Eur J Med Chem (1995) 30, 901–909

Research on heterocyclic compounds. XXXIV. Synthesis and SAR study of some imidazo[2,1-*b*]thiazole carboxylic and acetic acids with antiinflammatory and analgesic activities

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(Received 20 March 1995; accepted 10 July 1995)

imidazo[2,1-*b*]thiazole / antiinflammatory activity / analgesic activity / ulcerogenic activity

Introduction

In previous papers it was shown that the imidazo[2,1-*b*]-thiazole nucleus bearing an acidic (carboxylic or acetic) moiety conferred antiinflammatory and analgesic activities, without relevant ulcerogenic action [1–4]. These activities were improved by the introduction of other substituents. Lipophilic moieties seemed to be the most effective [5, 6].

There were notable structural differences between the most potent compounds obtained. The position of the substituents on the nucleus could change activity markedly. The acidic moiety in position 3, 5 or 6 is required for activity as is the presence of a lipophilic substituent.

A systematic study on the structure–activity relationships (SAR) aiming to find the best relative positions of the substituents on the heterocyclic nucleus in order to optimize the pharmacological activity was never carried out.

In this paper we report the synthesis and the pharmacological activity of 12 imidazo[2,1-*b*]thiazole carboxylic or acetic acids, bearing a phenyl or a 4-chlorophenyl moiety, with various relative positions of the substituents on the nucleus (table I). The phenyl and 4-chlorophenyl moieties were chosen as sub-

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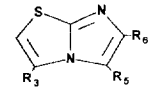
Table I. Imidazo[2,1-*b*]thiazole acids.



Compound	R_3	R_5	R_6
5a	$-CH_2COOH$	-H	-H
5b	$-CH_2COOH$	-H	$-C_6H_5$
5c	$-CH_2COOH$	-H	$-C_6H_4Cl$
5d	-H	-H	$-CH_2COOH$
5e	$-C_6H_5$	-H	-COOH
5f	$-C_6H_5$	-H	$-CH_2COOH$
5g	$-C_6H_4Cl$	-H	-COOH
5h	$-C_6H_4Cl$	-H	$-CH_2COOH$
5i	-H	-COOH	$-C_6H_5$
5j	-H	-COOH	$-C_6H_4Cl$
5k	-H	$-CH_2COOH$	$-C_6H_5$
5l	-H	$-CH_2COOH$	$-C_6H_4Cl$

stituents because they improved the pharmacological activity in other series of imidazo-heteroaryl compounds possessing antiinflammatory activity [7, 8].

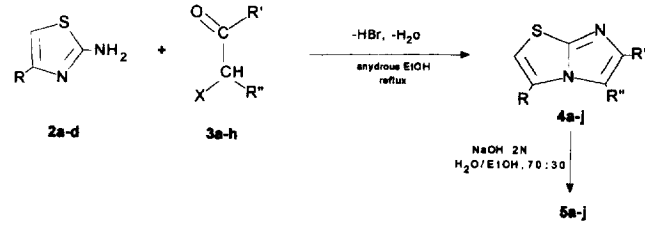
Some of these compounds are not new, but were prepared and reexamined in order to allow us more exhaustive SAR considerations.

Chemistry

The desired products were obtained *via* two synthetic pathways which are depicted in schemes 1 and 2. Compounds **5a**, **5b** and **5c** were prepared by reaction of ethyl 2-amino-4-thiazolylacetate **2a** with the suitable α-bromocarbonyl compound: bromoacetaldehyde **3a**, ω-bromoacetophenone **3b** and ω-bromo-*p*-chloroacetophenone **3c**, respectively, as previously described for analogous imidazo[2,1-*b*]thiazole derivatives [9]. The ethyl esters (**4a**, **4b**, **4c**) so obtained were converted into the desired acids by alkaline hydrolysis (scheme 1).

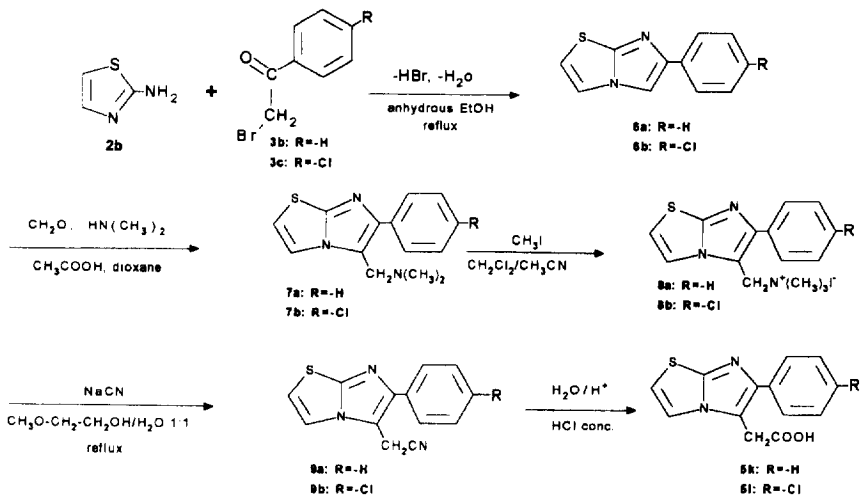
Compounds **5d–j** were synthesized *via* the same pathway, following the method employed to obtain derivatives with an acidic moiety in position 5 or 6 of the imidazo[2,1-*b*]thiazole ring [1–3], reacting a 4-(un)substituted 2-aminothiazole with the appropriate α-halo-β-ketoester.

