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4-Dialkylamino-1-(5-substituted or unsubstituted 1-phenyl-1*H*-pyrazol-4-yl)butan-1-ols: synthesis and evaluation of analgesic, anti-inflammatory and platelet anti-aggregating activities

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Abstract

A number of 4-dialkylamino-1-(5-substituted or unsubstituted 1-phenyl-1*H*-pyrazol-4-yl)butan-1-ols **2a**–**n** were synthesized and tested in vivo for anti-inflammatory and analgesic activities and in vitro for platelet anti-aggregating activity. Dimethylaminoderivatives **2b**, **e**, **g** showed good analgesic activity; almost all of them had strong platelet anti-aggregating properties at a final concentration of 1×10^{-3} M; pyrazoles **2c**, **d**, **f**–**h** showed weak anti-inflammatory activity.

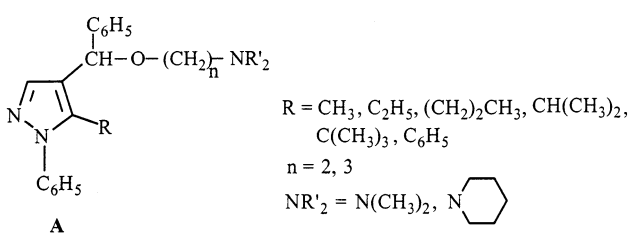
Keywords: Pyrazole derivatives; Anti-inflammatory agents; Analgesic agents; Platelet anti-aggregating agents

1. Introduction

Part of our research concerns the synthesis of 1-aryl-1*H*-pyrazole derivatives and the evaluation of their anti-inflammatory and analgesic properties [1].

In a recent study, carried out at the Searle Research and Development laboratories, a number of 1,5-diarylpyrazole derivatives were identified as potent and selective cyclo-oxygenase 2 inhibitors [2]. Among these compounds, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib) demonstrated potent, oral anti-inflammatory activity and, after its approval in December 1998, it is currently marketed in the USA [3].

Moreover, a Ciba–Geigy patent reports a series of 1-aryl-1*H*-pyrazoles bearing a tetrahydropyridylhydroxyalkyl chain in position 4 of the heterocycle, endowed with anti-inflammatory activity [4].



A

In a previous paper, we reported the synthesis and pharmacological results of a number of ω-dialkylaminoalkyl ethers of phenyl-(5-substituted 1-phenyl-1*H*-pyrazol-4-yl)methanols (**A**) [5].

Several of these compounds exhibited good anti-nociceptive activity in the writhing test in mice and weak anti-inflammatory activity in the carrageenan-induced edema assay in rats. The weakness of compounds **A** towards any acid agent, which caused the cleavage of the ether linkage, prevented their transformation into water-soluble salts.

Therefore, so as to improve the pharmacological profile of aminoethers **A**, we have now synthesized a number of novel 1-aryl-1*H*-pyrazoles (**2a**–**n**), which

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maintain basic side chain like derivatives **A**, but which lack the ether linkage and bear an alcoholic function instead of the phenyl ring, similar to the tetrahydropyridylhydroxyalkyl derivatives reported in the above mentioned patent. The removal of the oxygen bridge led to acid-proof molecules which could be transformed into the respective hydrochlorides.

Thus, aminoalcohols **2a–n** were investigated in vivo regarding their analgesic and anti-inflammatory properties; furthermore, as hydrochlorides, they were tested in vitro as inhibitors of platelet aggregation.

2. Chemistry

1-Phenyl-1*H*-pyrazole-4-carbaldehyde (**1a**), first prepared by Finar and later by other authors with different methods [6a–c], was obtained via oxidation of its corresponding carbinol [7] by pyridinium chlorochromate, as described for aldeydes **1b–g** [5].

Starting from **1a–g**, by reaction with 3-dimethylamino- or 3-(1-piperidinyl)-propylmagnesium chloride, the corresponding 4-dimethylamino-1-(5-substituted or unsubstituted 1-phenyl-1*H*-pyrazol-4-yl)-butan-1-ols (**2a–g**) and 4-(1-piperidinyl)-1-(5-substituted or unsubstituted 1-phenyl-1*H*-pyrazol-4-yl)-butan-1-ols (**2h–n**), were obtained in generally good yields, according to Scheme 1.

