}N_3O_3S$)

Yield: 75%; m.p.: 118–120°C (benzene/petroleum ether 60–80°C); IR: $\nu = 3294$ (NH), 3085 (CH, aromatic), 2931 (CH, aliphatic), 1620 (C=O), 1496 (C=N), 1442 (C=C), 1326 (SO_2) cm^{-1}; ^1H NMR (90 MHz, δ, *DMSO*-d_6): 1.8 (s, 3H, CH_3), 1.9 (s, 3H, CH_3), 3.3–3.5 (m, 2H, CH_2), 4.8–5.1 (m, 2H, $=CH_2$) 5.3–5.6 (m, 1H, C=CH), 6.9 (t, 1H, NH, exch.), 7.1–7.7 (m, 5H, ArH + CH of pyrazole) ppm.

2-(3-Methyl-5-phenyl-1H-pyrazol-1-ylcarbonyl)-N-allylbenzenesulfonamide (**11**; $C_{20}H_{19}N_3O_3S$)

Yield: 73%; m.p.: 114–116°C ($EtOH/H_2O$); IR: $\nu = 3290$ (NH), 3080 (CH, aromatic), 2925 (CH, aliphatic), 1640 (C=O), 1520 (C=N), 1470 (C=C), 1330 (SO_2) cm^{-1}; ^1H NMR (250 MHz, δ, $CDCl_3$): 1.98 (s, 3H, CH_3), 3.3–3.5 (m, 2H, CH_2), 4.91–5.11 (m, 2H, $=CH_2$), 5.5 (t, 1H, NH, exch.), 5.58–5.69 (m, 1H, C=CH), 7.30–7.99 (m, 10H, ArH + CH of pyrazole) ppm.

2-(N-Maleimidoaminocarbonyl)-N-ethylbenzenesulfonamide (**12**; $C_{13}H_{13}N_3O_5S$)

A mixture of acid hydrazide **4** (5 mmol) and maleic anhydride (5 mmol) in 20 cm^3 glacial acetic acid was heated under reflux for 8 h. The reaction mixture was cooled and then poured into 30 cm^3 ice water. The separated product was filtered and recrystallized from EtOH.

Yield: 85%; m.p.: 226–228°C; IR: $\nu = 3225$ (NH), 3080 (CH, aromatic), 2930 (CH, aliphatic), 1730, 1630 (C=O), 1520 (C=C), 1325 (SO_2) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 1.05 (t, 3H, CH_3), 2.9–3.05 (m, 2H, CH_2), 5.93 (t, 1H, NH, exch.), 7.12–7.95 (m, 6H, ArH + CH=CH), 10.52 (s, 1H, NH, exch.) ppm.

(1,2-Benzoisothiazol-3(2H)one-1,1-dioxid-2-yl)-acetic acid hydrazide (**14**; $C_9H_9N_3O_4S$)

A mixture of equimolar amounts (10 mmol) of ester **13** and hydrazine hydrate in 30 cm^3 EtOH was heated under reflux for 1 h. The reaction mixture was cooled and then poured into 30 cm^3 cold H_2O. The separated product was filtered, washed with H_2O, dried, and recrystallized from aqueous EtOH.

Yield: 93%; m.p.: 150–152°C; IR: $\nu = 3386$ (NH_2), 3293 (NH), 3091 (CH, aromatic), 2975 (CH, aliphatic), 1670, 1616 (C=O), 1570 (C=C), 1336 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 3.44 (s, 2H, CH_2), 4.13 (s, 2H, NH_2, exch.), 7.49–7.89 (m, 4H, ArH), 9.08 (s, 1H, NH, exch.) ppm; MS: m/z (rel. int.) = 255 (M^+, 4.9), 224 (21.8), 196 (100), 169 (17.8), 132 (15.1), 104 (36.0), 77 (45.3).

General procedure for the preparation of **15–17**

An equimolar amount (10 mmol) of acid hydrazide **14** and ethyl acetoacetate or acetylacetone or benzoylacetone was reacted similarly as described for **6–11**.