This method furnished very poor yields when we tried to prepare 6-phenylimidazo[2,1-*b*]thiazole-5-acetic acid **5k** and 6-(*p*-chlorophenyl)imidazo[2,1-*b*]-thiazole-5-acetic acid **5l**. This result is probably due to the steric bulk of the α-halo-β-ketoesters that we had to employ, *ie* the ethyl 3-bromo-3-benzoylpropionate and ethyl 3-bromo-3-(4'-chlorobenzoyl)propionate. These two intermediates were not commercially available, but had to be prepared from the corresponding unbrominated acids.



Scheme 1. Synthesis of esters **4a–j** and acids **5a–j**. **2a**: R = CH_2COOEt; **2b**: R = H; **2c**: R = Phe; **2d**: R = 4-Cl-Phe. **3a**: R' = R" = H, X = Br; **3b**: R' = Phe, R" = H, X = Br; **3c**: R' = 4-Cl-Phe, R" = H, X = Br; **3d**: R' = CH_2COOEt, R" = H, X = Br; **3e**: R' = COOEt, R" = H, X = Br; **3f**: R' = CH_2COOEt, R" = H, X = Cl; **3g**: R' = Phe, R" = COOEt, X = Br; **3h**: R' = 4-Cl-Phe, R" = COOEt, X = Br. **4a**: R = CH_2COOEt, R' = R" = H; **4b**: R = CH_2COOEt, R' = Phe, R" = H; **4c**: R = CH_2COOEt, R' = 4-Cl-Phe, R" = H; **4d**: R = R" = H, R' = CH_2COOEt; **4e**: R = Phe, R' = COOEt, R" = H; **4f**: R = Phe, R' = CH_2COOEt, R" = H; **4g**: R = 4-Cl-Phe, R' = COOEt, R" = H; **4h**: R = 4-Cl-Phe, R' = COOEt, R" = H; **4i**: R = H, R' = Phe, R" = COOEt; **4j**: R = H, R' = 4-Cl-Phe, R" = COOEt; **5a**: R = CH_2COOH, R' = R" = H; **5b**: R = CH_2COOH, R' = Phe, R" = H; **5c**: R = CH_2COOH, R' = 4-Cl-Phe, R" = H; **5d**: R = R" = H, R' = CH_2COOH; **5e**: R = Phe, R' = COOH, R" = H; **5f**: R = Phe, R' = CH_2COOH, R" = H; **5g**: R = 4-Cl-Phe, R' = COOH, R" = H; **5h**: R = 4-Cl-Phe, R' = COOH, R" = H; **5i**: R = H, R' = Phe, R" = COOH; **5j**: R = H, R' = 4-Cl-Phe, R" = COOH.

Therefore, **5k** and **5l** were synthesized from 6-[4'-(un)substituted phenyl]imidazo[2,1-*b*]thiazole, which underwent a Mannich reaction, a quaternization with



Scheme 2. Synthesis of acids **5k** and **5l**.

methyl iodide, a substitution with a CN^- group, and an acidic hydrolysis (scheme 2), as was described for a series of 2-phenylimidazo[2,1-*b*]benzothiazole-3-acetic acids [10].

All structures were confirmed by ^1H and ^{13}C NMR spectra and by elemental analysis (tables II–IV).

Pharmacology

All acids were subjected to a series of *in vivo* tests in order to evaluate their pharmacological activity. The antiinflammatory activity was studied by means of the carrageenan rat paw edema assay, whereas the acetic

Table II. ^1H-NMR spectra of compounds **4a–j**.

Compound	*Chemical shifts, δ*							*Coupling constants (Hz)*
	H-2	*H-3*	*H-5*	*H-6*	*-CH_2COO-*	*Ethyl*	*Aryl*	
4a	6.52 s	–	7.22 d*	7.15 d*	3.57 s (2H)	3.98 q (2H), 1.10 t (3H)	–	$J_{5,6}$ = 0.8
4b	6.58 s	–	7.59 s	–	3.65 s (2H)	4.12 q (2H), 1.20 t (3H)	6-Phenyl: 7.76 d (2H), 7.33 d (2H), 7.18 t (1H)	–
4c	6.65 s	–	7.65 s	–	3.73 s (2H)	4.22 q (2H), 1.28 t (3H)	6-*p*-Chlorophenyl: 7.73 d (2H), 7.36 d (2H)	–
4d $J_{2,3}$ = 4.5	6.72 d	7.32 d	7.46 s	–		3.62 s (2H)	4.12 q (2H), 1.19 t (3H)	–
4e	6.88 s	–	8.24 s	–	–	4.38 q (2H), 1.37 t (3H)	3-Phenyl: 7.60 d (2H), 7.51 m (3H)	
4f	6.73 s	–	7.60 s	–	3.76 s (2H)	4.20 q (2H), 1.26 t (3H)	3-Phenyl: 7.58 m (2H), 7.49 m (3H)	–
4g	6.96 s	–	8.21 s	–	–	4.42 q (2H), 1.41 t (3H)	3-*p*-Chlorophenyl: 7.50–7.31 m (4H)	
4h	6.72 s	–	7.48 s	–	3.77 s (2H)	4.08 q (2H), 1.18 t (3H)	3-*p*-Chlorophenyl: 7.45 d (2H), 7.38 d (2H)	–
4i	6.95 d	8.17 d	–	–	–	4.38 q (2H), 1.37 t (3H)	6-Phenyl: 7.79 d (2H), 7.37 m (3H)	$J_{2,3}$ = 4.5
4j	6.95 d	8.18 d	–	–	–	4.38 q (2H), 1.32 t (3H)	6-*p*-Chlorophenyl: 7.80 d (2H), 7.39 d (2H)	$J_{2,3}$ = 5.0

All spectra were recorded in $CDCl_3$ solution. *Assignment uncertain.

Table III. ^{13}C NMR spectra of compounds **4a–j**.

