ELSEVIER

www.elsevier.com/locate/farmac

Il Farmaco 56 (2001) 939–945

IL FARMACO

Synthesis and pharmacological activity of 1,2,4-triazolo[4,3-*a*]quinolines

Luisa Savini [a,*], Luisa Chiasserini [a], Cesare Pellerano [a], Walter Filippelli [b], Giuseppe Falcone [b]

[a] *Dipartimento Farmaco Chimico Tecnologico, Facoltà di Farmacia, Università degli Studi di Siena, Via Aldo Moro, 53100 Siena, Italy*
[b] *Istituto di Farmacologia e Tossicologia, Facoltà di Medicina e Chirurgia, Il Università di Napoli, Via Costantinopoli, 16, 80138 Naples, Italy*

Received 12 October 2000; accepted 30 May 2001

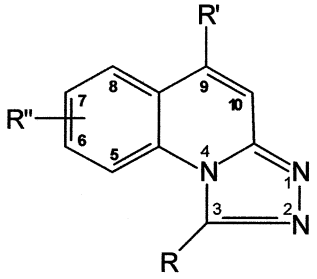
Abstract

The synthesis of a series of 1,2,4-triazolo[4,3-*a*]quinoline derivatives is described; their structures were assigned by ^{1}H NMR and analytical data. The new compounds were tested in vivo for their antiinflammatory and analgesic activities, as well as for their ulcerogenic action. Some of the tested triazoles showed an analgesic activity in the acetic acid writhing test and antiinflammatory properties on carrageenan paw edema assay.

Keywords: 1,2,4-Triazoloquinoline derivatives; Antiinflammatory activity; Analgesic activity; Ulcerogenic activity

1. Introduction

It is observed from the literature that *s*-triazole moiety has great versatility in fusing to various ring systems and that *N*-bridged heterocycles derived from them are associated with different pharmacological activities, such as antiinflammatory [1,2], analgesic and hypnotic [2,3], hypotensive [4] and antifungal [5]. Therefore, on account of the above, pursuing our researches on new quinoline derivatives, in an attempt to obtain new biologically active agents, particularly as antiinflammatory and analgesic, we prepared a series of 1,2,4-triazoloquinolines (**I**).



(I)

R, R' and R'' as reported in Table 1

The title triazoloquinolines (**I**) (Table 1) were tested in vivo to evaluate their pharmacological properties. The antiinflammatory activity was studied by means of the carrageenan rat paw edema assay, whereas the acetic acid writhing test was used to assess the analgesic activity in mice.

2. Chemistry

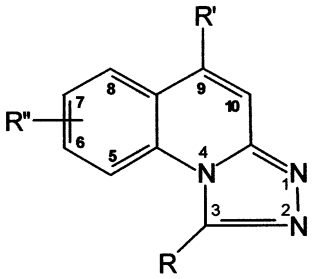
The required 1,2,4-triazoloquinolines (**I**) were obtained using known procedures developed for other ring systems, the substituted 2-quinolylhydrazines (**A**) readily cyclized with the appropriate aliphatic acids or *ortho* esters to the *s*-triazolo[4,3-*a*]quinoline derivatives (**I**) (Scheme 1); the use of *ortho* esters however seems to be the most efficient method of synthesis.

The structures assigned to the synthesized compounds are in good agreement with elemental analyses and ^{1}H NMR data (Table 2). In the ^{1}H NMR spectra of compounds (**I** *1*→*8*) a singlet appears between 9.63 and 9.86 δ which, in accordance with literature data [6], can be unambiguously assigned to H-3 proton of the triazole ring, since it disappears upon substitution at that position (compounds **I** *9*→*20*); further evidence in

* Corresponding author.
E-mail address: savini@unisi.it (L. Savini).

