Full Paper

2-Sulfonyliminodihydropyrimidines: A Novel Class of Analgesic Compounds

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A series of 2-sulfonyliminodihydropyrimidine derivatives have been synthesized and evaluated *in vivo* for their antinociceptive and anti-inflammatory activities. The results were compared with that of acetyl salicylic acid. Compounds **6Ab–d** and **6Be** displayed an interesting analgesic profile in the acetic acid-induced abdominal contractions test. Based on the results of the carrageenan-hind paw edema test, compound **6Af** showed potential anti-inflammatory activity.

Keywords: Anti-inflammatory activity / Antinociceptive activity / Dihydropyrimidines

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Introduction

Various types of heterocyclic compounds have been synthesized in the search for more effective and safer drugs [1]. In this context, pyrimidine derivatives with analgesic and anti-inflammatory activity have been reported in the literature [2–9]. Although there is a large amount of experimental work on this heterocyclic system, it still remains an area of active research.

In the course of an ongoing research project aimed at the synthesis and pharmacological evaluation of new bioactive compounds, we previously described the anti-inflammatory profile of imidazo[1,2-*a*]pyrimidines **1** [10], imidazo[1,2-*c*]pyrimidines **2** [11], and tosyldihydropyrimidine derivatives **3** [12]. Compounds from series **2**, particularly the *p*-fluoro derivative **2a**, showed a interesting anti-inflammatory activity when administered to mice orally.

As continuation of our research program on the synthesis of heterocyclic systems exhibiting biological activity, we designed the pyrimidine derivatives **6** employing the molecular simplification strategy, and we evaluated their analgesic and anti-inflammatory activities (Scheme 1).

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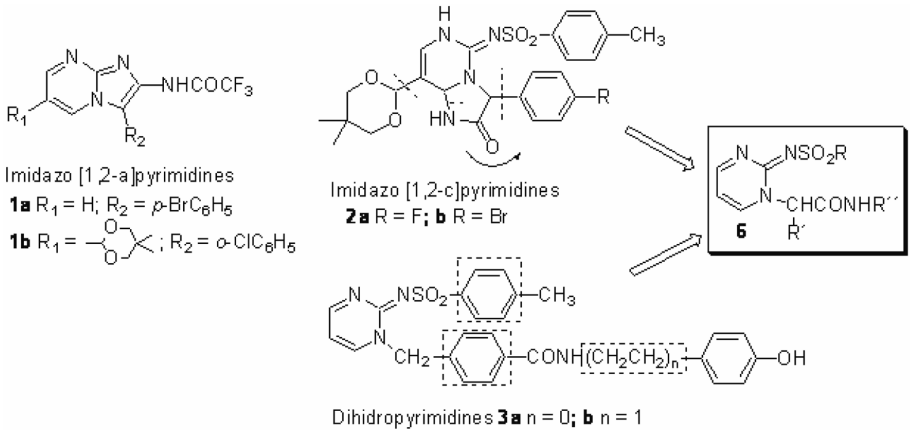
Results and discussion

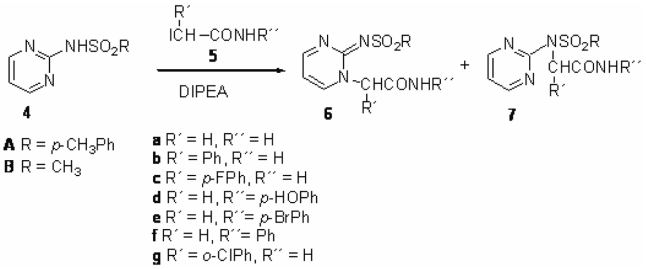
The pyrimidine derivatives **6** were prepared according to the literature procedure [13]. Reaction of 2-sulfonylaminopyrimidines **4A**, **B** with the appropriate iodocarboxamide **5a–g** in the presence of Hünig's base in DMF provided the corresponding 2-tosylimino-1-substituted dihydropyrimidines **6Aa–g** and 2-mesyliminodihydropyrimidines **6Bd**, **e**. In some cases, pyrimidines **7** were obtained along with dihydropyrimidines **6** (Scheme 2).