Compound	*Chemical shifts, δ*								
	C-2	*C-3*	*C-5*	*C-6*	*C-7a*	*C=O*	*-CH_2COO-*	*Ethyl*	*Aryl*
4a	110.08	*124.21*	111.02	134.59	*149.20*	*167.40*	33.80	61.56–13.89	–
4b	109.76	*124.27*	106.59	*147.65*	*149.47*	*167.46*	33.77	61.63–13.96	6-Phenyl: *134.03*, 128.46 (2C), 127.19, 125.07 (2C)
4c	110.07	*124.39*	106.81	*146.75*	*149.77*	*167.40*	33.92	61.77–14.04	6-*p*-Chlorophenyl: *132.93, 132.74*, 128.71 (2C), 126.44 (2C)
4d	110.25	118.04	111.28	*140.01*	*148.38*	*170.08*	34.40	60.44–14.11	–
4e	110.77	*132.32*	116.62	*138.79*	*150.25*	*162.67*	–	60.79–14.27	3-Phenyl: 129.87, 129.32 (2C), *129.04*, 126.75
4f	110.11	*132.55*	107.80	*140.96*	*149.17*	*170.78*	35.27	60.83–14.10	3-Phenyl: *129.97*, 129.46, 129.16 (2C), 126.78 (2C)
4g	110.95	*131.59*	116.19	*138.95*	*150.33*	*162.47*	–	60.57–14.05	3-*p*-Chlorophenyl: 129.87 (2C), 128.24 (2C), *128.23*
4h	110.09	*131.40*	109.03	*131.40*	*148.89*	*170.47*	34.81	61.03–14.10	3-*p*-Chlorophenyl: 129.50 (2C), 128.04 (2C), *128.03*
4i	113.29	121.49	*114.44*	*153.76*[a]	*152.60*[a]	*159.76*	–	60.51–13.90	6-Phenyl: *133.46*, 129.64 (2C), 128.49, 127.43 (2C)
4j	113.53	121.69	*114.71*	*152.78*[b]	*152.63*[b]	*159.72*	–	60.79–14.11	6-*p*-Chlorophenyl: *134.63, 132.10*, 131.10 (2C), 127.81 (2C)

All spectra were recorded in $CDCl_3$ solution. Quaternary carbons are written in italics. [a,b]Assignment uncertain.

Table IV. Physical data of compounds **4a–j** and **5a–j**.

Compound	*Yield (%)*	*Mp (C°)*	*Molecular formula*	*Elemental analyses*[a]
4a	29.4	Oil	$C_9H_{10}N_2O_2S$	C, H, N, S
4b	45.8	74–76	$C_{15}H_{14}N_2O_2S$	C, H, N, S
4c	55.1	96–98	$C_{15}H_{13}ClN_2O_2S$	C, H, Cl, N, S
4d	19.0	Oil	$C_9H_{10}N_2O_2S$	C, H, N, S
4e	18.0	158–160	$C_{14}H_{12}N_2O_2S$	C, H, N, S
4f	10.8	63–65	$C_{15}H_{14}N_2O_2S$	C, H, N, S
4g	10.8	158–160	$C_{14}H_{11}ClN_2O_2S$	C, H, Cl, N, S
4h	23.4	101–103	$C_{15}H_{13}ClN_2O_2S$	C, H, Cl, N, S
4i	26.0	53–55	$C_{14}H_{12}N_2O_2S$	C, H, N, S
4j	28.7	129–131	$C_{14}H_{11}ClN_2O_2S$	C, H, Cl, N, S
5a	88.2	95–98	$C_7H_6N_2O_2S$	C, H, N, S
5b	75.2	210–212	$C_{13}H_{10}N_2O_2S$	C, H, N, S
5c	81.3	235–237	$C_{13}H_9ClN_2O_2S$	C, H, Cl, N, S
5d	71.2	185–187	$C_7H_6N_2O_2S$	C, H, N, S
5e	42.7	186–188	$C_{12}H_8N_2O_2S$	C, H, N, S
5f	74.1	145–148	$C_{13}H_{10}N_2O_2S$	C, H, N, S
5g	79.2	215–217	$C_{12}H_7ClN_2O_2S$	C, H, Cl, N, S
5h	84.4	175–177	$C_{13}H_9ClN_2O_2S$	C, H, Cl, N, S
5i	70.8	140–142	$C_{12}H_8N_2O_2S$	C, H, N, S
5j	82.0	155–157	$C_{12}H_7ClN_2O_2S$	C, H, Cl, N, S

[a]Elemental analyses indicated by the symbols of the elements were within ±0.4% of theoretical values.

acid writhing test was used to assess the analgesic activity in mice. Higher doses were administered to rats in order to study the irritative and ulcerogenic action on the mucosa of the stomach and small intestine up to the distal ileum. Indomethacin (IMA) was included in all tests as a reference drug.

This series of tests was intended to provide information about the effect on the pharmacological activity of the introduction of a lipophilic moiety on the heterocyclic ring of imidazo[2,1-*b*]thiazole acids, and to establish the best relative position of the substituents on the nucleus.

Results and discussion

Results of the antiinflammatory assay are shown in table V; results of the analgesic assay are shown in table VI; the ulcerogenic activity is shown in table VII.

As regards the four carboxylic acids, the phenyl-substituted **5e** and **5i** are more active than the corresponding 4-chlorophenyl-substituted **5g** and **5j** in both antiinflammatory and analgesic assays. It must be noted that compound **5i**, *ie* 6-phenylimidazo[2,1-*b*]-thiazole-5-carboxylic acid, gave the best results in the writhing test displaying the highest analgesic activity. In this group of compounds, the presence of a phenyl moiety in position 6 with the carboxylic function in position 5 (acid **5i**) seems to give rise to the best activity. Compound **5e** and **5i** also displayed the most significant irritative and ulcerogenic action.