2-(3-Methyl-5-oxo-1H-pyrazolin-1-ylcarbonylmethyl)-1,2-benzoisothiazol-3(2H)one-1,1-dioxide (**15**; $C_{13}H_{11}N_3O_5S$)

Yield: 72%; m.p.: 110–112°C (ethyl acetate/petroleum ether 60–80°C); IR: $\nu = 3080$ (CH, aromatic), 2900 (CH, aliphatic), 1690, 1610 (C=O), 1510 (C=N), 1470 (C=C), 1330 (SO_2) cm^{-1}; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 1.96 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 4.2 (s, 2H, CH_2 of pyrazoline), 7.39–7.92 (m, 4H, ArH) ppm.

2-(3,5-Dimethyl-1H-pyrazol-1-ylcarbonylmethyl)-1,2-benzoisothiazol-3(2H)one-1,1-dioxide (**16**; $C_{14}H_{13}N_3O_4S$)

Yield: 70%; m.p.: 103–105°C (ethyl acetate/petroleum ether 60–80°C); IR: $\nu = 3075$ (CH, aromatic), 2970 (CH, aliphatic), 1720, 1660 (C=O), 1570 (C=N), 1520 (C=C), 1330 (SO_2) cm^{-1}; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 1.8 (s, 3H, CH_3), 1.9 (s, 3H, CH_3), 3.9 (s, 2H, CH_2), 7.2–7.8 (m, 5H, ArH + CH of pyrazole) ppm.

2-(3-Methyl-5-phenyl-1H-pyrazol-1-ylcarbonylmethyl)-1,2-benzoisothiazol-3(2H)one-1,1-dioxide (**17**; $C_{19}H_{15}N_3O_4S$)

Yield: 73%; m.p.: 125–127°C (EtOH/H_2O); IR: $\nu = 3076$ (CH, aromatic), 2975 (CH, aliphatic), 1738, 1673 (C=O), 1583 (C=N), 1512 (C=C), 1335 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz, δ, $CDCl_3$): 2.0 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 7.25–7.85 (m, 10H, ArH + CH of pyrazole) ppm.

2-(N-Maleimido-acetamide)-1,2-benzoisothiazol-3(2H)one-1,1-dioxide (**18**; $C_{13}H_9N_3O_6S$)

A mixture of equimolar amounts (5 mmol) of the acid hydrazide **14** and maleic anhydride was reacted as described for **12**.

Yield: 82%; m.p.: 288–290°C (EtOH); IR: $\nu = 3224$ (NH), 3070 (CH, aromatic), 2939 (CH, aliphatic), 1735, 1627 (C=O), 1496 (C=C), 1326 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz, δ, *DMSO*-d_6): 4.40 (s, 2H, CH_2), 7.22–8.21 (m, 6H, ArH + CH=CH), 10.48 (s, 1H, NH, exch.) ppm.

2-(5-Mercapto-1,3,4-oxadiazol-2-yl)-N-ethylbenzenesulfonamide (**19**; $C_{10}H_{11}N_3O_3S_2$)

To a solution of acid hydrazide **4** (10 mmol) in 80 cm^3 EtOH (90%) containing KOH (15 mmol), 10 cm^3 CS_2 were added. The reaction mixture was heated under reflux for 8 h while stirring, then

concentrated, cooled, and acidified with diluted HCl. The separated product was filtered, washed with H_2O, and recrystallized from aqueous EtOH.

Yield: 90%; m.p.: 150–152°C; IR: $\nu = 3294$ (NH), 3163 (CH, aromatic), 2977 (CH, aliphatic), 2561 (SH), 1596 (C=N), 1488 (C=C), 1326 (SO_2) cm^{-1}; ^1H NMR (300 MHz, δ, $CDCl_3 + D_2O$): 1.09 (t, 3H, CH_3), 3.05 (q, 2H, CH_2), 7.25–8.26 (m, 4H, ArH) ppm.