As it is outlined in Table 1, higher yields of compounds **6** resulting from the pyrimidine nitrogen alkylation were obtained in comparison with compounds **7** from the exocyclic nitrogen alkylation. In some cases, compounds **7** were not even detected. These results are in accordance with the literature [14, 15].

The antinociceptive activity of compounds **6Aa–g** and **6Bd**, **e** was evaluated in mice intraperitoneally (i.p.) in two different noxious stimuli: acetic acid writhing test [16] and hot plate test [17] as a measure of peripheral and central acute pain, respectively. In the writhing test, the 2-sulfonyliminodihydropyrimidines **6Ab–d** and **6Be** dis-



Scheme 1. Imidazopyrimidines **1** and **2** and sulfonyldihydropyrimidine **3** and **6** derivatives.



Scheme 2. Synthesis of compounds **6** and **7**.

Table 1. Yields obtained in the preparation of sulfonylpyrimidines **6** and **7**.

R	R′	R″	**6** (%)	**7** (%)
p-$CH_3C_6H_5$	H	H	**6Aa** (85)	**7Aa** (–)
p-CH_3Ph	Ph	H	**6Ab** (80)	**7Ab** (–)
p-CH_3Ph	*p*-FPh	H	**6Ac** (70)	**7Ac** (–)
p-CH_3Ph	H	*p*-HOPh	**6Ad** (50)	**7Ad** (10)
p-CH_3Ph	H	*p*-BrPh	**6Ae** (90)	**7Ae** (–)
p-CH_3Ph	H	Ph	**6Af** (71)	**7Af** (12)
p-CH_3Ph	*o*-ClPh	H	**6Ag** (90)	**7Ag** (–)
CH_3	H	*p*-HOPh	**6Bd** (70)	**7Bd** (20)
CH_3	H	*p*-BrPh	**6Be** (72)	**7Be** (18)

played an interesting analgesic profile. These four compounds showed a dose–dependet effect with significant decrease of the number of writhing movements (Fig. 1).

The results of the nociceptive experiments are shown in Table 2. The percentage of inhibition was calculated from the difference in the writhing response between the treated and the control group (vehicle). Acetylsalicylic acid was used as a reference substance in the experiments. Compounds **6Ab–d** inhibited significantly the response to the acetic acid at all doses tested. The highest percent of inhibition (83.9%) was shown by compound

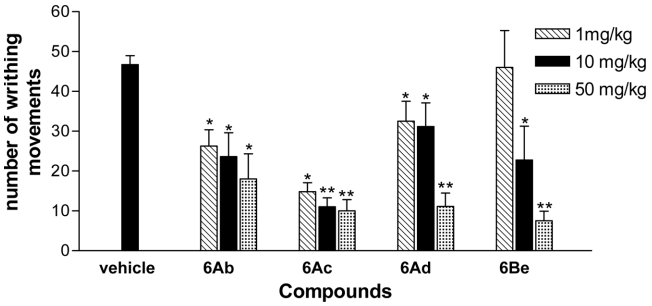


Figure 1. Effect of compounds **6Ab–6Ad** and **6Be** on acetic acid-induced writhing test in mice. Groups of 6-24 mice received acetic acid (0.1 mL/10 g, i.p., 0.6%) 30 min after administration of the compounds. Data represent mean ± SEM, * P <0.05 and ** P <0.01.

6Be at the dose of 50 mg/kg, whereas this compound was not effective at the lowest dose (1 mg/kg). Compounds **6Ae** and **6Bd** significantly inhibited the response, but this effect was not dose-dependent. Finally, compounds **6Aa**, **6Af**, and **6Ag** did not show any effect. In the hot plate test, no antinociceptive effect was observed for any of the compounds.

As regards to the anti-inflammatory activity the behavior of the sulfonyliminodihydropyrimidines **6** was different. The anti-inflammatory effect of compounds **6Ac**, **d**, **6Af**, and **6Bd** was tested by the carrageenan hind paw edema assay [18]. It was found that among the compounds examined, the only compound that significantly inhibited formation of edema was **6Af**, having a phenyl group on the carboxamide moiety (Fig. 2). The inhibition of the edema produced by this compound was significant 2, 3, and 5 hours after the intraplantar administration of carrageenan.

