Eur. J. Med. Chem. 33 (1998) 163–170

Research on heterocyclic compounds – Part XXXIX. 2-Methylimidazo[1,2-*a*]pyrimidine-3-carboxylic derivatives: Synthesis and antiinflammatory activity

Sonia Laneri[a]*, Antonia Sacchi[a], Marina Gallitelli[a], Francesca Arena[a], Elena Luraschi[a], Enrico Abignente[a], Walter Filippelli[b], Francesco Rossi[b]

[a]*Dipartimento di Chimica Farmaceutica e Tossicologica, Facoltà di Farmacia, Università di Napoli Federico II, Via Domenico Montesano 49, I-80131 Napoli, Italy*
[b]*Istituto di Farmacologia e Tossicologia, Facoltà di Medicina e Chirurgia, Seconda Università di Napoli, Via Costantinopoli 16, I-80138 Napoli, Italy*

(Received 7 April 1997; accepted 30 September 1997)

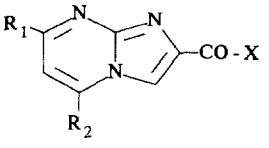
Abstract – The synthesis of a group of 2-methylimidazo[1,2-*a*]pyrimidine-3-carboxylic esters, acids and amides is described. The structures of new compounds are supported by ^1H and ^{13}C NMR spectra. These compounds were tested in vivo for their antiinflammatory, analgesic and ulcerogenic activity. Eight new compounds out of fifteen showed remarkable dose-dependent antiinflammatory action in the carrageenan rat paw edema (1/2–1/3 x indomethacin) but weak analgesic activity in the acetic acid writhing test together with negligible ulcerogenic action. The new compounds were found to be lacking in inhibitory activity on cyclooxygenase in vitro.

imidazo[1,2-*a*]pyrimidines / antiinflammatory activity / analgesic activity / ulcerogenic activity / cyclooxygenase inhibition

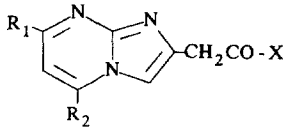
1. Introduction

In the course of our research on fused imidazo-heterocyclic derivatives and their antiinflammatory activity [1], we have synthesized and pharmacologically tested a series of imidazo[1,2-*a*]pyrimidine-2-carboxylic derivatives **1** [2] and a series of 2-acetic analogues **2** [3] (*figure 1*). Almost all the carboxylic derivatives (ethyl esters, acids and amides) showed a remarkable analgesic activity, whereas only a few of them displayed also a comparable antiinflammatory action. As regards the second series, the replacement of the carboxylic moiety with the acetic one decreased the pharmacological activity, particularly the analgesic potential. All compounds showed low ulcerogenic action at the gastrointestinal level and lack of inhibitory activity on cyclooxygenase in vitro.

However, in other series of analogues such as imidazo[1,2-*a*]pyrazines we obtained good results with 2-methyl-3-carboxylic derivatives [4], so that we decided to synthesize some 2-methylimidazo[1,2-*a*]-



1



2

R_1= CH_3, OCH_3
R_2= Cl, OCH_3, OC_2H_5
X= OH, OCH_3, OC_2H_5, NH_2

Figure 1.

*Correspondence and reprints

pyrimidine-3-carboxylic esters, acids and amides (*figure 2*) in order to explore the possibility of improving the activity in this series.

2. Chemistry

The required compounds were prepared using a synthetic method closely related to the general procedure that we normally employ to obtain bicyclic imidazo derivatives [1]. In the present case (*figure 3*) the starting 2-aminopyrimidines **3** were refluxed with ethyl 2-chloroacetoacetate **4** in alcoholic solution to obtain the corresponding ethyl 2-methylimidazo[1,2-*a*]-pyrimidine-3-carboxylates **5**. These products underwent alkaline hydrolysis to afford the carboxylic acids **6**, some of which were then converted into the corresponding carboxamides **7** via the acyl chlorides.

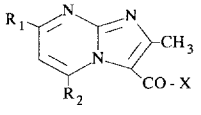


Figure 2.

