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Synthesis and anti-inflammatory activity of esters derived from 5-aryl-1,2-dihydro-2-(2-hydroxyethyl)-3*H*-1,2,4-triazole-3-thiones

Silvia Schenone[a,*], Olga Bruno[a], Angelo Ranise[a], Francesco Bondavalli[a], Walter Filippelli[b], Francesca Rossi[b], Giuseppe Falcone[b]

[a]*Dipartimento di Scienze Farmaceutiche dell'Università, Viale Benedetto XV 3, I-16132 Genoa, Italy*
[b]*Istituto di Farmacologia e Tossicologia, Facoltà di Medicina e Chirurgia, Il Università degli Studi, Via S. Andrea delle Dame 8, I-80138 Naples, Italy*

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Abstract

Some aliphatic and aromatic esters **2a–l** were prepared starting from 5-aryl-1,2,4-triazoline-3-thiones bearing a 2-hydroxyethyl chain in position 2. The title compounds were evaluated for antipyretic and anti-inflammatory activities. Nearly all derivatives and in particular **2f**, **2h**, **2k** exhibited antiphlogistic properties but were lacking in antipyretic activity. © 1998 Elsevier Science S.A. All rights reserved.

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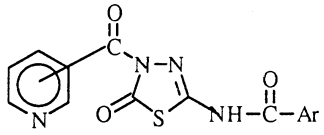
1. Introduction

Several examples of non-steroidal anti-inflammatory drugs (NSAIDs) having a triazole structure have been recorded in the medicinal chemistry literature. Among them, 1,2,4-triazolinethione derivatives are of particular interest and have been studied and patented in recent years [1–3].

Our continuing interest in the preparation and pharmacological evaluation of derivatives of simple five-membered heterocycles with more heteroatoms endowed with antiphlogistic properties prompted us to synthesize firstly a series of 1,3,4-thiadiazol-2(3*H*)-ones [4] and finally, at present, a number of substituted 1,2-dihydro-3*H*-1,2,4-triazole-3-thiones **2a–l**.



These new compounds have as a distinctive feature an aryl group and an esterified hydroxyalkyl chain. Substituents on the aryl ring and in the acyl moiety were selected in order to vary the electronic and lipophilic properties to enable us to gather some structure–activity relationships (SAR).

2. Chemistry

The synthetic route to the title compounds **2a–l** is outlined in Scheme 1. The most nucleophilic secondary nitrogen atom of hydrazinoethanol attacks the electrophilic carbon atom of the heterocumulene function and the primary amino group dehydrates with the carbonyl group by catalysis of *p*-toluenesulphonic acid. This triazolinethione structure **1**, and not other possible ones, was confirmed by UV and ^{13}C NMR spectral data: two UV absorption maxima, at $\lambda = 255$ nm ($\log\epsilon = 4.32$) and 2.89 nm ($\log\epsilon = 3.98$), were present in accordance with the data reported by Durant [5] for similar derivatives and a resonance was detected in the ^{13}C NMR spectrum at δ 166, typical of a heterocyclic C=S group (cf. for example **1a**).

It was noteworthy that the subsequent acylation reaction took place on the alcoholic hydroxy group instead of on the NH group, as we could ascertain through IR and ^{1}H NMR spectral data of the respective esters **2a–l** (Table 1).

3. Pharmacology

Compounds **2a–l** were tested in vivo for antipyretic and anti-inflammator activities.

* Corresponding author.

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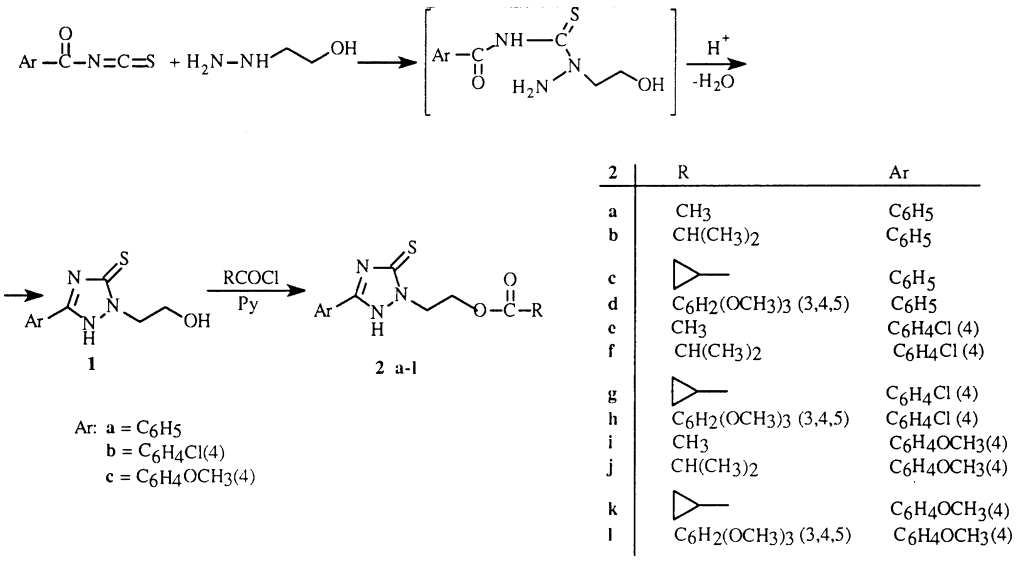