Due to the small number of compounds evaluated and the diversity of types involved, it does not seem reason-

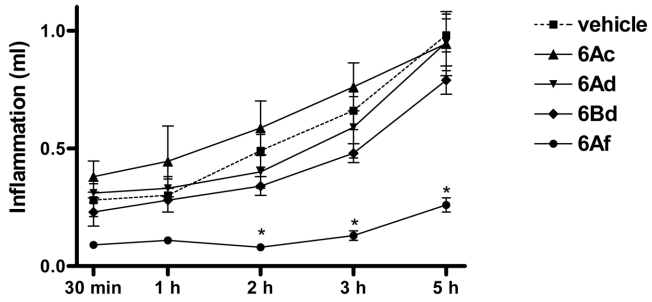


Figure 2. Effect of compounds **6Ac**, **d**, **f** and **6Bd** (50 mg/kg, i.p.), 30 min, 1 h, 2 h, 3 h, and 5 h after intraplantar carrageenan injection (0.1 mL; 2%). Data represent mean ± SEM, * P <0.05 (n = 9–12).

Table 2. Effects of compounds **6Aa–g** and **6Bd**, **e** on the number of writhing movements induced by acetic acid (0.6%, i.p.) in mice (n = 6–24). Data are presented as row data and as percentage of inhibition.

Compound	Dose[a] (mg/kg)	Number of writhing movements	Inhibition (%)[b]
Vehicle		46.7 ± 2.3	
AAS		2.4 ± 0.3	89.8**
6Aa	1	45.2 ± 7.0	3.2
	10	55.8 ± 7.7	−19.4
	50	35.4 ± 7,2	24.1
6Ab	1	26.5 ± 4.1*	43.3*
	10	23.6 ± 6.0*	49.5*
	50	18.0 ± 6.3*	61.5*
6Ac	1	14.8 ± 2.3*	68.3*
	10	11.0 ± 2.3**	76.4**
	50	10.0 ± 2.8**	78.6**
6Ad	1	32.5 ± 5.0*	30.4*
	10	31.2 ± 5.9*	33.3*
	50	11.1 ± 3.3**	76.2**
6Ae	1	29.0 ± 1.2*	37.9*
	10	31.0 ± 2.9*	33.6*
	50	31.0 ± 2.6*	33.6*
6Af	1	46.3 ± 5.8	0.9
	10	43.2 ± 6.1	7.5
	50	38.1 ± 7.1	18.4
6Ag	1	39.8 ± 8.0	14.9
	10	32.8 ± 12.7	29.8
	50	29.2 ± 5.6	37.5
6Bd	1	30.0 ± 3.3*	35.8*
	10	33.5 ± 2.9*	28.3*
	50	31.3 ± 2.0*	32.9*
6Be	1	46.0 ± 9.3	1.5
	10	22.8 ± 8.5*	51.3*
	50	7.5 ± 2.4**	83.9**

[a] All compounds were administered i.p.
[b] %-inhibition obtained by comparison with vehicle group.
* P <0.05.
** P <0.01. Results are expressed as mean ± SEM

able to attempt to analyze the structure-activity relationship (SAR), although several comparisons on the results could be made. Compounds **6Ab**, **c** with a phenyl ring as a substituent on the C carboxamide moiety could be considered as the open ring analogous of the imidazo [1,2-*c*]pyrimidines **2**. In addition, it is interesting to note the presence of a *p*-fluoro substituent in compound **6Ac** similarly to the imidazo[1,2-*c*]pyrimidine derivative **2a** (Scheme 1). The displacement of the phenyl ring to the *N*-carboxamide moiety led to **6Ad–f** and **6Bd**, **e**. In this series, most of the compounds showed a fairly good activity. The *p*-bromo mesyl derivative **6Be** exhibited stronger antinociceptive activity than the corresponding tosyl derivative **6Ae**, whereas in the case of the *p*-hydroxy derivatives, which could be considered structurally related to *p*-acetaminophen, the compound **6Bd** with the mesyl group was less active than the tosylated **6Ad**. Thus, the influence of the sulfonyl substituent toward the antinociceptive activity cannot be clearly expressed.