In the ^{1}H NMR spectra of compounds **2b**,**h–n**, hydroxylic proton resonated in the range of 7.2–8.4 δ, as a very broad singlet, which disappeared with deuterium oxide. Dimethylaminoderivatives **2a**,**c–g** did not give any signals corresponding to the hydroxylic proton. The methyne proton of the side chain of all compounds **2** resonated as a multiplet in the range of 4.5–5 δ (data are reported in Table 2).

3. Pharmacology and biology

All compounds **2** (free bases) were subjected to preliminary in vivo pharmacological screening for:

- analgesic activity, evaluated by writhing test and hot plate test in mice;
- anti-inflammatory activity, evaluated by carrageenan-induced paw edema in rats.

In addition, the same compounds (converted into hydrochlorides) were tested in vitro for their inhibitory activity on human platelet aggregation induced in platelet-rich plasma (PRP) by adenosine diphosphate (ADP), collagen or adrenaline.

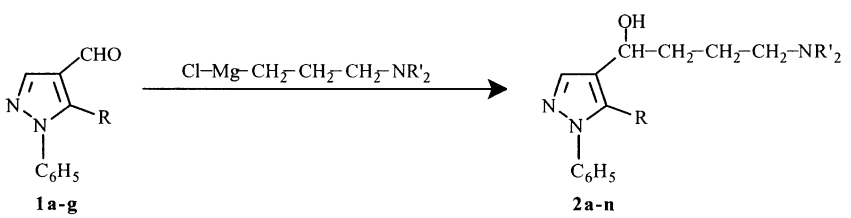
4. Experimental

4.1. Chemistry

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. The IR spectra were registered on a Perkin–Elmer 398 spectrophotometer in $CHCl_3$ as solvent. The ^{1}H NMR spectra were registered on a Varian Gemini 200 (200 MHz) spectrometer; chemical shifts are reported as δ (ppm) relative to TMS as internal standard; J in Hz; $CDCl_3$ as solvent. Elemental analyses were performed using a Carlo Erba Elemental Analyzer model 1106 and the results were within $\pm 0.3\%$ of the calculated values.

4.1.1. Intermediates

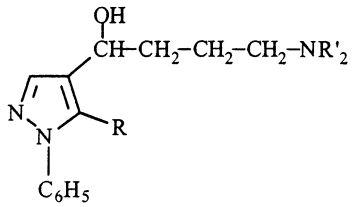
Aldehydes **1a–g**, used as intermediates for the synthesis of title compounds, were prepared as already described [5].



R		R	NR'$_2$	R	NR'$_2$
1a	H	**2a** H	$N(CH_3)_2$	**2h** H	N⟨ ⟩
1b	CH_3	**2b** CH_3	"	**2i** CH_3	"
1c	C_2H_5	**2c** C_2H_5	"	**2j** C_2H_5	"
1d	$(CH_2)_2CH_3$	**2d** $(CH_2)_2CH_3$	"	**2k** $(CH_2)_2CH_3$	"
1e	$CH(CH_3)_2$	**2e** $CH(CH_3)_2$	"	**2l** $CH(CH_3)_2$	"
1f	$C(CH_3)_3$	**2f** $C(CH_3)_3$	"	**2m** $C(CH_3)_3$	"
1g	C_6H_5	**2g** C_6H_5	"	**2n** C_6H_5	"

Scheme 1.

Table 1
4-Dialkylamino-1-(5-substituted or unsubstituted 1-phenyl-1*H*-pyrazol-4-yl)-butan-1-ols (**2a–n**)