0014-827X/01/$ - see front matter
PII: S0014-827X(01)01166-1

Table 1
Physicochemical data of triazoloderivatives (**I**) and (**II**)



(I) (II)

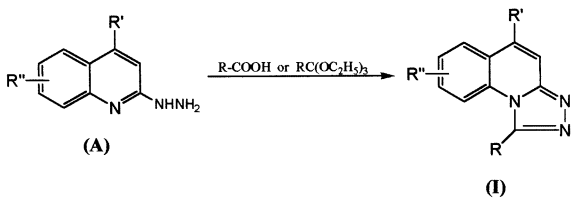
Comp.	R	R′	R″	m.p. (°C)	Cryst. solvent	Molecular formula	Anal. *
I *1* [a]	H	H	H	170–172	H_2O	$C_{10}H_7N_3$	C, H, N
I *2*	H	CH_3	5-CH_3	228–230	H_2O	$C_{12}H_{11}N_3$	C, H, N
I *3*	H	CH_3	7-CH_3	246–249	Ethanol	$C_{10}H_7N_3 \cdot 1/4H_2O$	C, H, N
I *4*	H	CH_3	6-OCH_3	269–271	Ethanol	$C_{12}H_{11}N_3O$	C, H, N
I *5*	H	CH_3	6-OH	>300	Ethanol	$C_{11}H_9N_3O$	C, H, N
I *6*	H	CH_3	7-OCH_3	253–255	Ethanol	$C_{12}H_{11}N_3O$	C, H, N
I *7*	H	CH_3	7-OH	>300	Ethanol	$C_{11}H_9N_3O$	C, H, N
I *8*	H	CH_3	6,7,8-OCH_3	174–177	Ethyl acetate	$C_{14}H_{15}N_3O_3 \cdot 1/4H_2O$	C, H, N
I *9*	CH_3	CH_3	7-CH_3	206–208	H_2O	$C_{13}H_{13}N_3$	C, H, N
I *10*	CH_3	CH_3	6-OCH_3	209–212	Ethanol–H_2O	$C_{13}H_{13}N_3O$	C, H, N
I *11*	CH_3	CH_3	6-OH	>300	Ethanol	$C_{12}H_{11}N_3O$	C, H, N
I *12*	CH_3	CH_3	7-OCH_3	186–189	Ethanol–H_2O	$C_{13}H_{13}N_3O \cdot 1/4H_2O$	C, H, N
I *13*	CH_3	CH_3	7-OH	>300	Ethanol	$C_{12}H_{11}N_3O^{\bullet} \cdot 1/4H_2O$	C, H, N
I *14*	CH_3	CH_3	6,7,8-OCH_3	207–209	H_2O	$C_{15}H_{17}N_3O_3^{\bullet} \cdot 1/2H_2O$	C, H, N
I *15*	C_2H_5	CH_3	7-CH_3	157–160	H_2O	$C_{14}H_{15}N_3$	C, H, N
I *16*	C_2H_5	CH_3	6-OCH_3	208–211	H_2O	$C_{14}H_{15}N_3O$	C, H, N
I *17*	C_2H_5	CH_3	6-OH	>300	H_2O	$C_{13}H_{13}N_3O \cdot 1/4H_2O$	C, H, N
I *18*	C_2H_5	CH_3	7-OCH_3	190–193	H_2O	$C_{14}H_{15}N_3O$	C, H, N
I *19*	C_2H_5	CH_3	7-OH	>300	Ethanol	$C_{13}H_{13}N_3O$	C, H, N
I *20*	C_2H_5	CH_3	6,7,8-OCH_3	151–153	Ethyl acetate	$C_{16}H_{19}N_3O_3$	C, H, N
II *1* [b]	H	[2,3-*a*]pyridine		34–36	AcOEt–Petr. Et	$C_6H_5N_3$	C, H, N
II *2* [c]	H	[2,3-*a*]pyrimidine		140–143	AcOEt–Petr. Et	$C_5H_4N_4$	C, H, N
II *3* [c]	H	[4,3-*a*]pyrimidine		205–208	Benzene	$C_5H_4N_4$	C, H, N
II *4* [d]	CH_3	[4,3-*a*]pyridine		53–56	Benzene	$C_7H_7N_3 \cdot 3H_2O$	C, H, N

* Water of crystallization was determined by Karl–Fischer method.
[a] Ref. [8].
[b] Ref. [9].
[c] Ref. [10].
[d] Ref. [11].

support of [4,3-*a*] system was obtained from NOE spectra, in fact for all compounds (**I**) on presaturation of the 3-H proton (compounds **I** *2*→*8*), of the 3-methyl protons (compounds **I** *9*→*14*) and of the methylene protons of ethyl group (compounds **I** *15*→*20*), there is a NOE effect on the H-5 proton (Table 3).

The intermediate 2-quinolylhydrazines employed were prepared from the corresponding 2-chloroquinolines and hydrazine hydrate (98%), in absolute ethanol [7].