In summary, we report on the synthesis and evaluation of the antinociceptive and anti-inflammatory activities of sulfonyliminodihydropyrimidine derivatives. *In-vivo* evaluation of compounds **6** has shown that exhibit interesting pharmacological properties when administered by the intra-peritoneal route. These preliminary results indicate a test and structure dependent antinociceptive responses for the 2-tosyliminodihydropyrimidine derivatives **6A** and 2-mesyliminodihydropyrimidine derivatives **6B**. No clear-cut relationship could be recognized between pharmacological activities and chemical structure. Synthesis and pharmacological evaluation of related 2-sulfonyliminodihydropyrimidines to determine structural features for the antinociceptive and anti-inflammatory activities are in progress.

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The authors have declared no conflict of interest.

Experimental

Chemistry

All reagents were purchased from Aldrich (Sigma-Aldrich, Madrid, Spain) and used without purification unless stated otherwise. All experiments were carried out under nitrogen atmosphere. Melting points were determined with a Kofler hot-stage apparatus (C. Reichert, Vienna, Austria) and are uncorrected. Flash column chromatography was performed using silica gel (Merck 60, 70–230 mesh; Merck, Germany). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-300 instrument (Bruker BioScience, Billerica, MA, USA) unless otherwise indicated. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz respectively. HRMS were obtained using a VG Autospec TRIO 1000 instrument (Fisons, Manchester, UK). The ionization mode used in mass spectra was electron impact

(EI) or fast atom bombardment (FAB). ^{1}H- and ^{13}C-NMR assignments have been confirmed by homonuclear two dimensional correlations and DEPT experiments. Compounds **6Aa – c** and **6Ag** were prepared as described in the literature [13].

*General Procedure for the synthesis of 2-(sulfonamido)pyrimidines **4A, B***

To a solution of 2-aminopyrimidine (20 mmol) in dry pyridine (8 mL) at 0°C was slowly added the corresponding sulfonyl chloride (30 mmol) in pyridine (6 mL) The solution was stirred for 2 h and allowed to reach room temperature. Water was added (100 mL) and the solid was collected and recrystallized.

*2-(p-Toluenesulfonamido)pyrimidine **4A***

Recrystallized from chloroform. Yield 90%; m.p.: 208 – 210°C (lit [13] 204 – 206°C).

*2-Methanesulfonamidopyrimidine **4B***

Yield: 65%; m.p.: 258.6 – 260°C. ^{1}H-NMR (300 MHz, DMSO-d_6): 3.36 (s, 3H), 7.13 (t, *J* = 4.9 Hz, 1H), 8.61 (d, *J* = 4.9 Hz, 2H), 11.33 (br, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) 41.6 (CH_3), 40.5 (CH_2), 116.1(CH), 117.9 (C), 158.9 (CH).

*General procedure for the synthesis of iodoacetamides **5d – f** [19]*

Powdered KI (5 mmol) was added to a solution of the corresponding chlorocarboxamide (1 mmol) in dry acetone (1 mL). The reaction mixture was refluxed for 8 h and filtered. The solvent was evaporated and the residue was used without further purification.

*N-(4-Hydroxyphenyl)-2-iodoacetamide **5d***

Yield: 80%; m.p.: 155 – 157°C (lit [19] 153°C); ^{1}H-NMR (300 MHz, DMSO-d_6): 3.7 (s, 2H), 6.6 (d, *J* = 7.8 Hz, 2H), 7.3 (d, *J* = 8.2 Hz, 2H), 9.1 (br, 1H, O*H*), 9.8 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 0.1 (CH_2), 113.3 (CH), 118.9 (CH) 128.6 (C), 151.7 (C), 163.8 (CO).