Comp.	R	NR'_2	Yield(%)	M.p. (°C) or b.p. (°C) (mm Hg)	Molecular formula	*Anal.*
2a	H	$N(CH_3)_2$	51	57–58 [a]	$C_{15}H_{21}N_3O$	C, H, N
2b	CH_3	$N(CH_3)_2$	75	45–46 [a] 185–190 (0.4)	$C_{16}H_{23}N_3O$	C, H, N
2c	C_2H_5	$N(CH_3)_2$	71	74–75 [b] 177–180 (0.4)	$C_{17}H_{25}N_3O$	C, H, N
2d	$(CH_2)_2CH_3$	$N(CH_3)_2$	83	53–54 [a] 160–165 (0.1)	$C_{18}H_{27}N_3O$	C, H, N
2e	$CH(CH_3)_2$	$N(CH_3)_2$	79	106–107 [b]	$C_{18}H_{27}N_3O$	C, H, N
2f	$C(CH_3)_3$	$N(CH_3)_2$	90	119–120 [b]	$C_{19}H_{29}N_3O$	C, H, N
2g	C_6H_5	$N(CH_3)_2$	68	114–115 [b]	$C_{21}H_{25}N_3O$	C, H, N
2h	H		84	88–89 [a]	$C_{18}H_{25}N_3O$	C, H, N
2i	CH_3		73	60–61 [a] 195–200 (0.05)	$C_{19}H_{27}N_3O$	C, H, N
2j	C_2H_5		44	75–76 [a] 195–200 (0.1)	$C_{20}H_{29}N_3O$	C, H, N
2k	$(CH_2)_2CH_3$		70	74–75 [c]	$C_{21}H_{31}N_3O$	C, H, N
2l	$CH(CH_3)_2$		87	102–103 [a]	$C_{21}H_{31}N_3O$	C, H, N
2m	$C(CH_3)_3$		72	114–115 [a]	$C_{22}H_{33}N_3O$	C, H, N
2n	C_6H_5		64	104–105 [a]	$C_{24}H_{29}N_3O$	C, H, N

[a] From anhydrous diethyl ether–petroleum ether (b.p. 40–70°C).
[b] From anhydrous diethyl ether.
[c] From petroleum ether (b.p. 40–70°C).

*4.1.2. 1-Phenylpyrazol-4-ylcarbaldehyde (**1a**)*

Yield 91%, m.p. 85–86°C from anhydrous diethyl ether–petroleum ether (b.p. 40–70°C). IR ($CHCl_3$): 1680 cm^{-1}. ^1H NMR ($CDCl_3$): 7.35–7.6 (m, 3H, ar.), 7.7–7.8 (m, 2H, ar.), 8.21 (s, 1H, H-3), 8.44 (s, 1H, H-5), 9.96 (s, 1H, CHO). *Anal.* $C_{10}H_8N_2O$ (C, H, N).

*4.1.3. General procedure for the preparation of 4-dimethylamino-1-(5-substituted or unsubstituted 1-phenyl-1H-pyrazol-4-yl)-butan-1-ols (**2a–g**) and for 4-(1-piperidinyl)-1-(5-substituted or unsubstituted 1-phenyl-1H-pyrazol-4-yl)-butan-1-ols (**2h–n**)*

A solution of aldehydes **1a–g** (10 mmol) in anhydrous tetrahydrofuran (40 ml) was added dropwise to an ice-cooled solution of the appropriate 3-dialkylamino-1-propylmagnesium chloride, prepared from magnesium turnings (0.48 g, 20 mmol) and 3-dialkylamino-1-propylchloride (20 mmol) in the same solvent (70 ml). The mixture was refluxed overnight, cooled at 0°C and diluted with diethyl ether (100 ml). Hydrochloric acid (30 ml, 3 M) was then added with vigorous stirring. The organic layer, separated from the acid phase, was again extracted with hydrochloric acid (2 × 20 ml, 3 M). Then a 10% sodium hydroxide solution was added to the combined acid extracts, previously washed

twice with diethyl ether and cooled at 0°C, and the basic mixture (pH ~ 10) was then thoroughly extracted with diethyl ether (**2a**,**b**,**d**,**h**–**n**) or chloroform (**2c**,**e**–**g**). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a residue, which was roughly purified by flash chromatography on Florisil, using diethyl ether (**2a**,**b**,**d**,**h**–**n**) or chloroform (**2c**,**e**–**g**) as eluent. Compounds **2a**,**e**–**h**,**k**–**n** were further purified by recrystallization from a suitable solvent; **2b**–**d**,**i**,**j** by bulb to bulb distillation in vacuo, followed by recrystallization from a suitable solvent.

Yields, m.p. or b.p. values and recrystallization solvents are reported in Table 1.

4.2. Pharmacology

Pyrazoles **2a**–**n** were screened in vivo for their analgesic and anti-inflammatory activities. All compounds were administered orally, at the initial dose of 200 mg/kg. Compounds which exhibited a statistically significant activity at this dose were further tested at doses decreasing by a factor of two.