The hydroxyderivatives (**I** *5*, *7*, *11*, *13*, *17*, *19*) were conveniently obtained from the corresponding alkoxyderivatives (**I** *4*, *6*, *10*, *12*, *16*, *18*) by hydrolysis with 48% HBr in glacial acetic acid. The known compounds (**I** *1*, **II** *1*→*4*) were also resynthesized and their physical and spectral properties are consistent with literature values.



Scheme 1.

Table 2
^{1}H NMR of triazoloderivatives (**I**)

Comp.	^{1}H NMR (**I**)
I *2*	(DMSO-d_6): 2.50 and 2.85 (2s, 6H, $2CH_3$); 7.53–7.77 (m, 4H, quinoline protons); 9.63 (s, 1H, triazole).
I *3*	(DMSO-d_6): 2.45 (2s, 6H, $2CH_3$); 7.45–7.50 (2u d, 2H, H-(6,8)); 7.65 (s, 1H, H-10); 8.17 (d, 1H, H-5, $J_{5-6} = 8.5$); 9.75 (s, 1H, CH triazole).
I *4*	(DMSO-d_6): 2.52 (s, 3H, CH_3); 3.94 (s, 3H, OCH_3); 7.18 (dd, 1H, H-7, $J_{7-8} = 8.9$, $J_{7-5} = 2.8$); 7.36 (s, 1H, H-10); 7.86–7.91 (m, 2H, H-(5,8)); 9.85 (s, 1H, triazole).
I *5*	(DMSO-d_6): 2.52 (s, 3H, CH_3); 7.09 (dd, 1H, H-7, $J_{7-8} = 8.8$, $J_{7-5} = 1.8$); 7.31 (s, 1H, H-10); 7.70 (d, 1H, H-5, $J_{5-7} = 1.8$); 7.82 (d, 1H, H-8, $J_{8-7} = 8.8$); 9.72 (s, 1H, CH triazole); 10.55 (s, 1H, OH, D_2O exchangeable).
I *6*	(DMSO-d_6): 2.56 (s, 3H, CH_3); 3.90 (s, 3H, OCH_3); 7.36 (s, 1H, H-10); 7.41 (d, 1H, H-8, $J_{8-6} = 2.6$); 7.53 (u d, 1H, H-5); 8.34 (udd, 1H, H-6); 9.80 (s, 1H, CH triazole).
I *7*	(DMSO-d_6): 2.50 (s, 3H, CH_3); 7.20 (dd, 1H, H-6, $J_{6-5} = 8.8$, $J_{6-8} = 2.2$); 7.26 (d, 1H, H-8, $J_{8-6} = 2.2$); 7.51 (s, 1H, H-10); 8.24 (dd, 1H, H-5, $J_{5-6} = 8.8$); 9.75 (s, 1H, CH triazole); 10.03 (s, 1H, OH, D_2O exchangeable).
I *8*	(DMSO-d_6): 2.69 (s, 3H, CH_3); 3.83, 3.92 and 4.16 (3s, 9H, $3OCH_3$); 7.31 (s, 1H, H-10); 7.75 (s, 1H, H-5); 9.86 (s, 1H, CH triazole).
I *9*	(DMSO-d_6): 2.41 and 2.43 (2s, 6H, $2CH_3$ quinoline); 2.92 (s, 3H, CH_3 triazole); 7.34 (s, 1H, H-10); 7.43 (u dd, 1H, H-6); 7.61 (ud, 1H, H-8); 8.02 (d, 1H, H-5, $J_{5-6} = 8.4$).
I *10*	(DMSO-d_6): 2.49 (s, 3H, CH_3 quinoline); 3.04 (s, 3H, CH_3 triazole); 3.96 (s, 3H, OCH_3); 7.21 (dd, 1H, H-7, $J_{7-8} = 9$, $J_{7-5} = 1.9$); 7.25 (s, 1H, H-10); 7.67 (d, 1H, H-5, $J_{5-7} = 1.9$); 7.87 (d, 1H, H-8, $J_{8-7} = 9$).