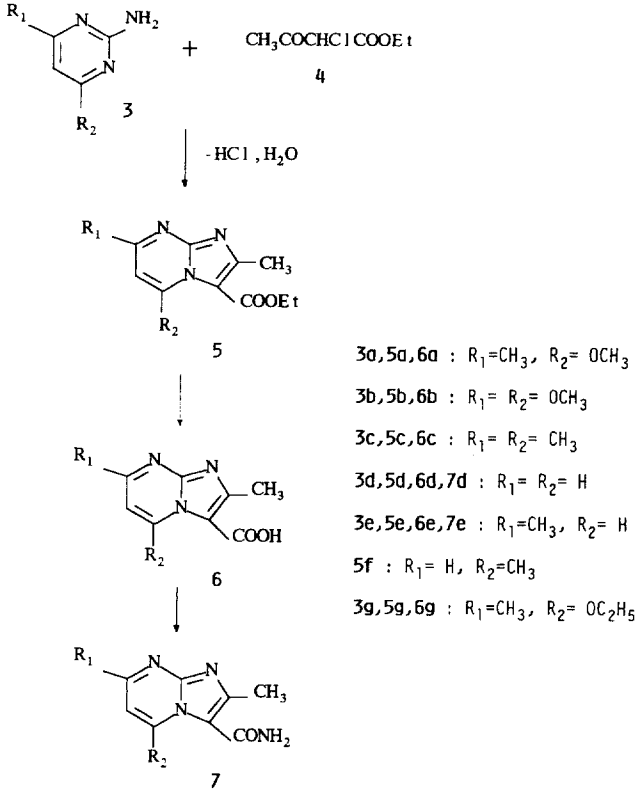


Figure 3.

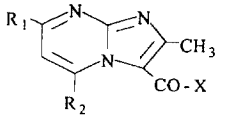
The correct structural assignments to these products were performed by the ^{1}H and ^{13}C NMR spectra (see *tables I* and *II*), on the basis of experimental evidence quite similar to that already discussed in the case of the preceding series of carboxylic [2] and acetic analogues [3].

In particular, it must be pointed out that a correct interpretation of the NMR spectra of the ethyl ester **5d** gave us the basis for correct structural assignments to all other products. Compound **5d** was obtained by reaction of 2-aminopyrimidine **3d** with ethyl 2-chloroacetoacetate **4**. It must be noted that **5d** is the only compound of type **5** without substituents on the pyrimidine ring, so that the protons in positions 5, 6 and 7 appeared in the ^{1}H NMR spectrum (see *table I*) as a system of three double doublets at δ 9.54, 7.03 and 8.64 ppm, respectively. The H-5 proton is strongly deshielded and downfield shifted by the presence of the –COOEt moiety in the 3 position: this is the same effect first observed in a series of imidazo[1,2-*a*]pyridines by Hand and Paudler [4] and then observed by us in various series of fused imidazole derivatives [2, 5–7].

As regards the ^{13}C NMR spectrum of **5d**, the spectral data reported in *table II* are consistent with data reported for imidazo[1,2-*a*]pyrimidines by Pugmire et al. [8] and also by us in the above-cited paper [2]. In particular, the attribution of peaks at 135.47 and 151.85 ppm to C-5 and C-7, respectively, is coherent with data reported by both Pugmire et al. [8] and us [2] for these two carbon atoms in similar compounds.

As regards the other compounds **5**, it must be pointed out that the starting compounds **3a** (2-amino-4-methoxy-6-methylpyrimidine), **3e** (2-amino-4-methylpyrimidine), and **3g** (2-amino-4-ethoxy-6-methylpyrimidine) are differently substituted in the 4 and 6 positions. Consequently, it was possible, in theory, to obtain a pair of isomeric products of the **5** type from the cyclocondensation reaction of such amines with the α-haloketo-derivative **4**. However, we have experimentally verified that only starting from **3e** a pair of isomers was obtained, i.e. the ethyl esters **5e** and **5f**. The correct structural assignment to these compounds was easily made on the basis of the presence or absence in the ^{1}H NMR spectra of the H-5 proton strongly deshielded by the –COOEt group in position 3 [2]. Consequently, the signal at δ 9.29 ppm in the spectrum of compound **5e** was clearly attributable to the H-5 proton, whereas compound **5f** is 5-methyl-substituted and showed the H-7 signal at δ 8.47 ppm. Such assignments were further confirmed by the different values of coupling constants with the H-6 proton.

