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Preparation of new 5-aroylamino substituted 3-nicotinoyl/isonicotinoyl-1,3,4-thiadiazol-2(3*H*)-ones with anti-inflammatory activity

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Abstract

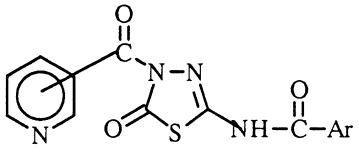
A series of 1,3,4-thiadiazol-2(3*H*)-ones (**2a–j**) with a nicotinoyl/isonicotinoyl group in position 3 and an aroylamino substituent in position 5 of the ring was prepared and evaluated for antipyretic and anti-inflammatory activities. All the title compounds and in particular **2e**, **2i** and **2j** exhibited anti-inflammatory activity and were devoid of antipyretic properties. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: 1,3,4-Thiadiazol-2(3*H*)-ones; Substituted thiadiazolones; Anti-inflammatory agents

1. Introduction

Within the framework of a research programme on anti-inflammatory agents, we focused our attention on five-membered heterocyclic structures with three heteroatoms, at present on the thiadiazole ring.

Such a ring system has been studied previously for its many and interesting pharmacological properties but only recently as a potential source of antiphlogistic and antiplatelet agents, either as a simple monocycle [1–7] or as a member of heteropolycyclic systems [8–13]. In particular we have been concerned about monocyclic 1,3,4-thiadiazoles having a carbonyl group in position 2 and heteroaroyl and amidic substituents in positions 3 and 5, respectively, of the ring:



Our aim was to verify whether such thiadiazolones, so far not investigated and resembling the well known pyrazolones analogues, were actually endowed with antipyretic and anti-inflammatory activities.

As acyl substituents, we selected at the beginning the nicotinoyl and isonicotinoyl moieties and an aroylamino function with some *para*-substituent groups having different electronic and lipophilic properties to verify their possible influence on the above-mentioned activities.

2. Chemistry

The synthesis of the title compounds was accomplished as illustrated in Scheme 1 and Table 1, by reacting nicotinoyl/isonicotinoyl hydrazide with the relevant acylisothiocyanates to give the corresponding acylthiosemicarbazides (**1a–j**). Subsequent cyclization with phosgene, in the presence of sodium acetate, led to the expected 1,3,4-thiadiazol-2(3*H*)-ones (**2a–j**) in good to excellent yields (Scheme 1). The intermediate isonicotinoyl thiosemicarbazides (**1f–j**) were prepared in the past as potential antitubercular agents [14,15], but their physical and spectral data were not available.

The thiadiazole instead of triazole structure was confirmed by ^{13}C NMR spectroscopy, which showed only three typical amide carbonyl resonances in the range of 160–170 ppm and no thiocarbonyl signal beyond 170 ppm (for example see the ^{13}C NMR spectrum of **2g**).

Yields, m.p., IR and NMR spectral data are given in Tables 2 and 3.

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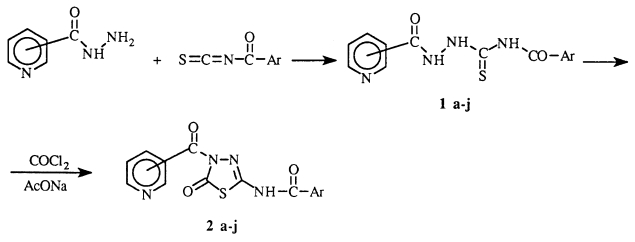

Scheme 1.

Table 1

Compounds	Ar	Compounds
		
1,2		**1,2**
a	C_{6H_5}	**f**
b	C_6H_4-pCH_3	**g**
c	C_6H_4-pOCH_3	**h**
d	C^6H^4-pCl	**i**
e	2-Furyl	**j**

3. Pharmacology

Compounds **2a–j** were evaluated for antipyretic and anti-inflammatory activities.

4. Experimental

4.1. Chemistry

Melting points were determined with a Büchi 530 apparatus. IR spectra were measured in KBr with a Perkin–Elmer 398 spectrophotometer. ^{1}H NMR spectra were recorded in $(CD_3)_2SO$ solution on a Hitachi Perkin–Elmer R-600 (60 MHz) instrument, ^{13}C NMR spectra were measured with a Varian Gemini 200 (50.30 MHz) spectrometer in $(CD_3)_2SO$ solution, chemical shifts are reported as δ (ppm) relative to TMS as internal standard; J in Hz. Analyses for C, H, N were within $\pm$ 0.3% of the theoretical values.

*4.2. General procedure for acylthiosemicarbazides (**1a–j**)*

To a suspension of nicotinoyl or isonicotinoyl hydrazide (2.74 g, 20 mmol) in anhydrous tetrahydrofuran (THF) (40 ml), a solution of the relevant acylisothiocyanate (21 mmol) in anhydrous THF (10 ml) was added dropwise with stirring at room temperature. The reaction mixture was stirred overnight at room temperature, the solvent was evaporated under reduced pressure and the residue treated with water (50 ml).