4.2.1. Anti-inflammatory activity

The carrageenan-induced paw edema test [8] was used on groups of five rats. Sixty minutes after administering the test compound, 0.1 ml of a 1% carrageenan solution in saline was injected into the plantar surface of the right hind paw of each rat. Paw volume, as determined by measuring the amount of water displaced after immersing the paw up to the lateral malleolus level, was recorded immediately after the carrageenan injection and again 3 h later. The difference between these two values was taken as edema volume. The inhibition percentage of the edema of treated rats, with respect to controls, was calculated and compared to that which

Table 2
IR and ^1H NMR spectral data of compounds **2a**–**n**

Comp.	IR ($CHCl_3$) (cm^{-1})	^1H NMR ($CDCl_3$), δ (ppm)
2a	3350, 2825, 2785	1.6–2.15 (m, 4H, $2CH_2$), 2.25 (s, 6H, $(CH_3)_2N$), 2.3–2.45 (m, 2H, CH_2N), 4.7–4.8 (m, 1H, CHO), 7.15–7.25 (m, 1H, H-5 pyrazole), 7.35–7.45 (m, 2H, aromatic), 7.6–7.7 (m, 3H, aromatic), 7.89 (s, 1H, H-3 pyrazole)
2b	3340, 2825, 2785	1.65–2.2 (m, 4H, $2CH_2$), 2.30 (s, 6H, $(CH_3)_2N$), 2.33 (s, 3H, CH_3), 2.35–2.55 (m, 2H, CH_2N), 4.6–4.7 (m, 1H, CHO), 7.25 (br s, 1H, OH, disappears with D_2O), 7.35–7.5 (m, 5H, C_6H_5), 7.64 (s, 1H, H-3 pyrazole)
2c	3330, 2820, 2775	1.05 (t, $J = 7.5$, 3H, CH_3), 1.6–2.1 (m, 4H, $2CH_2$), 2.29 (s, 6H, $(CH_3)_2N$), 2.3–2.5 (m, 2H, CH_2N), 2.65–2.85 (m, 2H, CH_2), 4.6–4.7 (m, 1H, CHO), 7.3–7.5 (m, 5H, C_6H_5), 7.62 (s, 1H, H-3 pyrazole)
2d	3370, 2820, 2780	0.81 (t, $J = 7.4$, 3H, CH_3), 1.3–2.1 (m, 6H, $3CH_2$), 2.29 (s, 6H, $(CH_3)_2N$), 2.3–2.5 (m, 2H, CH_2N), 2.6–2.75 (m, 2H, CH_2), 4.6–4.7 (m, 1H, CHO), 7.3–7.5 (m, 5H, C_6H_5), 7.64 (s, 1H, H-3 pyrazole)
2e	3350, 2825, 2780	1.24 and 1.31 (2d, $J = 7.2$, 6H, $(CH_3)_2C$), 1.65–2.1 (m, 4H, $2CH_2$), 2.30 (s, 6H, $(CH_3)_2N$), 2.35–2.55 (m, 2H, CH_2N), 3.12 (h, $J = 7.2$, 1H, $CHMe_2$), 4.75–4.85 (m, 1H, CHO), 7.3–7.5 (m, 5H, C_6H_5), 7.65 (s, 1H, H-3 pyrazole)