2	R	Ar
a	CH_3	C_6H_5
b	$CH(CH_3)_2$	C_6H_5
c		C_6H_5
d	$C_6H_2(OCH_3)_3$ (3,4,5)	C_6H_5
e	CH_3	C_6H_4Cl (4)
f	$CH(CH_3)_2$	C_6H_4Cl (4)
g		C_6H_4Cl (4)
h	$C_6H_2(OCH_3)_3$ (3,4,5)	C_6H_4Cl (4)
i	CH_3	$C_6H_4OCH_3$(4)
j	$CH(CH_3)_2$	$C_6H_4OCH_3$(4)
k		$C_6H_4OCH_3$(4)
l	$C_6H_2(OCH_3)_3$ (3,4,5)	$C_6H_4OCH_3$(4)

Scheme 1.

4. Experimental

4.1. Chemistry

Melting points were determined with a Büchi 530 apparatus. UV spectra were measured in 95% ethanol on a Perkin–Elmer Lambda 3 spectrophotometer. 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.

4.1.1. General procedure for 5-aryl-1,2-dihydro-2-(2-hydroxyethyl)-3H-1,2,4-triazole-3-thiones (1a–c)

2-Hydrazinoethanol (97%) (3.15 g, 40 mmol) were added slowly to a cooled and stirred solution of the proper aroylisothiocyanate (40 mmol) in anhydrous benzene. The viscous mixture was then refluxed with a Dean & Stark apparatus for 3 h, in the presence of a catalytical amount of *p*-toluenesulphonic acid.

The solvent was removed under reduced pressure and the residue was dissolved in 1 M sodium hydroxide. The basic solution, eventually filtered from any undissolved residue, was cooled and acidified with 1 M acetic acid to pH 5.

After 1 h cooling in a refrigerator the precipitate was filtered and washed with water to neutrality. The solid collected was then crystallized from 95% ethanol.

1a: yield 90%; white crystals, m.p. 168–169°C. UV (EtOH): $\lambda = 255$ nm ($\log\epsilon = 4.32$) and 2.89 nm ($\log\epsilon = 3.98$). IR (KBr): 3230 (NH and OH) cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.90–4.20 and 4.30–4.70 (2 near t, 4H, $2CH_2$), 7.30–7.70 and 7.80–8.50 (2m, 5H ar), NH and OH not detectable. ^{13}C NMR (DMSO): δ 50.30 (CH_2N), 58.34 (CH_2O), 125.43 (C ar), 125.94 (2CH ar), 129.41 (2CH ar), 131.02 (CH ar), 148.61 (C=N), 166.45 (C=S). Assignments of C signals were confirmed through DEPT experiment. *Anal.* $C_{10}H_{11}N_3OS$ (C, H, N).

1b: yield 70%; white crystals, m.p. 226–227°C. IR (KBr): 3400–2700 (NH and OH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.80–4.10 and 4.20–4.50 (2m, 4H, $2CH_2$), 7.66 and 7.99 (2d, $J = 9.0$, 4H ar), OH and NH not detectable. *Anal.* $C_{10}H_{10}N_3OSCl$ (C, H, N).

1c: yield 80%; white crystals, m.p. 210–212°C. IR (KBr): 3380 and 3100 (NH and OH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 3.70–4.00 and 4.10–4.40 (2m, 4H, $2CH_2$), 7.10 and 7.89 (2d, $J = 9.0$, 4H ar), OH and NH not detectable. *Anal.* $C_{11}H_{13}N_3O_2S$ (C, H, N).

4.1.2. General procedure for esters 2a–l

A solution of the proper acyl chloride (11 mmol) in toluene (5 ml) was added dropwise with stirring to an ice-cooled solution of each **1** (10 mmol) in dry pyridine (10 ml). The resulting mixture was allowed to react at room temperature overnight. Solvents were then removed under reduced pressure, the residue was added with water (50 ml), filtered and washed in sequence with 1 M hydrochloric acid and water. The resulting solids were dried and crystallized from 70% ethanol. Yields, melting points, IR and NMR spectral data are recorded in Table 1.