The white solids obtained were filtered and crystallized from THF/dry ethanol (1:1) (Table 2).

*4.3. General procedure for 1,3,4-thiadiazol-2(3H)-ones (**2a–j**)*

To a suspension of each acylthiosemicarbazide **1a–j** (20 mmol) and anhydrous sodium acetate (4.1 g, 50 mmol) in anhydrous THF (60 ml), a phosgene solution (20% in toluene, 12 ml, $\sim$ 22 mmol) was added dropwise with stirring and cooling with water.

The reaction mixture was stirred overnight at room temperature, the solvent was evaporated under reduced pressure and the residue treated with water (50 ml).

The resulting white solids were filtered and crystallized from *N,N*-dimethylformamide (DMF) (Table 3).

4.4. Pharmacology

The following pharmacological activities were evaluated by standard procedures [16]:

1. antipyretic activity by yeast-induced pyrexia in albino rats (5 rats/group);
2. anti-inflammatory activity, evaluated by carrageenan-induced paw edema in rats (Table 4).

For the most active compounds **2e**, **2i**, **2j**, the respective ED_{50} values were determined by administration of three dosages (25, 50, 100 mg/kg).

5. Results and conclusions

All the compounds tested **2a–j** were devoid of antipyretic activity, unlike the pyrazolone analogues, but were endowed with anti-inflammatory properties (Table 4).

The most active derivatives were **2e**, with an ED_{50} of 44.97 (22.90–88.33) mg/kg and **2i** and **2j** with an ED_{50} of 51.29 (44.37–59.29) and 16.98 (8.86–32.53) mg/kg, respectively, 4 h after the treatment.

It was interesting to remark that the best results were obtained in the isonicotinoyl set (**2i** and **2j**) and that the furoyl substituent showed superior influence over the benzoyl groups in both series (**2e** and **2i**).

In conclusion, we found that the present 1,3,4-thiadiazol-2(3*H*)-ones are in general effective as antiphlogistic but not as antipyretic agents. As far as the acylamino substitution at the 5-position of the ring is concerned, no clear structure–activity relationship was derivable from *para*-substitution into the phenyl ring, the unique elicitable remark being that the electron-withdrawing Cl group was more effective than other electron-releasing groups, but only in the isonicotinoyl series.

Table 2
Yields, physical and spectroscopic data of compounds **1a–j**

Compound	M.p. (°C)	Yield (%)	IR (cm^{-1})	^1H NMR δ (ppm)	Analyses (C,H,N)
1a	189–190	83	3235 (NH) 1665, 1655 (C=O)	7.40–7.70 and 7.90–8.50 (2m, 7H, 5H Ar + 2H Py), 8.70–8.90 and 9.10–9.30 (2m, 2H, Py), 11.40, 11.57 and 12.90 (3s, 3H, 3NH, disappear with D_2O)	$C_{14}H_{12}N_4O_2S$
1b	185–186	85	3270 1670, 1650	2.43 (s, 3H, CH_3), 7.35 and 7.97 (2d, $J = 7.8$, 4H, C_6H_4), 7.50–7.70, 8.20–8.50, 8.70–8.90 and 9.10–9.30 (4m, 4H, Py), 10.7–11.2 (m, 3H, 3NH, disappear with D_2O)	$C_{15}H_{14}N_4O_2S$
1c	280 (dec.)	90	3285 1676, 1661	3.90 (s, 3H, OCH_3), 7.02 and 8.10 (2d, $J = 9.6$, 4H, C_6H_4), 7.35–7.70, 8.25–8.50, 8.70–8.90, 9.10–9.30 (4m, 4H, Py), 12.24 and 12.5–12.8 (2m, 3H, 3NH, disappear with D_2O)	$C_{15}H_{14}N_4O_3S$
1d	270 (dec.)	90	3215 1697, 1675	7.53 and 8.11 (2d, $J = 9.0$, 4H, C_6H_4), 7.35–7.70, 7.95–8.50, 8.70–8.90 and 9.10–9.30 (4m, 4H, Py), 11.2, 11.6 and 12.6 (3m, 3H, 3NH, disappear with D_2O)	$C_{14}H_{11}N_4O_2SC1$
1e	192 (dec.)	85	3130 1676, 1655	6.60–6.80 (m, 1H, H-4 Fur), 7.30–8.10 (m, 3H, 2H Fur + 1H Py), 8.20–8.60, 8.60–9.00 and 9.10–9.40 (3m, 3H, Py), 11.0–11.6 (m, 3H, 3NH, disappear with D_2O)	$C_{12}H_{10}N_4O_3S$
1f	200–202	75	3210 1690, 1670	7.30–7.80 (m, 2H, Ar), 7.80–8.30 (m, 5H, 3H Ar + 2H Py), 8.70–8.90 (m, 2H, Py), 11.40, 11.60 and 12.60 (3m, 3H, 3NH, disappear with D_2O)	$C_{14}H_{12}N_4O_2S$
1g	187–188	75	3255 1675, 1660	2.42 (s, 3H, CH_3), 7.33 (d, $J = 8.0$, 2H, Ar), 7.70–8.15 (m, 4H, 2H Ar + 2H Py), 8.65–8.95 (m, 2H, Py), 11.20 (s, 3H, 3NH, disappear with D_2O)	$C_{15}H_{14}N_4O_2S$
1h	259–260 (dec.)	73	3260 1675, 1660	3.84 (s, 3H, OCH_3), 7.01 and 8.08 (2d, $J = 9.0$, 4H, C_6H_4), 7.88 and 8.78 (2d, $J = 6.0$, 4H, Py), 11.40 (s, 3H, 3NH, disappear with D_2O)	$C_{15}H_{14}N_4O_3S$
1i	280 (dec.)	93	3290 1676, 1660	7.54 and 8.11 (2d, $J = 8.0$,4H, C_6H_4), 7.92 and 8.83 (2d, $J = 6.0$, 4H, Py), 11.3, 11.7 and 12.7 (3m, 3H, 3NH, disappear with D_2O)	$C_{14}H_{11}N_4O_2SCl$
1j	184–185	65	3185 1685, 1675	6.60–7.00 (m, 1H, H-4 Fur), 7.70–8.30 (m, 4 H, 2H Py + 2H Fur), 8.86 (d, J = 6.0, 2H, Py), 10.8–12.3 (br s, 3H, NH, disappear with D_2O)	$C_{12}H_{10}N_4O_3S$