The results obtained with the eight acetic acids are more complex. First of all, we can divide such compounds into three groups: i) **5a**, **5b** and **5c** which bear the acetic moiety in position 3; ii) **5d**, **5f** and **5h** with the same function in the 6 position; and iii) the pair of 6-aryl-5-acetic acids **5k** and **5l**. The acids **5a** and **5d** can be considered as the parent compounds, in that they have only the acidic function.

Table V. Carrageenan rat paw edema: antiinflammatory activity.

Compound	*Dose (μmol/kg po)*	*% Edema inhibition relative to control at:*			
		3rd hour		*4th hour*	
IMA	14	–69		–70	
5a	150	–31		–45	
5b	150	–29		–20	
5c	150	–48		–52	ED_{50} = 137 μmol/kg (102–184)
	75	–41		–37	
	37.5	–27		–24	
5d	150	–36		–48	
5e	150	–37		–44	
5f	150	–43		–51	ED_{50} = 132 μmol/kg (90–193)
	75	–33		–43	
	37.5	–33		–29	
5g	150	–20		–19	
5h	150	–57	ED_{50} = 125 μmol/kg (97–160)	–60	ED_{50} = 105 μmol/kg (87–127)
	75	–33		–42	
	37.5	–24		–18	
5i	150	–38		–44	
5j	150	–16		–14	
5k	150	–22		–23	
5l	150	–31		–40	

Table VI. Acetic acid writhing test: analgesic activity.

Compound	*Dose (μmol/kg po)*	*Mean number of writhes in 25 min period after treatment ± SE*	*% Decrease relative to control*	
Controls	–	43.2 ± 2.4	–	
IMA	14	21.4 ± 4.1	–50	
5a	150	33.4 ± 4.8	–23	
5b	150	21.9 ± 0.1	–49	
5c	150	36.7 ± 5.6	–15	
5d	150	23 5 ± 9.1	–46	
5e	150	27.5 ± 2.9	–36	
5f	150	22.7 ± 7.9	–47	
5g	150	39.1 ± 4.5	– 9	
5h	300	19.3 ± 2.7	–55	ED_{50} = 230 μmol/kg (168–314)
	150	25.1 ± 6.7	–42	
	75	31.5 ± 3.6	–28	
5i	150	20.8 ± 3.7	–52	ED_{50} = 143 μmol/kg (114–178)
	75	31.5 ± 3.8	–28	
	37.5	36.9 ± 6.1	–12	
5j	150	40.9 ± 5.0	– 5	
5k	150	23.7 ± 8.9	–45	
5l	150	21.3 ± 3.8	–51	

Table VII. Induction of gastric lesions in rats.

Compound	*Dose (μmol/kg po)*	*6 h after treatment*	
		Hyperaemia (% animals)	*Ulcers (% animals)*
IMA	14	80	60
5a	375	60	40
5b	375	30	10
5c	375	50	50
5d	375	50	30
5e	375	50	30
5f	375	60	40
5g	375	30	20
5h	375	40	20
5i	375	60	20
5j	375	20	10
5k	375	20	20
5l	375	30	10

In the first group, **5a** showed a fairly good antiinflammatory activity, which was clearly depressed by the introduction of a phenyl moiety in position 6 (**5b**) and, *vice versa*, increased by a *p*-chlorophenyl group (**5c**). No parallelism was found between antiinflammatory and analgesic activity. In fact, **5b** was the only compound with a good level of activity in the writhing test.

In the second group, **5d** showed a level of antiinflammatory activity very similar to that of **5a**. However, the activity was increased by the introduction of a phenyl group in position 3 (**5f**) and much more by the insertion of the *p*-chlorophenyl group (**5h**). Moreover, in this case, the profile of the analgesic activity was different in that all these acids showed similar effects in writhing test. The ulcerogenic activity was not negligible. As regards the third group, the 6-aryl-5-acetic acids **5k** and **5l** showed a mediocre antiinflammatory activity and a fairly good analgesic activity, accompanied by low ulcerogenic action.

In conclusion, 3-(*p*-chlorophenyl)imidazo[2,1-*b*]-thiazole-6-acetic acid (**5h**) was the best antiinflammatory agent. The best analgesic activity was exhibited by 6-phenylimidazo[2,1-*b*]thiazole-5-carboxylic acid (**5i**), although all the acetic acids showed significant analgesic activity.

The results obtained with this group of imidazo[2,1-*b*]thiazole derivatives seem to provide further support for the hypothesis that the pharmacological activity of these imidazo derivatives could be due to multiple different mechanisms of action which are differently affected by structural changes.

Experimental protocols

Chemistry

Precoated silica gel Merck 60 F254 plates were used for thin layer chromatography: detection of components was made by UV light (254 nm) and/or treatment with iodine vapors. Chromatographic separations were performed in columns packed with silica gel 60 (Carlo Erba 70–230 mesh ASTM). Melting points were determined with a Kofler hot stage microscope and are uncorrected. Elemental analyses indicated by the symbols of the elements were performed on a Perkin-Elmer model 240 elemental analyzer, and were within ±0.4% of theoretical values. The ^{1}H and ^{13}C NMR measurements were performed on a Bruker WM250 spectrometer and/or on a Bruker AMX-500 spectrometer equipped with a Bruker X-32 computer.