I *11*	(DMSO-d_6): 2.39 (s, 3H, CH_3 quinoline); 2.70 (s, 3H, CH_3 triazole); 7.02 (dd, 1H, H-7, $J_{7-8} = 8.8$, $J_{7-5} = 1.9$); 7.18 (s, 1H, H-10); 7.65 (d, 1H, H-5, $J_{5-7} = 1.9$); 7.74 (d, 1H, H-8, $J_{8-7} = 8.8$); 10.45 (s, 1H, OH, D_2O exchangeable).
I *12*	(DMSO-d_6): 2.46 (s, 3H, CH_3 quinoline); 2.95 (s, 3H, CH_3 triazole); 3.93 (s, 3H, OCH_3); 7.20 (ud, 1H, H-8); 7.25 (dd, 1H, H-6, $J_{6-5} = 9$, $J_{6-8} = 2.8$); 7.39 (s, 1H, H-10); 8.06 (d, 1H, H-5, $J_{5-6} = 9$).
I *13*	(DMSO-d_6): 2.43 (s, 3H, CH_3 quinoline); 2.94 (s, 3H, CH_3 triazole); 7.14 (dd, 1H, H-6, $J_{6-5} = 8.9$, $J_{6-8} = 2.5$); 7.20 (d, 1H, H-8, $J_{8-6} = 2.5$); 7.39 (s, 1H, H-10); 8.01 (d, 1H, H-5, $J_{5-6} = 8.9$); 9.97 (s, 1H, OH, D_2O exchangeable).
I *14*	(DMSO-d_6): 2.64 (s, 3H, CH_3 quinoline); 3.06 (s, 3H, CH_3 triazole); 3.81, 3.87 and 4.00 (3s, 9H, $3OCH_3$); 7.18 (s, 1H, H-10); 7.60 (s, 1H, H-5).
I *15*	(DMSO-d_6): 1.42 (t, 3H, CH_3–CH_2O); 2.41 (s, 6H, $2CH_3$); 3.26 (q, 2H, CH_3–CH_2O); 7.33 (s, 1H, H-10); 7.42 (dd, 1H, H-6, $J_{6-5} = 8.7$, $J_{6-8} = 1.2$); 7.60 (u d, 1H, H-8); 7.95 (d, 1H, H-5, $J_{5-6} = 8.7$).
I *16*	(DMSO-d_6): 1.49 (t, 3H, CH_3–CH_2O); 2.53 (s, 3H, CH_3); 3.49 (q, 2H, CH_3–CH_2O); 3.97 (s, 3H, OCH_3); 7.25 (dd, 1H, H-7, $J_{7-8} = 9$, $J_{7-5} = 2.4$); 7.34 (s, 1H, H-10); 7.68 (d, 1H, H-5, $J_{5-7} = 2.4$); 7.93 (d, 1H, H-8, $J_{8-7} = 9$).
I *17*	(DMSO-d_6): 1.43 (t, 3H, CH_3–CH_2O); 2.41 (s, 3H, CH_3); 3.34 (q, 2H, CH_3–CH_2O); 6.98 (u dd, 1H, H-7); 7.14 (s, 1H, H-10); 7.56 (u d, 1H, H-5); 7.70 (d, 1H, H-8, $J_{8-7} = 8.8$); 10.41 (s, 1H, OH, D_2O exchangeable).
I *18*	(DMSO-d_6): 1.44 (t, 3H, CH_3–CH_2O); 2.44 (s, 3H, CH_3); 3.27 (q, 2H, CH_3–CH_2O); 3.87 (s, 3H, OCH_3); 7.21 (s, 1H, H-10); 7.25 (u dd, 1H, H-6); 7.38 (u d, 1H, H-8); 8.02 (d, 1H, H-5, $J_{5-6} = 8.8$).
I *19*	(DMSO-d_6): 1.42 (t, 3H, CH_3–CH_2O); 2.61 (s, 3H, CH_3); 3.48 (q, 2H, CH_3–CH_2O); 7.33 (dd, 1H, H-6, $J_{6-5} = 9.2$, $J_{6-8} = 2.6$); 7.38 (d, 1H, H-8, $J_{8-6} = 2.6$); 7.63 (s, 1H, H-10); 8.28 (d, 1H, H-5, $J_{5-6} = 9.2$); 10.31 (s, 1H, OH, D_2O exchangeable).
I *20*	(DMSO-d_6): 1.45 (t, 3H, CH_3–CH_2O); 2.62 (s, 3H, CH_3); 3.44 (q, 2H, CH_3–CH_2O); 3.81, 3.87 and 3.98 (3s, 9H, $3OCH_3$); 7.17 (s, 1H, H-10); 7.48 (s, 1H, H-5).