*N-(4-Bromophenyl)-2-iodoacetamide **5e***

Yield: 90%; m.p.: 179 – 180°C (lit [20] 182 – 184°C); ^{1}H-NMR (300 MHz, DMSO-d_6): 3.75 (s, 2H), 7.45 (m, 4H), 10.4 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 0.1 (CH_2), 114.0 (C), 120.1 (CH), 130.3 (CH), 137.0 (C), 165.4 (CO).

*2-Iodo-N-phenylacetamide **5f***

Yield: 80%; m.p.: 143 – 146°C (lit [21] 141 – 142°C); ^{1}H-NMR (300 MHz, DMSO-d_6): 3.8 (s, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.3 (t, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 10.3 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 0.2 (CH_2), 117.8 (CH), 122.0 (CH), 127.2 (CH), 137.2 (C), 165.0 (CO).

*General procedure for the preparation of compounds **6** and **7***

Diisopropylethylamine, DIPEA (0.65 mL, 3.6 mmol) was added dropwise to a stirred suspension of 2-sulfonamidopyrimidine **4** (3 mmol) in dry DMF (12 mL) under argon. After 40 min, the corresponding iodocarboxamide **5** (3.6 mmol) was added. The reaction mixture was stirred at room temperature for 16 h and then poured onto water (100 mL). The resulting solid was collected, air dried, and purified by flash column chromatography to give the exocyclic nitrogen alkylated compounds **7** (hexane : EtOAc 1 : 1) and the endocyclic nitrogen alkylated compounds **6** (EtOAc:MeOH 9 : 1).

*N-(4-Hydroxyphenyl)-2-[{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1(2H)-yl]acetamide **6Ad***

Yield: 50%; m.p.: 221 – 223°C; ^{1}H-NMR (300 MHz, DMSO-d_6): 2.3 (s, 3H), 4.89 (s, 2H), 6.72 (d, *J* = 9 Hz, 2H), 6.87 (dd, *J* = 4.5 Hz, *J* = 6 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 9 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 8.41 (dd, *J* = 2.4 Hz, *J* = 6 Hz), 8.64 (dd, *J* = 2.4 Hz, *J* = 4.5 Hz, 1H), 10.25 (br, 1H, N*H* or O*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 21.2 (CH_3), 48.9 (CH_2), 108.1 (CH), 115.5 (CH), 121.2 (CH), 126.9 (CH), 128.9 (CH), 130.5 (C), 141.2 (C), 141.3 (C), 152.0 (CH), 153.9 (C), 154.6 (C), 163.6 (CO), 164.8 (CH); HRMS (EI$^+$) *m/z* calcd for $C_{19}H_{19}N_4O_4S_1$: 399.1127; found: 399.1127.

*N^1-(4-Hydroxyphenyl)-N^2-[(4-methylphenyl)sulfonyl]-N^2-pyrimidin-2-ylglycinamide **7Ad***

Yield: 10%; m.p.: 168 – 173°C; ^{1}H-NMR (300 MHz, DMSO-d_6): 2.39 (s, 3H), 4.91 (s, 2H), 6.66 (d, *J* = 9 Hz, 2H), 7.01 (t, *J* = 4.8 Hz, 1H), 7.32 (d, *J* = 7.95 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 8.0 (d, *J* = 9 Hz, 2H), 8.47 (d, *J* = 4.5 Hz, 2H), 9.2 (br, 1H). 10.01 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): 21.4 (CH_3), 48.7 (CH_2), 115.5 (CH), 116.3 (CH), 121.1 (CH), 128.9 (CH), 129.3 (CH), 130.9 (C), 137.8 (C), 143.9 (C), 153.7 (C), 157.7 (C), 158.1 (CH), 165.7 (CO).