Usually, commercially available solvents and chemicals were used for syntheses, with some exceptions: 1) 2-amino-4-

phenylthiazole was obtained from its hydrobromide salt; 2) ω-bromo-*p*-chloroacetophenone, ethyl 4-bromoacetoacetate, ethyl 2-bromo-2-benzoylacetate and ethyl 2-bromo-2-(*p*-chlorobenzoyl)acetate were obtained through bromination in CCl_4 of the corresponding unbrominated compounds, which are commercially available, with the exception of ethyl 2-(*p*-chlorobenzoyl)acetate, which was prepared by a literature method [11]. The general bromination procedure was the following. The starting compound was dissolved in CCl_4. An equimolar amount of bromine dissolved in CCl_4 was added dropwise at 0°C in an ice bath. The reaction mixture was stirred for 1 h at 0°C, 2 h at room temperature and at 60°C for 30 min, until the solution becomes clear. The HBr given off was collected in a trap. After cooling, CCl_4 was evaporated *in vacuo*, and the residue was chromatographed on a silica-gel column, to afford the required product; yields: 75–90%.

Ethyl imidazo[2,1-b]thiazole-3-acetate ***4a***
Bromoacetaldehyde diethyl acetal (6 g; 30 mmol) was refluxed 30 min in 50 ml of aqueous 3 N HCl. The solution was cooled and extracted with diethyl ether (3 x 15 ml). The organic layer containing the bromoacetaldehyde (**3a**) was dried on anhydrous sodium sulfate and added dropwise to a refluxing solution of 3.0 g (16 mmol) of ethyl 2-amino-4-thiazolyl-3-acetate (**2a**) in anhydrous ethanol (100 ml). The distilling diethyl ether was collected with a refrigerating system. After 8 h, the volume of the solution was reduced to 3–4 ml *in vacuo*, and a saturated solution of sodium hydrogen carbonate (50 ml) was added. This mixture was extracted three times with chloroform (3 x 50 ml), the organic extracts were combined, washed with water, dried over anhydrous sodium sulphate, concentrated *in vacuo* and then chromatographed on a silica-gel column eluted with chloroform to afford 1 g (4.7 mmol) of the required product.

Ethyl 6-phenylimidazo[2,1-b]thiazole-3-acetate ***4b***
A solution of 2.0 g (10.7 mmol) of **2a** and 2.2 g (11.0 mmol) of ω-bromoacetophenone (**3b**) in anhydrous ethanol (50 ml) was refluxed for 8 h. The solution was worked up as described for **4a**, with the difference that the silica-gel column was eluted with ethyl acetate/*n*-hexane (8:2) to afford 1.4 g (4.9 mmol) of the required product.

Ethyl 6-(4'-chlorophenyl)imidazo[2,1-b]thiazole-3-acetate ***4c***
A solution of 2.0 g (10.7 mmol) of **2a** and 2.7 g (11.5 mmol) of ω-bromo-*p*-chloroacetophenone (**3c**) in anhydrous ethanol (50 ml) was refluxed for 8 h. The solution was worked up as described for **4a**, with the difference that the silica-gel column was eluted with ethyl acetate/*n*-hexane (8:2) to obtain 1.9 g (5.9 mmol) of the required product.

Ethyl imidazo[2,1-b]thiazole-6-acetate ***4d***
A solution of 3.0 g (30 mmol) of 2-aminothiazole (**2b**) and 6.3 g (30 mmol) of ethyl 4-bromoacetoacetate (**3d**) in anhydrous ethanol (100 ml) was refluxed for 16 h. The solution was worked up as described for **4a**, to obtain 1.2 g (5.7 mmol) of the required product.

Ethyl 3-phenylimidazo[2,1-b]thiazole-6-carboxylate ***4e***
A solution of 1.8 g (10 mmol) of 2-amino-4-phenylthiazole (**2c**) and 2.0 g (10 mmol) of ethyl bromopyruvate (**3e**) in anhydrous ethanol (100 ml) was refluxed for 24 h. The solution was worked up as described for **4a**, with the difference that the silica-gel column was eluted with ethyl acetate/*n*-hexane (8:2), to afford 0.5 g (1.8 mmol) of the required product.

Ethyl 3-phenylimidazo[2,1-b]thiazole-6-acetate ***4f***
A solution of 1.8 g (10 mmol) of **2c** and 1.4 ml (10 mmol) of ethyl 4-chloroacetoacetate (**3f**) in anhydrous ethanol (100 ml) was refluxed for 24 h. The solution was worked up as described for **4a**, with the difference that the silica-gel column was eluted with ethyl acetate/*n*-hexane (8:2), to afford 0.4 g (1.4 mmol) of the required product.

Ethyl 3-(4'-chlorophenyl)imidazo[2,1-b]thiazole-6-carboxylate ***4g***
A solution of 2.6 g (12 mmol) of 2-amino-4-(*p*-chlorophenyl)thiazole (**2d**) and 2.4 g (12 mmol) of **3e** was refluxed for 24 h. The solution was worked up as described for **4a**, with the difference that the silica-gel column was eluted with ethyl acetate/*n*-hexane (8:2), to afford 0.4 g (1.3 mmol) of the required product.

Ethyl 3-(4'-chlorophenyl)imidazo[2,1-b]thiazole-6-acetate ***4h***
A solution of 2.0 g (9 mmol) of **2d** and 1.4 ml (10 mmol) of **3f** in anhydrous ethanol (100 ml) was refluxed for 40 h. The solution was worked up as described for **4a**, with the difference that the chromatographic column was eluted with ethyl acetate/*n*-hexane (6:4) to afford 0.7 g (2.2 mmol) of the required product.

Ethyl 6-phenylimidazo[2,1-b]thiazole-5-carboxylate ***4i***
A solution of 1.0 g (10 mmol) of **2b** and 3.0 g (11 mmol) of ethyl 2-benzoyl-2-bromoacetate (**3g**) in anhydrous ethanol (50 ml) was refluxed for 16 h. The solution was worked up as described for **4a**, with the difference that the silica-gel column was eluted with ethyl acetate/*n*-hexane (8:2), to afford 0.7 g (2.6 mmol) of the required product.