3. Experimental

3.1. Chemistry

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer elemental analyzer Mod. 240 and the data for C, H, N are within $\pm 0.4\%$ of calculated values. Spectral analyses (^{1}H NMR) are consistent with the chemical structures indicated. ^{1}H NMR spectra were recorded on a Varian XL-200 FT instrument. The chemical shifts (δ) are relative to tetramethylsilane (TMS) used as internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, dd = double doublet, q = quartet, m = multiplet, u = unresolved. The coupling constants J were in Hertz. TLC on silica gel plates (Merck, 60, F_{254}) was used for purity check and reaction monitoring. Column chromatography on silica gel (Merck, 70-230 mesh) was applied, when necessary, to isolate and purify the different reaction products. The *ortho* esters and carboxylic acids were purchased from a commercial firm.

Physicochemical properties of the newly synthesized triazoles are summarized in Table 1.

3.1.1. General procedure for the preparation of 1,2,4-triazolo[4,3-a]quinolines (**I** 1 → 8)

3.1.1.1. Method A. The 2-quinolylhydrazine (10 mmol) and 98% formic acid (30 ml) were heated under reflux for a variable time (6–8 h). After evaporation under reduced pressure of excess acid, the resulting solution was poured onto ice water and the reaction mixture was neutralized with Na_2CO_3. The obtained precipitate was filtered off and purified by crystallization from a suitable solvent.

Table 3
NOE spectra

Comp.	Irradiated	Observed	NOE (%)
I *1→8*	H-3 (C-3)	H-5	6.7
I *9→14*	CH_3 (C-3)	H-5	9.8
I *15→20*	CH_2 (ethyl) (C-3)	H-5	7.5

3.1.1.2. Method B. The 2-quinolylhydrazine (2 mmol), the triethyl orthoformate (5 ml) and dry xylene (10 ml) were refluxed for 1–4 h (for compound **I** *2*, 9 h were required). All traces of solvent were evaporated and the resulting solid recrystallized from a suitable solvent.

*3.1.2. General procedure for the preparation of 3-methyl-1,2,4-triazolo[4,3-a]quinolines (**I** 9→14)*

A mixture of 2-quinolylhydrazine (2.5 mmol) and glacial acetic acid (5 ml) was refluxed for 5–7 h under the same conditions described above in the method A for compounds (**I** *1→8*).

In the case of compound **I** *14*, after neutralization with Na_2CO_3, the resulting solution was extracted with CH_2Cl_2 to afford the product.

*3.1.3. General procedure for the preparation of ethyl-1,2,4-triazolo[4,3-a]quinolines (**I** 15→20)*

2-Quinolylhydrazine (2.5 mmol) and triethyl orthopropionate (5 ml) were refluxed for a variable time (1–6

Table 4
Antiinflammatory activity (carrageenan rat paw edema test)

Comp.	Dose (mg/kg) p.o.	% Edema inhibition relative to control at (h)				ED_{50} mg/kg (fiducial limits; at (h))	
		1st	2nd	3rd	4th	3rd	4th
IMA	2.5	−41	−52	−57	−59	1.945	1.385
	5	−44	−54	−62	−68	(1.371–2.760)	(0.984–1.949)
	10	−52	−63	−79	−83		
I *1*	20	−20	−16	−30	−25	178.42	56.34
	40	−48	−35	−46	−54	(79.10–402.45)	(42.38–74.90)
	80	−32	−29	−40	−50		
I *2*	40	−44	−32	−43	−36		
I *3*	40	−16	−10	−5	−20		
I *4*	20	−80	−67	−72	−66	9.30	6.22
	40	−31	−49	−57	−62	(5.41–16.01)	(3.24–11.96)
	80	−58	−65	−70	−74		
I *5*	40	−61	−54	−59	−52		
I *6*	40	−52	−39	−48	−43		
I *7*	40	−55	−43	−52	−42		
I *8*	40	−20	−35	−27	−39		
I *9*	40	−16	−32	−24	−20		
I *10*	20	−16	−11	−5	−5	129.35	82.16
	40	−8	−3	−19	−32	(93.48–178.78)	(3.335–2011.97)
	80	−24	−19	−32	−43		
I *11*	40	−35	−27	−38	−46		
I *12*	40	−48	−58	−46	−39		
I *13*	20	−35	−27	−25	−34	31.15	29.59
	40	−61	−67	−72	−62	(2.29–42.29)	(24.69–35.46)
	80	−77	−81	−84	−86		
I *14*	20	−20	−16	−11	−9	113.78	79.55
	40	−24	−39	−32	−43	(84.15–153.84)	(64.26–98.46)
	80	−32	−25	−37	−47		
I *15*	40	−52	−39	−32	−29		
I *16*	40	−48	−35	−27	−25		
I *17*	40	−72	−55	−43	−52		
I *18*	40	−44	−55	−43	−52		
I *19*	20	−8	−3	−19	−13	484.60	146.50
	40	−20	−13	−11	−25	(288.49–814.01)	(103.08–208.18)
	80	−16	−9	−24	−36		
I *20*	40	−40	−26	−19	−13		
II *1*	40	−58	−46	−39	−46		
II *2*	40	−61	−49	−57	−50		
II *3*	40	−61	−67	−59	−64		
II *4*	40	−24	−19	−16	−29		