2f	3330, 2820, 2775	1.25 (s, 9H, $(CH_3)_3C$), 1.65–2.2 (m, 4H, $2CH_2$), 2.30 (s, 6H, $(CH_3)_2N$), 2.35–2.55 (m, 2H, CH_2N), 4.9–5.0 (m, 1H, CHO), 7.3–7.45 (m, 5H, C_6H_5), 7.67 (s, 1H, H-3 pyrazole)
2g	3330, 2825, 2780	1.45–2.0 (m, 4H, $2CH_2$), 2.26 (s, 6H, $(CH_3)_2N$), 2.3–2.5 (m, 2H, CH_2N), 3.5–3.6 (m, 1H, CHO), 7.15–7.4 (m, 10H, $2C_6H_5$), 7.86 (s, 1H, H-3 pyrazole)
2h	3340, 2805, 2765	1.3–2.15 (m, 10H, $5CH_2$), 2.2–2.6 (m, 6H, $3CH_2N$), 4.65–4.8 (m, 1H, CHO), 7.15–7.25 (m, 1H, H-5 pyrazole), 7.35–7.5 (m, 2H, aromatic), 7.55–7.75 (m, 3H, aromatic), 7.91 (s, 1H, H-3 pyrazole), ~8.4 (very br s, 1H, OH, disappears with D_2O)
2i	3320, 2805, 2765	1.35–2.1 (m, 10H, $5CH_2$), 2.32 (s, 3H, CH_3), 2.35–2.7 (m, 6H, $3CH_2N$), 4.55–4.65 (m, 1H, CHO), 7.3–7.5 (m, 5H, C_6H_5), 7.63 (s, 1H, H-3 pyrazole), 7.77 (br s, 1H, OH, disappears with D_2O)
2j	3320, 2805, 2765	1.06 (t, $J = 7.5$, 3H, CH_3), 1.4–2.1 (m, 10H, $5CH_2$), 2.3–2.85 (m, 8H, $3CH_2N + CH_2Me$), 4.6–4.7 (m, 1H, CHO), 7.3–7.55 (m, 5H, C_6H_5), 7.65 (s, 1H, H-3 pyrazole), 7.70 (br s, 1H, OH, disappears with D_2O)
2k	3320, 2805, 2765	0.82 (t, $J = 7.4$, 3H, CH_3), 1.3–2.1 (m, 12H, $6CH_2$), 2.3–2.8 (m, 8H, $3CH_2N + CH_2$), 4.55–4.65 (m, 1H, CHO), 7.3–7.5 (m, 5H, C_6H_5), ~7.6 (very br s, 1H, OH, disappears with D_2O), 7.65 (s, 1H, H-3 pyrazole)
2l	3320, 2805, 2765	1.25 and 1.33 (2d, $J = 7.2$, 6H, $(CH_3)_2C$), 1.4–2.15 (m, 10H, $5CH_2$), 2.3–2.7 (m, 6H, $3CH_2N$), 3.11 (h, $J = 7.2$, 1H, $CHMe_2$), 4.75–4.85 (m, 1H, CHO), 7.3–7.5 (m, 6H, $C_6H_5 + OH$, 1H disappears with D_2O), 7.66 (s, 1H, H-3 pyrazole)
2m	3320, 2805, 2760	1.25 (s, 9H, $(CH_3)_3C$), 1.4–2.2 (m, 10H, $5CH_2$), 2.3–2.7 (m, 6H, $3CH_2N$), 4.85–4.95 (m, 1H, CHO), 7.25–7.45 (m, 5H, C_6H_5), 7.54 (br s, 1H, OH, disappears with D_2O), 7.68 (s, 1H, H-3 pyrazole)
2n	3330, 2805, 2765	1.35–2.0 (m, 10H, $5CH_2$), 2.25–2.6 (m, 6H, $3CH_2N$), 4.45–4.55 (m, 1H, CHO), 7.1–7.4 (m, 10H, $2C_6H_5$), 7.81 (br s, 1H, OH, disappears with D_2O), 7.86 (s, 1H, H-3 pyrazole)