Ethyl 6-(4'-chlorophenyl)imidazo[2,1-b]thiazole-5-carboxylate ***4j***
A solution of 1.6 g (16 mmol) of **2b** and 5.0 g (16 mmol) of ethyl 2-bromo-2-(*p*-chlorobenzoyl)acetate (**3h**) in anhydrous ethanol (50 ml) was refluxed for 16 h. The solution was worked up as described for **4a**, with the difference that the silica-gel column was eluted with ethyl acetate/*n*-hexane (8:2), to afford 1.4 g (4.6 mmol) of the required product.

Preparation of acids ***5a–j***
These acids were obtained by alkaline hydrolysis of the respective esters in hydro-alcoholic sodium hydroxide (2 N, ethanol/water 7:3), refluxing the reaction mixture for 1 h. After cooling the solution was added with diluted HCl up to pH 4-5. The precipitate obtained was recrystallized from ethanol (see also table IV).

Imidazo[2,1-b]thiazole-3-acetic acid ***5a***. ^{1}H NMR (CD_3OD): 7.62 (1H, d, H-5), 7.25 (1H, d, H-6), 6.84 (1H, s, H-2), 3.70 (2H, s, 3-CH_2-); $J_{5,6}$ = 0.8 Hz.

6-Phenylimidazo[2,1-b]thiazole-3-acetic acid ***5b***. ^{1}H NMR (CD_3OD): 8.08 (1H, s, H-5), 7.85 (2H, d, H-2',6'), 7.42 (2H, t, H-3',5'), 7.35 (1H, t, H-4'), 7.05 (1H, s, H-2), 4.02 (2H, s, 3-CH_2-).

6-(4'-Chlorophenyl)imidazo[2,1-b]thiazole-3-acetic acid ***5c***. ^{1}H NMR (CD_3OD): 8.28 (1H, s, H-5), 7.75 (2H, d, H-2',6'), 7.48 (2H, d, H-3',5'), 7.32 (1H, s, H-2), 4.08 (2H, s, 3-CH_2-).

Imidazo[2,1-b]thiazole-6-acetic acid ***5d***. ^{1}H NMR (CD_3OD): 7.95 (1H, d, H-3), 7.89 (1H, s, H-5), 7.45 (1H, d, H-2), 3.86 (2H, s, 3-CH_2-); $J_{2,3}$ = 4.5 Hz.

3-Phenylimidazo[2,1-b]thiazole-6-carboxylic acid ***5e***. ^{1}H NMR (CD_3OD): 8.52 (1H, s, H-5), 7.82 (2H, d, H-2',6'), 7.64 (3H, m, H-3',4',5'), 7.52 (1H, s, H-2).

3-Phenylimidazo[2,1-b]thiazole-6-acetic acid ***5f***. ^{1}H NMR (CD_3OD): 7.75 (1H, s, H-5), 7.70 (2H, d, H-2',6'), 7.58 (3H, t, H-3',4',5'), 7.22 (1H, s, H-2), 3.75 (2H, s, 3-CH_2-).

3-(4'-Chlorophenyl)imidazo[2,1-b]thiazole-6-carboxylic acid ***5g***. ^{1}H NMR (CD_3OD): 8.20 (1H, s, H-5), 7.81 (2H, d, H-2',6'), 7.62 (2H, d, H-3',5'), 7.28 (1H, s, H-2).

3-(4'-Chlorophenyl)imidazo[2,1-b]thiazole-6-acetic acid ***5h***. ^{1}H NMR (CD_3OD): 8.05 (1H, s, H-5), 7.65 (2H, d, H-2',6'), 7.60 (1H, s, H-2), 7.54 (2H, d, H-3',5').

6-Phenylimidazo[2,1-b]thiazole-5-carboxylic acid ***5i***. ^{1}H NMR (CD_3OD): 8.30 (1H, d, H-3), 7.84 (2H, d, H-2',6'), 7.44 (3H, m, H-3',4',5'), 7.34 (1H, d, H-2); $J_{2,3}$ = 4-5 Hz.

6-(4'-Chlorophenyl)imidazo[2,1-b]thiazole-5-carboxylic acid ***5j***. ^{1}H NMR (CD_3OD): 8.32 (1H, d, H-3), 7.99 (2H, d, H-2',6'), 7.59 (3H, m, H-3', H-5' and H-2); $J_{2,3}$ = 5.0 Hz.

6-Phenylimidazo[2,1-b]thiazole ***6a***
A solution of 5.0 g (50 mmol) of **2b** and 9.9 g (50 mmol) of **3b** in anhydrous ethanol (100 ml) was refluxed for 8 h. The volume of the solution was reduced to 3–4 ml *in vacuo*, and a saturated solution of sodium hydrogen carbonate (50 ml) was added. This mixture was extracted three times with methylene chloride (3 x 50 ml), the organic extracts were combined, washed with water, dried over anhydrous sodium sulphate, concentrated *in vacuo* and then chromatographed on a silica-gel column eluted with methylene chloride, to afford 8.9 g (44 mmol) of the required product. ^{1}H NMR ($CDCl_3$): 7.78 (2H, d, H-2', 6'), 7.65 (1H, s, H-5), 7.38–7.27 (3H, m, H-3',5', 3), 7.20 (1H, t, H-4'), 6.71 (1H, d, H-2). $J_{2,3}$ = 4.5 Hz. ^{13}C NMR ($CDCl_3$): 150.22 (C-7a), 148.16 (C-6), 134.28 (C-1'), 128.63 and 125.33 (*ortho*- and *meta*-phenyl carbons), 127.36 (C-4'), 118.43 (C-3), 112.23 (C-2), 107.88 (C-5).