Table 5
Analgesic activity (acetic acid writhing test in mice)

Comp.	Dose (mg/kg) p.o.	Mean number of writhes in 25 min period after treatment ± SE	% Decrease relative to controls	ED_{50} mg/kg (fiducial limits)
Controls		46.1 ± 4.7		–
IMA	2.5	35.0 ± 5.3	24.0	4.433
	5	22.9 ± 4.1	50.3	(2.738–7.226)
	10	11.4 ± 3.8	81.0	
I *1*	40	26.3 ± 3.7	42.9	
I *2*	40	31.3 ± 3.3	32.1	
I *3*	40	28.2 ± 2.8	38.8	
I *4*	20	25.3 ± 2.8	39.9	66.86
	40	24.7 ± 3.7	46.4	(48.16–92.81)
	80	22.9 ± 6.1	50.3	
I *5*	20	27.6 ± 4.1	36.7	77.32
	40	25.1 ± 2.5	45.5	(32.32–184.93)
	80	23.0 ± 5.8	50.1	
I *6*	20	28.3 ± 4.8	37.3	85.933
	40	25.6 ± 5.1	44.4	(41.846–176.470)
	80	23.3 ± 6.3	49.4	
I *7*	40	31.3 ± 1.8	32.1	
I *8*	20	27.9 ± 5.2	39.4	63.497
	40	23.7 ± 2.9	48.6	(30.737–131.174)
	80	22.2 ± 3.7	51.8	
I *9*	40	29.6 ± 5.3	35.8	
I *10*	40	27.4 ± 2.7	40.5	
I *11*	40	27.0 ± 4.1	41.4	
I *12*	40	30.2 ± 4.5	34.5	
I *13*	40	26.9 ± 3.2	41.6	
I *14*	40	25.5 ± 4.8	44.6	
I *15*	40	29.0 ± 3.9	37.0	
I *16*	40	31.8 ± 2.8	31.0	
I *17*	40	32.5 ± 3.4	29.5	
I *18*	20	25.6 ± 4.2	44.4	38.495
	40	22.3 ± 3.7	51.6	(18.518–80.022)
	80	20.1 ± 6.6	56.3	
I *19*	40	26.1 ± 4.2	43.3	
I *20*	20	28.1 ± 6.2	39.0	71.906
	40	24.3 ± 4.2	47.2	(32.616–158.529)
	80	22.7 ± 2.9	50.7	
II *1*	20	29.5 ± 4.2	36.0	117.92
	40	26.3 ± 2.9	42.9	(51.776–268.573)
	80	24.7 ± 3.7	46.4	
II *2*	40	28.2 ± 4.2	38.8	
II *3*	20	28.4 ± 5.1	38.4	79.93
	40	25.6 ± 3.2	44.4	(37.57–170.06)
	80	23.1 ± 4.9	50.1	
II *4*	20	27.2 ± 3.9	40.9	65.511
	40	24.8 ± 4.2	46.2	(30.674–131.498)
	80	22.0 ± 2.8	52.2	

h). Upon cooling, a precipitate was obtained, which was filtered off and purified by crystallization from a suitable solvent.