was produced by indomethacin (6 mg/kg p.o.), used as a reference standard.

4.2.2. Analgesic activity

The writhing test [9] was used on a group of six mice. One hour after the administration of the test compound, 0.01 ml/g of a 0.6% acetic acid solution was injected intraperitoneally in each mouse. The writhing movements of each animal were counted for 10 min (between the 5th and 15th minute after the injection of the irritant). The anti-nociceptive effect was expressed as the percentage of protection compared to the control group. Indomethacin (6 mg/kg p.o.) was used as a reference standard.

The hot plate test [10] was used on groups of five rats. The parameter evaluated was the latency time for the paw withdrawal after exposure to the hot plate surface (55°C ± 0.5); the maximum cut-off was 30 s. Latency time was recorded before and 45 min after the drug was administration. Morphine (15 mg/kg p.o.) was used as a reference standard.

4.3. Biological assays

4.3.1. Platelet aggregation

Human blood samples from normal subjects were drawn through a 19-gauge needle, avoiding carefully prolonged venous stasis. None of these subjects was treated with any drug known to influence the platelet function.

Blood was collected in plastic tubes containing 3.8% trisodium citrate aqueous solution. Platelet rich plasma (PRP) was obtained by centrifuging the blood at $100 \times g$ for 20 min. Platelet poor plasma (PPP) was obtained by centrifuging the remaining blood at $1100 \times g$ for 15 min.

Platelet count in PRP was maintained at 300 000/mmc.

Platelet aggregation, performed in a Aggrecorder II PA 3220 aggregometer (Menarini, Firenze, Italy), was measured according to Born's turbidimetric method [11] and quantified by the maximal light transmission after 5 min.

A first sample of PRP was pre-incubated at 37°C for 2 min before the addition of the agonist (2 and 5 μM adenosine diphosphate (ADP), collagen at final concentrations of 4 and 8 μg/ml, 5 μM adrenaline). A second sample of PRP was incubated for 2 min with a solution of the tested compound. Platelet aggregation was then performed adding the agonist.

Comparing the maximal light transmission of the aggregation curves obtained with and without the addition of the tested compound, the percentage of inhibition of platelet aggregation was calculated.

5. Results and discussion

5.1. Pharmacology

As concerns the analgesic activity, 13 of the 14 compounds produced a statistically significant anti-nociceptive effect in the acetic acid writhing test in mice. The degree of protection ranged from 40 to 92% at a dose of 200 mg/kg. The most active were compounds **2b**, **e**, **g**, which displayed a significant anti-nociceptive effect also at a dose of 100 mg/kg (49, 39 and 40%, respectively). Only compound **2n** was inactive.

However, when the hot plate test was used on the rat to verify the anti-nociceptive effect of the three compounds that produced a greater than 80% protection in the writhing test at the maximum dose, the degree of protection at the same dose was markedly lower, being 31% for **2b**, 35% for **2e** and 19% for **2g**. This discrepancy between the results of the two tests might be attributed to their different sensitivity: the writhing test is able to detect both peripherally and centrally acting analgesics, whereas the hot plate test has demonstrated to be predictive of centrally acting analgesics [12].

The low activity in the hot plate test associated with potent anti-nociceptive properties in the writhing test is in favor of a prevalent peripheral mechanism of action without a central analgesic effect.

Five compounds produced a statistically significant anti-inflammatory activity in the carrageenan-induced edema assay in the rat. At the 200 mg/kg dose, the degree of protection was 31% for **2c**, 41% for **2d**, 25% for **2f**, 29% for **2g** and 38% for **2h**. The most active compounds **2d**,**h** displayed a significant inhibition of the paw edema also at the 100 mg/kg dose (22 and 24%, respectively), whereas compounds **2c**,**f**,**g** did not show any statistically significant activity at such a dose.

The results of the pharmacological evaluation are listed in Table 3.

5.2. Biology

All the tested compounds, assayed at a concentration of 1×10^{-3} M, remarkably inhibited the aggregation of human platelets induced in platelet-rich plasma by 2 and 5 μM adenosine diphosphate (ADP), collagen at concentrations of 4 and 8 μg/ml, 5 μM adrenaline. Many of them maintained good activity at a concentration of 1×10^{-4} M. Almost all compounds were more active than acetylsalicylic acid at both concentrations.

The most active compounds were the 1,5-diphenyl-substituted pyrazoles **2g** (95–100% of inhibition at a concentration of 1×10^{-3} M and 62–98% at 1×10^{-4} M) and **2n** (93–100% at 1×10^{-3} M and 54–90% at 1×10^{-4} M). Derivatives **2g**,**n** were also tested at a concentration of 1×10^{-5} M, but at this dilution they turned out to be inactive.