4.2. Pharmacology

The following pharmacological activities were evaluated by standard procedures: (a) antipyretic activity by yeast-induced pyrexia in albino rats (5 rats/group) [6]; (b) anti-inflammatory activity, evaluated by carrageenan-induced paw edema in rats [7] (Table 2). For the most active

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

Comp.	M.p. (°C)	Yield (%)	IR (cm^{-1})	^1H NMR δ (ppm)	Formula
2a	167–168	94	3120 (N–H) 1730 (C=O)	2.04 (s, 3H, CH_3), 4.56 (s, 4H, $2CH_2$), 7.30–7.70 and 7.80–8.10 (2m, 5H ar), 13.47 (br s, 1H, NH, disappears with D_2O)	$C_{12}H_{13}N_3O_2S$
2b	129–130	95	3100 (N–H) 1730 (C=O)	1.06 (d, $J = 7.0$, 6H, $2CH_3$), 2.3–2.7 (m, $J = 7.0$, 1H, CH), 4.48 (s, 4H, $2CH_2$), 7.40–7.70 and 7.80–8.30 (2m, 5H ar), NH not detectable	$C_{14}H_{17}N_3O_2S$
2c	148–149	75	3130 (N–H) 1718 (C=O)	0.83 (d, $J = 7.0$, 4H, $2CH_2$ cycl.), 1.30–1.80 (qui, $J = 7.0$, 1H, CH), 4.44 (s, 4H, $2CH_2$), 7.40–7.70 and 7.80–8.20 (2m, 5H ar), 14.10 (s, 1H, NH, disappears with D_2O)	$C_{14}H_{15}N_3O_2S$
2d	184–185	78	3230 (N–H) 1680 (C=O)	3.80 (s, 9H, $3OCH_3$), 4.63 (s, 4H, $2CH_2$), 7.20–7.40, 7.40–7.70 and 7.80–8.20 (3m, 7H ar), 14.12 (br s, 1H, NH, disappears with D_2O)	$C_{20}H_{21}N_3O_5S$
2e	162–163	70	3120 (N–H) 1733 (C=O)	2.00 (s, 3H, CH_3), 4.45 (s, 4H, $2CH_2$), 7.65 and 8.02 (2d, $J = 9.0$, 4H ar), 14.18 (br s, 1H, NH, disappears with D_2O)	$C_{12}H_{12}N_3O_2SC$
2f	151–152	65	3100 (N–H) 1723 (C=O)	1.04 (d, $J = 7.0$, 6H, $2CH_3$), 2.30–2.60 (m, 1H, CH), 4.45 (s, 4H, $2CH_2$), 7.63 and 7.96 (2d, $J = 9.0$, 4H ar), NH not detectable	$C_{14}H_{16}N_3O_2SC$
2g	202–203	80	3120 (N–H) 1720 (C=O)	0.88 (d, $J = 7.0$, 4H, $2CH_2$ cycl.), 1.40–1.80 (m, 1H, CH), 4.43 (s, 4H, $2CH_2$), 7.64 and 8.00 (2d, $J = 9.0$, 4H ar), NH not detectable	$C_{14}H_{14}N_3O_2SCl$
2h	174–176	65	3220 (N–H) 1670 (C=O)	3.80 (br s, 9H, $3OCH_3$), 4.62 (br s, 4H, $2CH_2$), 7.20–7.40 (m, 2H ar), 7.59 and 7.91 (2d, $J = 9.0$, 4H ar), 14.1–14.3 (br s, 1H, NH, disappears with D_2O)	$C_{20}H_{20}N_3O_5SCI$
2i	162–163	90	3100 (N–H) 1725 (C=O)	1.98 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.41 (s, 4H, $2CH_2$), 7.14 and 7.94 (2d, $J = 9.0$, 4H ar), 13.92 (br s, 1H, NH, disappears with D_2O)	$C_{13}H_{15}N_3O_3S$
2j	152–153	51	3100 (N–H) 1725 (C=O)	1.04 (d, $J = 7.0$, 6H, $2CH_3$), 2.30–2.75 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 4.45 (s, 4H, $2CH_2$), 7.15 and 7.94 (2d, $J = 9.0$, 4H ar), 14.00 (br s, 1H, NH, disappears with D_2O)	$C_{15}H_{19}N_3O_3S$
2k	153–154	52	3100 (N–H) 1720 (C=O)	0.82 (d, $J = 7.0$, 4H, $2CH_2$ cycl.), 1.30–1.80 (m, 1H, CH), 3.84 (s, 3H, OCH_3), 4.41 (s, 4H, $2CH_2$), 7.13 and 7.92 (2d, $J = 9.0$, 4H ar), 13.90 (br s, 1H, NH, disappears with D_2O)	$C_{15}H_{17}N_3O_3S$
2l	223–224	48	3245 (N–H) 1680 (C=O)	3.75 (s, 3H, OCH_3), 3.82 (near s, 9H, $3OCH_3$), 4.60 (br s, 4H, $2CH_2$), 7.25 (s, 3H ar), 7.06 and 7.83 (2d, $J = 9.0$, 4H ar), 13.95 (s, 1H, NH, disappears with D_2O)	$C_{21}H_{23}N_3O_6S$