Table 3
Yields, physical and spectroscopic data of compound **2a–j**

Compound	M.p. (°C)	Yield (%)	IR (cm^{-1}) (C=O)	^1H NMR δ (ppm)	Analyses (C,H,N)
2a	234–235	86	1712, 1697, 1678	7.40–7.80 and 8.00–8.50 (2m, 7H, 5H Ar + 2H Py), 8.70–9.20 (m, 2H, Py), 12.2–13.2 (br m, 1H, NH, disappears with D_2O)	$C_{15}H_{10}N_4O_3S$
2b	232 (dec.)	90	1709, 1698 1676	2.41 (s, 3H, CH_3), 7.34 and 8.04 (2d, $J = 8.0$, 4H, C_6H_4), 7.50–7.70, 8.10–8.40, 8.70–8.90 and 9.00–9.20 (4m, 4H, Py), 12.50 (s, 1H, NH, disappears with D_2O)	$C_{16}H_{12}N_4O_3S$
2c	226–227	90	1710, 1696, 1670	3.89 (s, 3H, OCH_3), 7.10 and 8.12 (2d, $J = 9.0$, 4H, C_6H_4), 7.50–7.80, 8.25–8.45, 8.70–8.90, 9.00–9.20 (4m, 4H, Py), NH not detectable	$C_{16}H_{12}N_4O_4S$
2d	241–242	84	1702, 1685	7.55 and 8.13 (2d, $J = 9.0$, 4H, C_6H_4), 7.40–7.80, 8.10–8.40, 8.70–8.90 and 9.00–9.20 (4m, 4H, Py), 12.4–12.9 (br m, 1H, NH, disappears with D_2O)	$C_{15}H_9N_4O_3SCl$
2e	224 (dec.)	65	1740, 1720 1680	6.70–6.90 (m, 1H, H-4 Fur), 7.40–7.70 and 8.00–8.50 (2m, 4H, 2H Fur, + 2H Py), 8.70–8.90 and 9.00–9.20 (2m, 2H, Py), NH not detectable	$C_{13}H_8N_4O_4S$
2f	250 (dec.)	90	1745, 1660	7.20–7.90 and 8.00–8.40 (2m, 7H, 5H Ar + 2H Py), 8.70–9.00 (m, 2H, Py), 12.5–12.9 (m, 1H, NH, disappears with D_2O)	$C_{15}H_{10}N_4O_3S$
2g[a]	237 (dec.)	90	1740, 1660	2.40 (s, 3H, CH_3), 7.39 and 8.00 (2d, $J = 8.4$, 4H, C_6H_4), 7.77 and 8.82 (2d, $J = 6.0$, 4H, Py), 12.4–12.8 (br s, 1H, disappears with D_2O)	$C_{16}H_{12}N_4O_3S$
2h	224 (dec.)	55	1740, 1656	3.87 (s, 3H, OCH_3), 7.11 and 8.12 (2d, $J = 9.0$, 4H, C_6H_4), 7.77 and 8.83 (2d, $J = 6.0$, 4H, Py), 12.0–13.0 (br s, 1H, NH, disappears with D_2O)	$C_{16}H_{12}N_4O_4S$
2i	238 (dec.)	91	1742, 1662	7.58 and 8.13 (2d, $J = 8.0$, 4H, C_6H_4), 7.75 and 8.85 (2d, $J = 6.0$, 4H, Py), 12.3–12.9 (br s, 1H, NH, disappears with D_2O)	$C_{15}H_9N_4O_3SCl$
2j	235 (dec.)	45	1740, 1655	6.70–6.90 (m, 1H, H-4 Fur), 7.70–7.90 (m, 1H, H-3 Fur), 8.00–8.20 (m, 1H, H-5 Fur), 8.37 and 9.18 (2d, $J = 5.5$g, 4H, Py), NH not detectable	$C_{13}H_8N_4O_4S$