Table 3
Anti-inflammatory and analgesic activities of compounds **2a**–**n**

Comp.	Tested dose (mg/kg p.o.)	Anti-inflammatory activity [a] (% inhibition)	Analgesic activity (% protection)	
			Writhing test [b]	Hot plate test [c]
2a	200	17	62 *,[d]	
	100		21	
2b	200	0	92 *,[d]	31 *,[d]
	100		49 **,[d]	14
	50		29	
2c	200	31 **,[d]	63 *,[d]	
	100	13	19	
2d	200	41 **,[d]	44 **,[d]	
	100	22 **,[d]	12	
	50	9		
2e	200	16	87 *,[d]	35 *,[d]
	100		39 **,[d]	15
	50		25	
2f	200	25 **,[d]	46 **,[d]	
	100	10	17	
2g	200	29 **,[d]	83 *,[d]	19 *,[d]
	100	12	40 **,[d]	8
	50		17	
2h	200	38 **,[d]	50 **,[d]	
	100	24 **,[d]	19	
	50	10		
2i	200	0	63 *,[d]	
	100		25	
2j	200	0	64 *,[d]	
	100		24	
2k	200	18	40 **,[d]	
	100		13	
2l	200	0	40 **,[d]	
	100		15	
2m	200	16	67 *,[d]	
	100		23	
2n	200	17	19	
Indomethacin	6	65 *,[d]	85 *,[d]	15
Morphine	15		84 *,[d]	48 *,[d]

[a] Carrageenan-induced paw edema test (on groups of five rats).
[b] On groups of four mice.
[c] On groups of five rats.
[d] Statistical significance versus control group was evaluated by the Student's test:
* $P<0.01$.
** $P<0.05$.

Table 4
Platelet anti-aggregating activity of compounds **2a–n**

Comp.	Final concentration (M)	Inhibition of platelet aggregation induced by ADP, collagen and adrenaline in human plasma (%) [a]				
		ADP (5 μM)	ADP (2 μM)	Collagen (8 μg/ml)	Collagen (4 μg/ml)	Adrenaline (5 μM)
2a	1×10^{-3}	38	59	78	97	87
	1×10^{-4}	17	41	43	41	15
2b	1×10^{-3}	39	64	38	60	79
	1×10^{-4}	6	34	40	31	1
2c	1×10^{-3}	46	73	29	65	87
	1×10^{-4}	11	42	64	65	52
2d	1×10^{-3}	54	73	98	97	93
	1×10^{-4}	20	40	47	55	45
2e	1×10^{-3}	53	68	93	92	42
	1×10^{-4}	58	65	91	83	35
2f	1×10^{-3}	61	81	83	96	97
	1×10^{-4}	14	50	70	71	25
2g	1×10^{-3}	100	100	95	98	100
	1×10^{-4}	62	98	68	89	83
	1×10^{-5}	6	19	4	5	6
2h	1×10^{-3}	54	77	94	93	88
	1×10^{-4}	9	47	39	45	78
2i	1×10^{-3}	62	85	82	92	94
	1×10^{-4}	39	54	25	66	73
2j	1×10^{-3}	38	71	73	97	99
	1×10^{-4}	38	36	43	49	82
2k	1×10^{-3}	69	85	92	97	92
	1×10^{-4}	40	64	12	87	81
2l	1×10^{-3}	65	85	95	91	91
	1×10^{-4}	36	64	7	15	86
2m	1×10^{-3}	64	50	95	94	99
	1×10^{-4}	21	6	57	61	72
2n	1×10^{-3}	100	95	93	94	99
	1×10^{-4}	73	88	54	88	90
	1×10^{-5}	0	35	1	5	5
ASA	1×10^{-3}	45	41	41	37	68
	1×10^{-4}	9	34	3	3	30
	1×10^{-5}	2	15	0	2	0

[a] Mean value of two determinations.

The results of the biological evaluation are listed in Table 4.

6. Conclusions

In summary, the results of the preliminary pharmacological tests which are reported above indicate that aminoalcohols **2** have a predominant analgesic profile, similar to aminoethers **A** [5]. However, the anti-nociceptive properties of pyrazoles **2** seem to have increased compared to analogues **A**. Furthermore, the dimethylamino group, present in the side chain of the most effective compounds of the series (**2b**,**e**,**g**), seems to be generally better for analgesic activity rather than the 1-piperidinyl moiety (compounds **2h**–**n**) (Table 3).

The good analgesic properties of pyrazoles **2b**,**e**,**g** do not correlate with respective anti-inflammatory activities, which were weak or insignificant.

The strong platelet anti-aggregating activity of the majority of compounds **2**, not accompanied by remarkable anti-inflammatory properties, could be justified by a mechanism of selective cyclo-oxygenase-1 inhibition [13]. This hypothesis could be supported by the observation that the two compounds **2g**,**n**, endowed with the greatest anti-platelet activity, have a diarylpyrazole

skeleton, like many selective COX-2 inhibitors reported in the above mentioned paper [2], but unlike these, lacking the sulfonamide moiety, proved to be critical for good COX-2 inhibitory activity.