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

Compound	Dose (mg/kg p.o.)	Edema volume ml ± SE[b] at the following times (h) after treatment (% 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 (38)	1.6 ± 0.1 (65)	1.6 ± 0.1 (69)
2a	50	1.4 ± 0.1	1.6 ± 0.1 (30)	1.7 ± 0.1 (19)	1.8 ± 0.1 (30)	1.8 ± 0.1 (39)
2b	50	1.3 ± 0.1	1.5 ± 0.1 (25)	1.6 ± 0.1 (11)	1.7 ± 0.1 (25)	1.8 ± 0.1 (17)
2c	50	1.5 ± 0.1	1.8 ± 0.1 (0)	1.9 ± 0.1 (0)	1.9 ± 0.1 (35)	2.0 ± 0.1 (28)
2d	50	1.4 ± 0.1	1.6 ± 0.1 (30)	1.7 ± 0.1 (19)	1.8 ± 0.1 (30)	1.9 ± 0.1 (23)
2e	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)
2f	25	1.4 ± 0.1	1.6 ± 0.1 (30)	1.7 ± 0.1 (19)	1.8 ± 0.1 (30)	1.9 ± 0.1 (24)
	50	1.3 ± 0.1	1.5 ± 0.1 (25)	1.6 ± 0.1 (11)	1.6 ± 0.1 (42)	1.6 ± 0.1 (50)
	100	1.6 ± 0.1	1.8 ± 0.1 (40)	1.8 ± 0.1 (54)	1.8 ± 0.1 (70)	1.9 ± 0.1 (61)
2g	50	1.5 ± 0.1	1.7 ± 0.1 (35)	1.8 ± 0.1 (23)	1.9 ± 0.1 (35)	1.9 ± 0.1 (43)
2h	25	1.3 ± 0.1	1.5 ± 0.1 (25)	1.6 ± 0.1 (11)	1.7 ± 0.1 (25)	1.8 ± 0.1 (17)
	50	1.6 ± 0.1	1.8 ± 0.1 (40)	1.9 ± 0.1 (30)	1.9 ± 0.1 (55)	2.0 ± 0.1 (45)
	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)
2i	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)
2j	50	1.3 ± 0.1	1.5 ± 0.1 (25)	1.6 ± 0.1 (11)	1.6 ± 0.1 (42)	1.7 ± 0.1 (34)
2k	25	1.3 ± 0.1	1.5 ± 0.1 (25)	1.6 ± 0.1 (11)	1.7 ± 0.1 (25)	1.7 ± 0.1 (35)
	50	1.4 ± 0.1	1.6 ± 0.1 (30)	1.6 ± 0.1 (46)	1.7 ± 0.1 (47)	1.7 ± 0.1 (51)
	100	1.6 ± 0.1	1.8 ± 0.1 (40)	1.8 ± 0.1 (54)	1.9 ± 0.1 (55)	1.9 ± 0.1 (61)
2l	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)

[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.

compounds **2f**, **2h**, **2k**, the respective ED_{50} values were determined by administration of three dosages (25, 50, 100 mg/kg).

5. Results and conclusions

All the title compounds **2a–l** were devoid of antipyretic activity but were endowed in general with antiphlogistic properties. In particular **2f** showed an ED_{50} value of 54.64 (44.27–67.44) and 61.09 (48.84–76.42) mg/kg; **2h** an ED_{50} of 52.32 (42.92–63.77) and 73.73 (60.39–90.02) mg/kg; **2k** an ED_{50} of 71.70 (54.42–94.47) and 50.20 (36.01–69.98) mg/kg, respectively, after the third and fourth hour from treatment.

From the point of view of SAR it was evident that the acyl group exerted an irregular negligible influence on the anti-inflammatory activity: actually compounds **2a–d**, all having a phenyl group in position 5 of the heterocycle, were among the least active compounds. On the other hand, as regards the aryl group it can be seen that, with the exception of **2e**, in the main the most lipophilic electron-attracting *p*-Cl substituent gave better results.

Compounds **2f** and **2h** had a superior activity at the third hour with a smaller ED_{50}. Another curious feature was that several derivatives showed an activity comparable or superior to that of indomethacin just after the first hour from treatment.

Concluding we can say that the prepared compounds may be considered effective anti-inflammatory agents in the wake of other triazolinethione analogues, but only at fairly high dosages.

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