*N-(4-Bromophenyl)-2-[{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1(2H)-yl]acetamide **6Ae***

Yield: 90%; m.p.: 274.8 – 275.2°C; ^{1}H-NMR (DMSO-d_6): 2.4 (s, 3H), 4.93 (s, 2H), 6.89 (dd, *J* = 4.2 Hz, *J* = 6.3, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.55 (s, 4H), 7.62 (d, *J* = 8.1 Hz, 2H), 8.42 (dd, *J* = 2.4 Hz, *J* = 6.3 Hz, 1H), 8.67 (dd, *J* = 2.4 Hz, *J* = 4.2 Hz, 1H), 10.64 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 21.3 (CH_3), 55.9 (CH_2), 108.2 (CH), 115.6 (C), 121.3 (CH), 126.9 (CH), 128.9 (CH), 132.1 (CH), 138.3 (C), 141.0 (C), 141.3 (C), 151.1 (CH), 154.5 (C), 165.0 (CO), 165.5 (CH); HRMS (EI$^+$) *m/z* calcd for $C_{19}H_{17}BrN_4O_3S$: 460.0205; found: 460.0207.

*[2-{[(4-Methylphenyl)sulfonyl]imino}pyrimidin-1(2H)-yl]-N-phenylacetamide **6Af***

Yield: 71%; m.p.: 240 – 244°C; ^{1}H-NMR (300 MHz, DMSO-d_6): 2.44 (s, 3H), 4.90 (s, 2H), 6.91 (dd, *J* = 6.6 Hz, *J* = 4.51 Hz, 1H), 7.17 (m, 3H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 8.12 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 2H), 8.46 (dd, *J* = 6.6 Hz, *J* = 2.4 Hz, 1H), 8.7 (dd, *J* = 4.5 Hz, *J* = 2.4 Hz, 1H), 10.53 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 21.2 (CH_3), 55.9 (CH_2), 108.1 (CH), 119.4 (CH), 124.0 (C), 126.9 (CH), 128.9 (CH), 129.3 (CH), 138.9 (C), 141.2 (C), 141.3 (C), 152.0 (CH), 154.6 (C), 164.3 (CO), 164.9 (CH); HRMS (EI$^+$) *m/z* calcd for $C_{19}H_{18}N_4O_3S$: 382.1099; found: 382.1105.

*N^2-[(4-Methylphenyl)sulfonyl]-N^1-phenyl-N^2-pyrimidin-2-ylglycinamide **7Af***

Yield: 12%; m.p.: 148 – 150°C; ^{1}H-NMR (300 MHz, DMSO-d_6): 2.88 (s, 3H), 5.00 (s, 2H), 7.07 (m, 2H), 7.34 (t, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 5.4 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 8.1 Hz, 2H) 8.51 (d, *J* = 5.4 Hz, 2H), 10.30 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 21.8 (CH_3), 49.5 (CH_2), 119.9 (CH), 124.1(CH), 126.4 (CH), 129.4 (CH),

129.7 (CH), 129.9 (CH), 139.7 (C), 144.5 (C), 154.1 (C), 158.1 (C), 158.7 (CH), 163.2 (CO).

N-(4-Hydroxyphenyl)-2-[(2-[(methylsulfonyl)imino]pyrimidin-1(2H)-yl]acetamide ***6Bd***

Yield: 70%; m.p.: 180 – 184°C; ^{1}H-NMR (300 MHz, DMSO-d_6): 2.95 (s, 3H), 4.91 (s, 2H), 6.71 (d, *J* = 9 Hz, 2H), 6.91 (dd, *J* = 4.2 Hz, *J* = 6.6 Hz, 1H), 7.35 (d, *J* = 9 Hz, 2H), 8.44 (dd, *J* = 2.4 Hz, *J* = 6.6 Hz, 1H), 8.77 (dd, *J* = 2.4 Hz, *J* = 4.2 Hz, 1H), 9.25 (s, 1H), 10.25 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 40.7 (CH_3), 55.1 (CH_2), 107.7 (CH), 115.6 (CH), 121.2 (CH), 130.5 (C), 152.2(CH), 154.9 (C), 162.7 (C), 163.6 (CO), 164.9 (CH); HRMS (EI$^+$) *m*/*z* calcd for $C_{13}H_{14}N_4O_4S$: 322.0736; found: 322.0737.