*3.1.4. General procedure for the preparation of hydroxyderivatives (**I** 5, 7, 11, 13, 17, 19)*

A mixture of the appropriate alkoxytriazoloquinoline (0.8 mmol) in glacial acetic acid (~ 4 ml) was stirred under nitrogen for 10 min and then heated until a homogenous solution was obtained. Aqueous hydrogen bromide (48%, 10 ml) was added and the reaction mixture was refluxed on an oil bath and monitored to completeness by TLC (chloroform–methanol, 18:2 as eluent) for 2–3 h. After cooling under nitrogen, a precipitate was obtained by dilution with water; this precipitate was collected, washed with water and crystallized.

3.2. Pharmacological experimental section

Test compounds were administered orally by gavage in a 10% gum arabic suspension at the dosage level of

40 mg/kg. In some cases, lower and higher doses were then administered and the related values of ED_{50} were calculated when possible, in order to study dose-dependence of inflammatory and analgesic activity.

Higher doses (100 mg) were administered to rats in order to study the irritative and ulcerogenic action on the mucosa of both the stomach and small intestine up to the distal ileum.

Indomethacin (IMA) was included in all tests as reference drug.

The pharmacological studies on animals were carried out in agreement with the legal regulation of DL 116/92 (Italy).

3.2.1. Antiinflammatory activity

Paw edema inhibition test [12] was used on rats. Groups of ten rats of both sexes (body weight 220–280 g), pregnant females excluded, were given a dose of a test compound. Thirty minutes later, 0.2 ml of 1% carrageenan suspension in 0.95% NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw and the paw volume was measured by a mercury plethysmometer (Basile) and then measured again 1, 2, 3 and 4 h later. The mean increase of paw volume at each time interval was compared with that of the control group (five rats treated with carrageenan, but not treated with test compounds) at the same time intervals and percent inhibition values were calculated. Experimental results are listed in Table 4.

3.2.2. Analgesic activity

Acetic acid writhing test [13] was used on mice. Groups of ten mice (Mus musculus, body weight 20–30 g) of both sexes, pregnant females excluded, were given a dose of a test compound. Thirty minutes later the animals were injected intraperitoneally with 0.25 ml/mouse of 0.5% acetic acid solution and writhes were counted during the following 25 min. The mean number of writhes for each experimental group and percent decrease compared with the control group (five mice not treated with test compounds) were calculated. Experimental results are listed in Table 5.

3.2.3. Ulcerogenic action

Groups of ten rats (body weight 250–300 g) of both sexes, pregnant females excluded, fasted for 24 h, were treated with an oral dose of a test compound, except the control group. A constant dose for all compounds was used, independently from their ED_{50} as antiinflammatory drugs in order to study their intrinsic irritative potency. In fact not only the antiinflammatory drugs have ulcerogenic properties. All animals were killed 6 h after the dosing and their stomachs and small intestines were macroscopically examined to assess the incidence of hyperemia and ulcers. Experimental results are listed in Table 6.

Table 6
Induction of gastric lesions in rats

Comp.	Dose (mg/kg) p.o.	Remarks at the 6th h after treatment: % animals with	
		Ulcers	hyperaemia
IMA	5	60	80
I ***1***	100	40	50
I *2*	100	30	40
I *3*	100	20	40
I *4*	100	50	60
I *5*	100	20	20
I *7*	100	10	20
I *11*	100	40	40
I *12*	100	50	60
I *13*	100	40	50
I *18*	100	40	50
I *19*	100	30	50
II *1*	100	30	30
II *2*	100	20	40
II *3*	100	20	40

4. Results and discussion

The experimental results obtained for antiinflammatory activity in the carrageenan rat paw edema assay (Table 4) show that among the examined compounds **I** *1*, **I** *10* and **I** *14* showed the best results. Dose-dependence was unsatisfactory. ED_{50} values were calculated at the 3rd and 4th hours.

As regards analgesic activity, as summarized in Table 5, good activity on the writhing test on mice resulted for compounds **I** *4*, **I** *8* and **I** *18*; the compounds **I** *5*, and **II** *4* show a little analgesic activity not comparable for dose-dependence.

The irritative and ulcerative effect of the examined compounds is lower than that of indomethacine (IMA), in particularly in view of the high doses used in this test (Table 6). In fact, this does not seem to be the pharmacological profile of these inhibitors of the prostaglandin biosynthesis.

On the basis of such experimental results, it is plain that a great deal of work will be necessary to make clear the mode of action, or rather, the multiple modes of action of these compound.