[a] ^{13}C NMR, δ: 164.00, 166.42, 168.20 (3 C=O).

Table 4
Anti-inflammatory activity by carrageenan-induced rat paw edema test[a] of compounds **2a–j**

Compound	Dose (mg/kg p.o.)	Edema volume (ml ± SE)[b] at the following times (h) after treatment (in parentheses percent inhibition activity)				
		0	1	2	3	4
Control	–	1.5 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	2.1 ± 0.1	2.2 ± 0.1
Indomethacin	5	1.4 ± 0.1	1.6 ± 0.1 (30)	1.6 ± 0.1 (46)	1.6 ± 0.1 (65)	1.6 ± 0.1 (69)
2a	50	1.6 ± 0.1	1.8 ± 0.1 (40)	1.9 ± 0.1 (30)	2.0 ± 0.1 (37)	2.1 ± 0.1 (32)
2b	50	1.6 ± 0.1	1.9 ± 0.1 (10)	1.9 ± 0.1 (30)	2.0 ± 0.1 (37)	2.0 ± 0.1 (45)
2c	50	1.5 ± 0.1	1.7 ± 0.1 (35)	1.8 ± 0.1 (23)	1.8 ± 0.1 (50)	1.9 ± 0.1 (43)
2d	50	1.4 ± 0.1	1.6 ± 0.1 (30)	1.7 ± 0.1 (19)	1.7 ± 0.1 (47)	1.8 ± 0.1 (39)
2e	25	1.5 ± 0.1	1.7 ± 0.1 (35)	1.8 ± 0.1 (23)	1.9 ± 0.1 (35)	1.9 ± 0.1 (43)
	50	1.4 ± 0.1	1.6 ± 0.1 (30)	1.6 ± 0.1 (46)	1.7 ± 0.1 (47)	1.8 ± 0.1 (54)
	100	1.5 ± 0.1	1.7 ± 0.1 (35)	1.7 ± 0.1 (50)	1.7 ± 0.1 (67)	1.8 ± 0.1 (56)
2f	50	1.5 ± 0.1	1.8 ± 0.1 (0)	1.8 ± 0.1 (23)	1.9 ± 0.1 (35)	1.9 ± 0.1 (43)
2g	50	1.5 ± 0.1	1.7 ± 0.1 (35)	1.8 ± 0.1 (23)	1.8 ± 0.1 (50)	1.9 ± 0.1 (43)
2h	50	1.4 ± 0.1	1.6 ± 0.1 (30)	1.7 ± 0.1 (21)	1.8 ± 0.1 (30)	1.8 ± 0.1 (39)
2i	25	1.6 ± 0.1	1.9 ± 0.1 (5)	2.0 ± 0.1 (23)	2.1 ± 0.1 (22)	2.2 ± 0.1 (19)
	50	1.5 ± 0.1	1.7 ± 0.1 (35)	1.7 ± 0.1 (50)	1.8 ± 0.1 (50)	1.8 ± 0.1 (56)
	100	1.6 ± 0.1	1.8 ± 0.1 (40)	1.8 ± 0.1 (54)	1.8 ± 0.1 (70)	1.8 ± 0.1 (74)
2j	25	1.4 ± 0.1	1.6 ± 0.1 (30)	1.7 ± 0.1 (19)	1.7 ± 0.1 (47)	1.7 ± 0.1 (54)
	50	1.6 ± 0.1	1.8 ± 0.1 (40)	1.8 ± 0.1 (54)	1.9 ± 0.1 (55)	1.9 ± 0.1 (60)
	100	1.3 ± 0.1	1.5 ± 0.1 (25)	1.5 ± 0.1 (42)	1.5 ± 0.1 (62)	1.5 ± 0.1 (67)

[a] Each compound was tested on a group of five albino rats (180–250 g). Compounds were given by gastric probe 30 min before carrageenan (0.1 ml of 1% solution).
[b] SE was always smaller than ± 0.1 ml and so rounded up to this value.

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