Table I. ^{1}H-NMR spectral data of 2-methylimidazo[1,2-*a*]pyrimidine-3-carboxylic derivatives.



Compound	X	R1	R2	H-5	H-6	H-7	COX	Substituents and coupling constants (Hz)
5a	OEt	CH_3	OCH_3	–	6.30 s	–	4.31 q, 1.33 t	2- and 7-CH_3: 2.66 s, 2.61 s; 5-OCH_3: 4.04 s
5b	OEt	OCH_3	OCH_3	–	5.66 s	–	4.28 q, 1.32 t	2-CH_3: 2.47 s; 5- and 7-OCH_3: 3.96 s, 3.98 s
5c	OEt	CH_3	CH_3	–	6.58 s	–	4.31 q, 1.33 t	2-, 5- and 7-CH_3: 2.60 s, 2.57 s, 2.49 s
5d	OEt	H	H	9.54 dd	7.03 dd	8.64 dd	4.42 q, 1.43 t	2-CH_3: 2.73 s; $J_{5,6}$ = 7.5, $J_{6,7}$ = 4.4, $J_{5,7}$ = 2
5e	OEt	CH_3	H	9.29 d	6.85 d	–	4.36 q, 1.37 t	2- and 7-CH_3: 2.66 s; 2.59 s; $J_{5,6}$ = 7.4
5f	OEt	H	CH_3	–	6.76 d	8.47 d	4.37 q, 1.39 t	2- and 5-CH_3: 2.69 s; 2.65 s; $J_{6,7}$ = 3.7
5g	OEt	CH_3	OEt	–	6.22 s	–	4.37 q[a], 1.36 t[a]	2- and 7-CH_3: 2.60 s, 2.65 s; 5-OEt: 4.32 q[a], 1.35 t[a]
6a	OH	CH_3	OCH_3	–	6.02 s	–	–	2- and 7-CH_3: 2.49 s, 2.47 s; 5-OCH_3: 3.87 s
6b	OH	OCH_3	OCH_3	–	5.33 s	–	–	2-CH_3: 2.33; 5- and 7-OCH_3: 3.88 s (6H)
6c	OH	CH_3	CH_3	–	6.67 s	–	–	2-, 5- and 7-CH_3: 3.07 s, 2.93 s, 2.51 s
6d	OH	H	H	9.75 dd	7.12 dd	8.54 dd	–	2-CH_3: 2.70 s; $J_{5,6}$ = 7.5, $J_{6,7}$ = 4.5, $J_{5,7}$ = 2
6e	OH	CH_3	H	9.58 d	7.06 d	–	–	2- and 7-CH_3: 2.72 s, 2.62 s; $J_{5,6}$ = 6.9
6g	OH	CH_3	OEt	–	6.18 s	–	–	2- and 7-CH_3: 2.61 s, 2.52 s; 5-OEt: 4.40 q, 1.47 t
7d	NH_2	H	H	9.60 dd	7.31 dd	8.75 dd	7.56 bs (2H)	2-CH_3: 2.64 s; $J_{5,6}$ = 7.5, $J_{6,7}$ = 4.5, $J_{5,7}$ = 2
7e	NH_2	CH_3	H	9.60 d	7.88 d	–	8.47, 8.01 bs	2- and 7-CH_3: 2.83 s, 2.67 s; $J_{5,6}$ = 6.9

[a]Assignment uncertain; solvents: $CDCl_3$ for **5a–g**, CD_3OD for **6a–e,g**, DMSO-d'_6 for **7d,e**.

For the correct structural assignment to products **5a** and **5g**, it was necessary to obtain further experimental data by a nOe difference experiment. In this manner we were able to unequivocally establish that in **5a** the methoxyl group is in position 5 and the methyl group in 7, and similarly that in **5g** the ethoxyl group is in 5 and the methyl group in 7 again. In fact, in the case of **5a** a positive nOe effect was observed for the methoxyl group when the CH_3 of the ethyl ester moiety in position 3 was irradiated, whereas the methyl substituent was completely unaffected. On the other hand, irradiation of the methoxyl group caused a positive nOe effect for both H-6 and the ethyl ester group in 3, whereas irradiation of the methyl substituent caused a positive nOe effect only for H-6. These observations unequivocally show that compound **5a** is substituted in position 5 by the methoxyl group and in position 7 by the methyl group.