5-Dimethylaminomethyl-6-phenylimidazo[2,1-b]thiazole ***7a***
Compound **6a** (8.9 g; 44 mmol) in dioxane (150 ml) was added dropwise to a stirred mixture of aqueous dimethylamine (40% ,6.0 ml, 53 mmol), aqueous formalin (37%, 4.6 ml, 53 mmol) and acetic acid (15 ml) in dioxane (50 ml). The reaction mixture was stirred for 1 h at room temperature, and then it was refluxed for 5 h. The solvent was evaporated off *in vacuo*, and a solution of sodium carbonate (10%, 100 ml) was added to the viscous residue. The precipitated solid was extracted three times with chloroform (3 x 50 ml). The organic extracts were combined, washed with water, dried over anhydrous sodium sulphate, and concentrated *in vacuo*, to afford 11.0 g (42 mmol) of the required product. ^{1}H NMR ($CDCl_3$): 7.70 (2H, d, H-2',6'), 7.62 (1H, d, H-3), 7.45–7.22 (3H, m, H-3',4', 5'), 6.72 (1H, d, H-2), 3.73 (2H, s, $CH_2N(CH_3)_2$), 2.22 (6H, s, CH_2-$N(CH_3)_2$); $J_{2,3}$ = 4.5 Hz.

5-Dimethylaminomethyl-6-phenylimidazo[2,1-b]thiazole methiodide salt ***8a***
Methyl iodide (3.7 ml; 60 mmol) was added dropwise to a stirred solution of 11.0 g (42 mmol) of **7a** in methylene chloride/acetonitrile (3:1, 50 ml). The reaction mixture was left overnight at room temperature, and then refluxed for 2 h, and cooled. The precipitated white crystals were filtered, and washed with methylene chloride, to afford 7.7 g (19 mmol) of the required product. ^{1}H NMR (DMSO-d_6): 8.46 (1H, d, H-3), 7.88 (2H, d, H-2',6'), 7.60 (1H, d, H-2), 7.58–7.50 (3H, m, H-3',4',5'), 5.24 (2H, s, CH_2-$N^+(CH_3)_3$), 2.95 (9H, s, CH_2-$N^+(CH_3)_3$); $J_{2,3}$ = 4.5 Hz.

5-Cyanomethyl-6-phenylimidazo[2,1-b]thiazole ***9a***
A solution of 4.7 g (11.8 mmol) of **8a** in methoxyethanol (24 ml) was added dropwise to a refluxing solution of sodium cyanide (2.9 g, 60 mmol) in methoxyethanol/water (1:1, 24 ml). The reaction mixture was refluxed for 5 h, then the solvent was removed *in vacuo*. The residue was extracted with methylene chloride (100 ml), washed with water, concentrated *in vacuo*, and chromatographed on a flash-chromatography column, eluting with ethyl acetate/*n*-hexane (1:1), to afford 2.5 g (10.5 mmol) of the required product. ^{1}H NMR ($CDCl_3$): 7.49 (2H, d, H-2',6'), 7.40 (1H, d, H-3), 7.35–7.27 (3H, m, H-3',4',5'), 6.86 (1H, d, H-2), 3.98 (2H, s, CH_2-CN); $J_{2,3}$ = 4.5 Hz.

6-Phenylimidazo[2,1-b]thiazole-5-acetic acid ***5k***
Compound **9a** (2.5 g; 10.5 mmol) were suspended in 35 ml of hydrochloric acid (37%), and were refluxed for 12 h. The solvent was removed *in vacuo*, and the residue was treated with a saturated solution of sodium hydrogen carbonate (50 ml). The pH of the aqueous solution was adjusted to 3–4, and the precipitate was collected and washed, to afford 1.4 g (5.4 mmol) of the required product, recrystallized from ethanol. Mp: 238–240°C. Anal ($C_{13}H_{10}N_2O_2S$) C, H, N, S. ^{1}H NMR (DMSO-d_6): 8.02 (1H, d, H-3), 7.76 (2H, d, H-2', 6'), 7.53 (2H, t, H-3', 5'), 7.38 (2H, m, H-2, 4'), 4.12 (2H, s, CH_2-COOH); $J_{2,3}$ = 4.5 Hz. ^{13}C NMR (DMSO-d_6): 170.98 (COOH), 147.67 (C-7a), 143.37 (C-6), 134.56 (C-1'), 128.58 and 126.92 (*ortho*- and *meta*-phenyl carbons), 127.03 (C-4'), 119.21 (C-3), 116.30 (C-5), 112.77 (C-2), 30.97 (CH_2-COO).

6-(4'-Chlorophenyl)imidazo[2,1-b]thiazole ***6b***
A solution of 5.0 g (50 mmol) of **2b** and 12.0 g (50 mmol) of **3c** in anhydrous ethanol (100 ml) was refluxed for 8 h. The solution was worked up as described for **6a**, to afford 11.2 g (47.7 mmol) of the required product. ^{1}H NMR ($CDCl_3$): 7.64 (2H, d, H-2', 6'), 7.58 (1H, s, H-5), 7.31 (1H, d, H-3), 7.26 (2H, d, H-3',5'), 6.72 (1H, d, H-2); $J_{2,3}$ = 5.0 Hz. ^{13}C NMR ($CDCl_3$): 150.07 (C-7a), 147.22 (C-6), 132.62 and 132.41 (C-1' and C-4'), 128.55 and 126.18 (*ortho*- and *meta*-phenyl carbons), 118.22 (C-3), 112.28 (C-2), 107.89 (C-5).