General procedure for the preparation of **20–23**

A mixture of **19** (1 mmol) and the appropriate alkyl or aralkyl halide (1 mmol) in 30 cm^3 EtOH containing KOH (1.2 mmol) was stirred at room temperature for 2 h. The reaction mixture was poured into 30 cm^3 ice water. The separated product was filtered and recrystallized from the proper solvent.

2-(5-Methylthio-1,3,4-oxadiazol-2-yl)-N-ethylbenzenesulfonamide (**20**; $C_{11}H_{13}N_3O_3S_2$)

Yield: 85%; m.p.: 110–112°C (acetone/H_2O); IR: $\nu = 3290$ (NH), 3160 (CH, aromatic), 2970 (CH, aliphatic), 1590 (C=N), 1480 (C=C), 1320 (SO_2) cm^{-1}; ^1H NMR (250 MHz, δ, $CDCl_3$): 1.1 (t, 3H, CH_3), 2.77 (s, 3H, CH_3), 3.05–3.13 (m, 2H, CH_2), 7.11 (t, 1H, NH, exch.), 7.6–8.2 (m, 4H, ArH) ppm.

2-(5-Ethylthio-1,3,4-oxadiazol-2-yl)-N-ethylbenzenesulfonamide (**21**; $C_{12}H_{15}N_3O_3S_2$)

Yield: 90%; m.p.: 68–70°C (acetone/H_2O); IR: $\nu = 3294$ (NH), 3163 (CH, aromatic), 2977 (CH, aliphatic), 1596 (C=N), 1488 (C=C), 1326 (SO_2) cm^{-1}; ^1H NMR (300 MHz, δ, $CDCl_3$): 0.9 (t, 3H, CH_3), 1.1 (t, 3H, CH_3), 2.85 (q, 2H, CH_2), 3.10–3.18 (m, 2H, CH_2), 7.0 (t, 1H, NH, exch.), 7.55–8.20 (m, 4H, ArH) ppm.

2-(5-Allylthio-1,3,4-oxadiazol-2-yl)-N-ethylbenzenesulfonamide (**22**; $C_{13}H_{15}N_3O_3S_2$)

Yield: 92%; m.p.: 60–62°C (ethyl acetate/petroleum ether 60–80°C); IR: $\nu = 3298$ (NH), 3150 (CH, aromatic), 2960 (CH, aliphatic), 1570 (C=N), 1475 (C=C), 1330 (SO_2) cm^{-1}; ^1H NMR (90 MHz, δ, $CDCl_3$): 1.09 (t, 3H, CH_3), 3.07–3.15 (m, 2H, CH_2), 3.30 (d, 2H, CH_2), 4.81–4.91 (m, 2H, $=CH_2$), 5.41–5.53 (m, 1H, =CH), 7.05 (t, 1H, NH, exch.), 7.42–8.12 (m, 4H, ArH) ppm.

2-(5-Benzylthio-1,3,4-oxadiazol-2-yl)-N-ethylbenzenesulfonamide (**23**; $C_{17}H_{17}N_3O_3S_2$)

Yield: 87%; m.p.: 85–87°C ($CHCl_3$/petroleum ether 60–80°C); IR: $\nu = 3220$ (NH), 3100 (CH, aromatic), 2980 (CH, aliphatic), 1620 (C=N), 1560 (C=C), 1325 (SO_2) cm^{-1}; ^1H NMR (300 MHz, δ, *DMSO*-d_6): 0.94 (t, 3H, CH_3), 2.84–2.88 (m, 2H, CH_2), 4.55 (s, 2H, CH_2), 7.3–7.47 (m, 5H, ArH), 7.6 (t, 1H, NH, exch.), 7.82–8.05 (m, 4H, ArH) ppm; MS: m/z (rel. int.) = 375 (M^+, 4.5), 268 (19.3), 212 (18.5), 132 (32.6), 91 (100).