The obtained data support our interest in the triazole derivatives; the activity seems to be modulated by the substituents. In particular, the substitution on the quinoline nucleus has significant implication; the most favorable to biological activity resulted $-OCH_3$ and –OH groups; therefore is seems advisable to synthesize new compounds with different substituents on triazole and quinoline nucleus in order to draw a reliable conclusion and obtain definitive answers for structure–activity relationships.

Acknowledgements

Financial support from Italian MURST is gratefully acknowledged. This work constitutes part of the Ph. D. Dissertation of Cristina Nencini.

References

[1] C.J. Cavallito, A.P. Gray, (Mallinckrodt Chemical Works), Antiinflammatory *s*-triazolo[3,4-*a*]isoquinolines, Fr. Demande 2,135,297 (1973); Chem. Abstr. 79 (1973) 96989 j.

[2] A.R. Prasad, T. Ramalingam, A.B. Rao, P.V. Diwan, P.B. Sattur, Synthesis and biological evaluation of 3-aryloxyalkyl-6-aryl-7*H*-*s*-triazolo(3,4-*b*][1,3,4]thiadiazines, Eur. J. Med. Chem. 24 (1989) 199–201.

[3] M. Kanji, K. Yutaka, (Takeda Chemical Industries Ltd.), *s*-Triazolo[4,3-*a*][1,4]benzodiazepines or their 5-*N*-oxides useful as sedatives analgesics, muscle relaxants, hypnotics and tranquilizers, Jpn. Pat. 74 27,880 (1974); Chem. Abstr. 83 (1975) 28290 g.

[4] J. Sallè, M. Pesson, H. Koronowsky, Pharmacodynamic properties of certain *s*-triazolo[4,3-*b*]pyridazines, Arch. Intern. Pharmacodyn. Ther. 121 (1959) 154–168; Chem. Abstr. 54 (1960) 5925.

[5] A.R. Prasad, A.N. Rao, T. Ramalingam, P.B. Sattur, Fused triazoles: synthesis and antifungal activity of 2-arylidene-thiazolo[3′,2′:1,2]imidazo[5,4-*b*]pyridin-3(2*H*)-ones, 2-arylidene-thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones and 6-arylidene-thiazolo-[3,2-*b*]-*s*-triazol-5(6*H*)-ones, Ind. J. Chem. Sect. B 25 (1986) 776–778.

[6] K.T. Potts, A.J. Bhattacharryy, 1,2,4-Triazoles. XXXII. Synthesis and correlation of proton magnetic resonance spectral characteristics with molecular orbital parameters of derivatives of the *s*-triazolo[4,3-*a*]quinoline and *s*-triazolo[3,4-*a*]isoquinoline ring systems, J. Org. Chem. 37 (1972) 4410–4415.

[7] C. Pellerano, V. Brizzi, L. Savini, Idrazinochinoline e derivati: sintesi ed attività biologica, Atti Acc. Fisiocrit. Siena, Series XIV 3 (1971) 253–267.

[8] G.A. Reynolds, J.A. VanAllan, The synthesis of polyazaindenes and related compounds, J. Org. Chem. 24 (1959) 1478–1486.

[9] J.H. Boyer, R. Borgers, L.T. Wolford, The azomethine linkage of pyridine in ring closure isomerizations, J. Am. Chem. Soc. 79 (1957) 678–680.

[10] K. Shirakawa (Takeda Pharm. Inds.; Ltd., Osaka), Pyrimidine derivatives. II. 1,2,4-Triazolopyrimidines. 2. Yakugaku Zasshi 79 (1959) 899–903; Chem. Abstr. 54 (1960) 556 f.

[11] T. Kauffmann, K. Vogt, S. Barck, J. Schulz, Synthese 3-substituierter *s*-triazolo[4,3-*a*]pyridine, Chem. Ber. 99 (1966) 2593–2599.

[12] C.A. Winter, E.A. Risley, G.W. Nuss, Carrageenin-induced edema in hind paw of rat as an assay for antiinflammatory drugs, Proc. Soc. Exp. Biol. Med. 111 (1962) 544–547.

[13] J.E. Davies, D.N. Kellett, J.C. Pennington, The anti-inflammatory and analgesic effects of Norvedan, an novel, non steroidal agent, Arch. Int. Pharmacodyn. Ther. 221 (1976) 274–282.