5-Dimethylaminomethyl-6-(4'-chlorophenyl)imidazo[2,1-b]-thiazole ***7b***
Compound **6b** (11.2 g; 47.7 mmol) in dioxane (150 ml) was added dropwise to a stirred mixture of aqueous dimethylamine (40%, 6.4 ml, 58 mmol), aqueous formalin (37%, 4.8 ml, 58 mmol) and acetic acid (16 ml) in dioxane (50 ml). The reaction mixture was stirred for 1 h at room temperature, and then it was refluxed for 5 h. The solution was worked as described for **7a**, to afford 13.4 g (45.9 mmol) of the required product. ^{1}H NMR ($CDCl_3$): 7.63 (2H, d, H-2',6'), 7.60 (1H, d, H-3), 7.34 (2H, d, H-3', 5'), 6.73 (1H, d, H-2), 3.70 (2H, s, $CH_2N(CH_3)_2$), 2.21 (6H, s, $CH_2N(CH_3)_2$); $J_{2,3}$ = 5.0 Hz.

5-Dimethylaminomethyl-6-(4'-chlorophenyl)imidazo[2,1-b]-thiazole methiodide salt ***8b***
Methyl iodide (3.7 ml; 60 mmol) was added dropwise to a stirring solution of 13.4 g (45.9 mmol) of **7b** in methylene chloride/acetonitrile (3:1, 50 ml). The reaction mixture was left overnight at room temperature, then refluxed for 2 h and cooled. The precipitated white crystals were filtered, and

washed with methylene chloride, to afford 16.4 g (37.8 mmol) of the required product. ^{1}H NMR (DMSO-d_6): 8.44 (1H, d, H-3), 7.92 (2H, d, H-2',6'), 7.60–7.50 (3H, m, H-3', H-5' and H-2), 5.24 (2H, s, $CH_2N^+(CH_3)_3$), 2.96 (9H, s, $CH_2N^+(CH_3)_3$); $J_{2,3}$ = 5.0 Hz.

5-Cyanomethyl-6-(4'-chlorophenyl)imidazo[2,1-b]thiazole **9b**
A solution of 4.3 g (10.0 mmol) of **8b** in methoxyethanol (24 ml) was added dropwise to a refluxing solution of sodium cyanide (2.4 g, 50 mmol) in methoxyethanol/water (1:1, 24 ml). The reaction mixture was refluxed for 5 h, then the solvent was removed *in vacuo*. The residue was worked as described for **9a**, to afford 1.6 g (5.8 mmol) of the required product. ^{1}H NMR ($CDCl_3$): 7.60 (2H, d, H-2',6'), 7.56 (1H, d, H-3), 7.31 (2H, d, H-3', H-5'), 6.70 (1H, d, H-2), 3.95 (2H, s, CH_2-CN); $J_{2,3}$ = 5.0 Hz.

6-(4'-Chlorophenyl)imidazo[2,1-b]thiazole-5-acetic acid **5l**
Compound **9b** (1.6 g; 5.8 mmol) was suspended in 35 ml of hydrochloric acid (37%), and were refluxed for 12 h. The solvent was removed *in vacuo*, and the residue was treated as described for **5k**, to afford 0.5 g (1.7 mmol) of the required product, recrystallized from ethanol. Mp: 241–243°C. Anal ($C_{13}H_9ClN_2O_2S$) C, H, Cl, N, S. ^{1}H NMR (DMSO-d_6): 8.02 (1H, d, H-3), 7.76 (2H, d, H-2',6'), 7.53 (2H, t, H-3',5'), 7.38 (2H, m, H-2, 4'), 4.12 (2H, s, CH_2COOH); $J_{2,3}$ = 5.0 Hz. ^{13}C NMR (DMSO-d_6): 171.05 (COOH), 146.44 (C-7a), 143.03 (C-6), 133.86 and 132.79 (C-1' and C-4'), 129.00 and 126.53 (*ortho*- and *meta*-phenyl carbons), 119.03 (C-3), 116.45 (C-5), 113.59 (C-2), 31.29 (CH_2-COO).

Pharmacology

The test compounds were administered orally by gavage in 1% methylcellulose suspension, using first a dose of 150 μmol/kg (≅ 40 mg/kg) and then, if a significant activity was found, lower and/or higher doses in order to study dose-dependence of antiinflammatory and analgesic activity.

Gastric ulcerogenic action was studied in rats, which were treated orally with higher doses (375 μmol/kg, ≅ 100 mg/kg). Indomethacin was included in all tests for comparison purposes at the dose level of 14 μmol/kg (5 mg/kg). The following experimental procedures were employed.

Antiinflammatory activity
The paw edema inhibition test [12] was used on rats. Groups of 5 rats of both sexes (body weight 120–160 g), pregnant females excluded, were given a dose of a test compound. Thirty minutes later 0.2 ml of 1% carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw. The paw volume was measured by a water plethysmometer Socrel 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 (5 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 V.

Analgesic activity
Acetic acid writhing test [13] was used on mice. Groups of 5 mice (body weight 20–25 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 VI.

Ulcerogenic action
Groups of 10 rats (body weight 200–220 g) of both sexes, pregnant females excluded, were treated with an oral dose of a test compound, except the control group [14]. All animals were killed 6 h after dosing and their stomachs and small intestines were examined using a 2 x 2 binocular magnifier, to assess the incidence of hyperemia and ulcers. All the ulcers > 0.5 mm were recorded. Experimental results are listed in table VII.

Acknowledgments

The NMR spectra were performed at the Centro di Ricerca Interdipartimentale di Analisi Strumentale, Università di Napoli 'Federico II'. The assistance of the staff is gratefully appreciated. This research was financially supported by the National Research Council (CNR – Rome) and by the Italian Ministry of University and Scientific Technological Research (MURST – Rome).

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