Analgesic activity evaluation

The hot plate method of *Jacob* and *Bosovski* [16] was used to evaluate the analgesic activity. Mature albino mice of both sex weighing 20–25 g were classified into ten groups (each of six). The first group was left as control and injected i.p. with the solvent (*DMSO*), whereas the second group was injected i.p. with celecoxib at a dose of 1.7 mg/kg. Each of the remaining groups was injected i.p. with a test compound at a dose of 1.7 mg/kg. Ten minutes later, each mouse was placed in a two liter-beaker immersed in a water bath thermostatically controlled at 56°C. The time elapsed till the

mouse licks its paw or jumps was considered as the reaction time and was taken as a measure of the analgesic effect. Readings were taken at 10, 20, 30, 60, 90, and 120 minutes post treatment (Table 1).

Antiinflammatory activity evaluation

The rat hind paw oedema method [17] was applied to determine the antiinflammatory activity of the test compounds using celecoxib as a standard. Mature albino rats of both sex weighing 200–250 g were used. The animals were divided into ten equal groups (each of six). The first group was left as control, while the second group was injected (i.p.) with celecoxib at a dose of 18 mg/kg. The test compounds were injected (i.p.) to the remaining groups at a dose of 18 mg/kg. One hour later, oedema in the right hind paw was induced by injection of 0.1 cm^3 of 10% carrageenin. The thickness of the paw was measured 60, 120, 180 and 240 minutes after carrageenin injection to determine the antiinflammatory activity of the test compounds (Table 2).

Effect of the test compounds on the sleeping time of thiopentone anaesthesized mice

The method described by *Alpermann* [18] was applied for evaluation of the test compounds. Mature male albino mice weighing 20–25 g were divided into ten equal groups (each of six). The first group was left as control, while the second group was injected i.p. with celecoxib at a dose of 1.7 mg/kg. Each of the remaining groups was injected i.p. with the test compound at a dose of 1.7 mg/kg. One hour later, all animals were injected i.p. with thiopentone-Na at a dose of 20 mg/kg body weight. The time from losing consciousness to that of regaining the righting reflex was determined as the sleeping time (Table 3).

Anticonvulsant activity screening

The ability of the test compounds to protect animals against the convulsive and lethal effects of pentylenetetrazole was used as described by *Wallenstein* [19]. Mature albino mice of both sex weighing 20–25 g were divided into ten equal groups (each of six). The first group was left as a control, while the second group was injected i.p. with celecoxib at a dose of 1.7 mg/kg. The test compounds were injected i.p. to the other groups at a dose of 1.7 mg/kg. Ten minutes later, all animals were injected i.p. with pentylenetetrazole at a dose of 10 mg/kg and observed for the appearance of seizures and the onset of each (Table 4).

Ulcerogenic activity

Compounds **8**, **9**, **10**, **11**, **17** and celecoxib were tested for their ulcerogenic activity using indomethacin as reference drug. Male albino rats weighing 150–200 g were fasted for 12 h prior to drug administration. Water was given *ad libitum*. The animals were divided into eight equal groups (each of six). The first group received 1% gum acacia (suspending vehicle) orally once a day and was left as a control, whereas the second group received indomethacin at a dose of 18 mg/kg/day orally. The third group received celecoxib at a dose of 18 mg/kg/day orally. The remaining groups received the test compounds at a dose of 18 mg/kg/day orally. The drugs were administered once a day for three successive days. The animals were killed by an overdosage of ether 6 h after the last dose. The stomach was removed, opened along the greater curvature, and examined for ulceration. The number and severity of discrete areas of damage in the glandular mucosa were scored (Table 5). The ulcer score was calculated according to the 1 to 5 scoring system of *Wilhelmi* and *Menasse-Gdynia* [20] as follows: 1) 1 or 2 minute sporadic punctate lesions; 2) several small lesions; 3) one extensive lesion or multiple moderate-sized lesions; 4) several large lesions; 5) several large lesions with stomach perforation. Stomach ulceration was expressed in terms of ulcer index (*U.I.* = mean ulcer score of a group of animals similarly treated × % of ulcerated animals of this group [21].

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