N^1-(4-Hydroxyphenyl)-N^2-(methylsulfonyl)-N^2-pyrimidin-2-ylglycinamide ***7Bd***

Yield: 20%; m.p.: 297°C; ^{1}H-NMR (300 MHz, DMSO-d_6): 3.37 (s, 3H), 4.89 (s, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 7.12 (t, *J* = 4.8 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 8.61, (d, *J* = 4.8 Hz, 1H), 9.20 (br, 1H, O*H*), 10.03 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 42.7 (CH_3), 49.3 (CH_2), 116.0 (CH), 116.8 (CH), 121.6 (CH), 131.2 (C), 154.2 (C), 159.0 (C), 163.2 (CH), 166.6 (CO).

N-(4-Bromophenyl)-2-[(2-[(methylsulfonyl)imino]pyrimidin-1(2H)-yl]acetamide ***6Be***

Yield: 72%, decomp.; ^{1}H-NMR (300 MHz, DMSO-d_6): 3.15 (s, 3H), 5.14 (s, 2H), 7.13 (dd, *J* = 4.3 Hz, *J* = 6.5 Hz, 1H), 7.80 (m, 4H), 8.63 (dd, *J* = 2.4 Hz, *J* = 6.5 Hz, 1H), 8.99 (dd, *J* = 2.4 Hz, *J* = 4.3 Hz, 1H), 10.85 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): 40.8 (CH_3), 55.4 (CH_2), 107.6 (CH), 115.6 (C), 121.3 (CH), 132.1 (CH), 139.0 (C), 152.1 (CH), 154.9 (C), 164.8 (CO), 165.12 (CH), HRMS (EI$^+$) *m*/*z* calcd for $C_{13}H_{13}N_4O_3SBr$: 383.9892; found: 383.9887.

N^1-(4-Bromophenyl)-N^2-(methylsulfonyl)-N^2-pyrimidin-2-ylglycinamide ***7Be***

Yield: 18%, oil; ^{1}H-NMR (300 MHz, DMSO-d_6): 3.63 (s, 3H), 4.92 (s, 2H), 7.20 (t, *J* = 4.8 Hz, 1H), 7.45 (d, *J* = 9 Hz, 2H), 7.54 (d, *J* = 9 Hz, 2H), 8.68 (d, *J* = 4.8 Hz, 2H), 10.45 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): 42.0 (CH_3), 49.0 (CH_2), 115.3 (CH), 116.4 (C), 121.3 (CH), 132.0 (CH) 138.4 (C), 158.6 (CH), 162.6 (C), 167.1 (CO).

Pharmacology

Antinociceptive activity

The antinociceptive activity of the compounds administered i.p. was evaluated in male NMRY mice (20 – 25 g, n = 6 – 24 per group) in two different noxious stimuli: writhing [16] and hot plate test [17]. The doses tested were 1, 10, and 50 mg/kg administered i.p. (0.1 mL/kg). The vehicle was 10% saline/DMSO. In the writhing test, a saline solution of acetic acid (0.1 mL/10g, 0.6%) was administered i.p. 30 min after compound administration. The number of writhing movements was counted during the following 15 minutes. Antinociceptive activity was expressed as% of inhibition of contractions when compared with the control group. In the hot plate test, the nociceptive threshold was determined by employing the method of Eddy and Leimbach [17]. The device (Ugo Basile, Italy) consisted of a metal plate (25 × 25 cm) heated to a constant temperature (55°C), on which a plastic cylinder (20 cm diameter, 16 cm high) was placed. The maximum time allowed for an animal to respond was 90 s. Both licking and jumping movements (determined in seconds) were recorded.

Anti-inflammatory activity

The anti-inflammatory activity was studied in a carrageenan-induced rat paw oedema test [18]. Female Wistar rats (120 – 140 g, n = 9 – 12) were used. Compounds under evaluation or saline solution were administered intraperitoneally (50 mg/kg) 30 min before intraplantar injection of 0.1 mL of 2% carrageenan solution in saline. The paw volume was measured using a glass plethysmometer (Ugo Basile, Italy) 30 min, 1h, 2h, 3h, and 5 hours after carrageenan injection.

Statistics

Results are expressed as the mean ± SEM. The data were statistically analyzed by the one-way ANOVA test and post-hoc Tuckey test, with a significance level of $^*P < 0.05$ and $^{**}P < 0.01$.

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