The study of the action mechanism of new molecules could be a topic for future investigations, to obtain further information on the structure–activity relationships of 1-aryl-1*H*-pyrazole derivatives.

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References

[1] G. Menozzi, L. Mosti, P. Schenone, M. D'Amico, M. Falciani, W. Filippelli, 1-Aryl-1*H*-pyrazole-5-acetic acids with anti-inflammatory, analgesic and other activities, Farmaco 49 (1994) 115–119 and references cited therein.

[2] T.D. Penning, J.J. Talley, S.R. Bertenshaw, J.S. Carter, P.W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers, D.J. Rogier, S.S. Yu, G.D. Anderson, E.G. Burton, J.N. Cogburn, S.A. Gregory, C.M. Koboldt, W.E. Perkins, K. Seibert, A.W. Veenhuizen, Y.Y. Zhang, P.C. Isakson, Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1yl]benzenesulfonamide (SC-58635, celecoxib), J. Med. Chem. 40 (1997) 1347–1365.

[3] L.J. Marnett, A.S. Kalgutkar, Cyclooxygenase 2 inhibitors: discovery, selectivity and the future, TiPS 20 (1999) 465–469.

[4] V.P. Arya, 4-Tetrahydro pyridyl, hidroxy alkyl pyrazoles, U.S. 3 778 443 (1973); Chem. Abstr. 80 (1974) 82961c.

[5] G. Menozzi, L. Mosti, P. Fossa, F. Mattioli, M. Ghia, ω-Dialkylaminoalkyl ethers of phenyl(5-substituted 1-phenyl-1*H*-pyrazol-4-yl)methanols with analgesic and anti-inflammatory activities, J. Heterocycl. Chem. 34 (1997) 963–968.

[6] (a) I.L. Finar, K.E. Godfrey, The preparation and properties of some derivatives of 1-phenylpyrazole, J. Chem. Soc. (1954) 2293–2298. (b) I.L. Finar, G.H. Lord, The formilation of the pyrazole nucleus, J. Chem. Soc. (1957) 3314–3315. (c) K. Takagi, A. Bajnati, M. Hubert-Hubart, Direct synthesis of 2-substituted 5-formylpyrimidines and ring transformation of their phenylhydrazones into 4-formyl-1-phenylpyrazole, Heterocycles (1990) 1105–1109.

[7] G. Menozzi, P. Schenone, L. Mosti, F. Mattioli, Synthesis of 5-substituted 1-aryl-1*H*-pyrazole-4-acetonitriles, 4-methyl-1-phenyl-1*H*-pyrazole-3-carbonitriles and pharmacologically active 1-aryl-1*H*-pyrazole-4-acetic acids, J. Heterocycl. Chem. 30 (1993) 997–1002.

[8] C.A. Winter, E.A. Risley, G.W. Nuss, Anti-inflammatory and antipyretic activities of indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid, J. Pharmacol. Exp. Ther. 141 (1963) 369–376.

[9] R. Koster, M. Anderson, E.J. De Beer, Synthetic analgesics. Dithienbutenyl dithienbuthylamines, Fed. Proc. 18 (1959) 412–421.

[10] N.B. Eddy, C. Fuhrmeister Touchberry, J.E. Lieberman, Synthetic analgesics. Methadone isomers and derivatives, J. Pharmacol. Exp. Ther. 98 (1950) 121–137.

[11] G.V.R. Born, Aggregation of blood platelets by adenosine diphosphate and its reversal, Nature 194 (1962) 927–929.

[12] M.I. Serrano, J.S. Serrano, A. Fernàndez, J.M. Sànchez-Carrasco, J. Fuentes, M.A. Pradera, M.C. Ortiz, J.M. Garcia Fernàndez, Synthesis and analgesic activity of 2-amino-5-*tert*-butyl-2-oxazoline, Arzneim.-Forsch./Drug Res. 45 (1995), 22–26.

[13] J.R. Vane, Y.S. Bakhle, R.M. Botting, Cyclooxygenases 1 and 2, Annu. Rev. Pharmacol. Toxicol. 38 (1998) 97–120.