Table II. ^{13}C-NMR spectral data of ethyl esters **5**. All spectra were recorded in $CdCl_3$.

Compound	C=O	C-3	C-2	C-5	CH-5	CH-6	CH-7	C-7	C-8a	C_2H_5 ester	2-CH_3	Substituents
5a	*164.68*	*153.45*	*112.71*	*149.31*	–	101.66	–	*160.79*	*151.28*	60.81/14.48	16.49	5-OCH_3: 54.2; 7-CH_3: 21.65
5b	*166.50*	*158.10*	*111.2*	*151.30*	–	78.50	–	*160.0*	*150.5*	60.31/14.50	15.8	5- and 7-OCH_3: 56.9, 54.4
5c	*162.01*	*154.36*	*112.47*	*147.12*	–	111.80	–	*160.64*	*151.09*	60.80/14.36	16.57	5- and 7-CH_3: 24.34, 21.61
5d	*161.17*	*154.71*	*111.11*	–	135.47	109.84	151.85	–	*149.61*	60.68/14.42	16.71	–
5e	*162.47*	*154.35*	*110.80*	–	134.71	110.78	–	*161.22*	*149.78*	60.54/14.51	16.70	7-CH_3: 24.99
5f	*160.52*	*153.39*	*112.93*	*148.01*	–	111.12	151.48	–	*150.75*	61.00/14.32	16.45	5-CH_3: 21.79
5g	*164.61*	*153.50*	*112.74*	*149.36*	–	102.04	–	*160.87*	*151.43*	60.87/14.48	16.10	7-CH_3: 21.74; 5-OCH_2CH_3: 63.00/14.59

Quite similar positive nOe effects were observed for compound **5g** when the CH_3 of the ethyl ester moiety in position 3, the CH_3 of the ethoxyl group on the pyrimidine ring and the methyl group on the same ring were in turn irradiated, showing that this compound is 5-OC_2H_5- and 7-CH_3-substituted.

3. Pharmacology

The new esters **5a–g**, acids **6a–e,g** and amides **7d,e** were tested in vivo in order to evaluate their pharmacological activity. The carrageenan-induced rat paw edema [9] was used to study the antiinflammatory activity, whereas the analgesic activity was studied by means of the acetic acid writhing test in mice [10]. Higher doses were administered to rats in order to evaluate the irritative and ulcerogenic action on the mucosa of the stomach and small intestine.

Indomethacin was used in all tests as reference drug. These tests were selected to provide information about the mode of action of these compounds. In fact, they should display a similar level of activity in all three tests if they act as inhibitors of prostaglandin biosynthesis. In order to unequivocally remove this doubt, some new compounds were also subjected to a cyclooxygenase activity assay in vitro [11].

As regards the experiments carried out in vivo, test compounds were administered orally by gavage in 1% methylcellulose suspension. In the edema and writhing tests each compound was first tested at 40 mg/kg. If a significant activity was observed, lower and/or higher doses were administered in order both to study the dose-dependence of the pharmacological activity and to calculate ED_{50} values, when possible. Gastric ulcerogenic action was studied in rats which were treated orally with higher doses (100 mg/kg).

The experimental results are reported in *tables III–V* both for test compounds and for indomethacin (IMA). All the experimental procedures were already described in detail in a previous paper [2].

4. Results and discussion

The results obtained in the carrageenan-induced rat paw edema are reported in *table III*. All compounds display significant antiinflammatory activity, with the only exception of the acid **6b**. The most active compounds are the ethyl esters **5a**, **5b**, **5c**, **5f** and **5g**, the acids **6c** and **6d**, and the amide **7d**: all these compounds are approximately equipotent (~ 1/3 x indomethacin). The other compounds are less active or lack dose-dependency.

The analgesic activity in the acetic acid writhing test reported in *table IV* is sharply lower and without any parallelism with the results of the preceding test. A low level of ulcerogenic action (*table V*) at higher doses was observed.

The pharmacological profile resulting from the above experimental data for these 2-methylimidazo-[1,2-*a*]pyrimidine-3-carboxylic derivatives is quite

Table III. Antiinflammatory activity by the carrageenan rat paw edema test.

Compound	Dose mg/kg p.o.	% Edema inhibition rel. to control after		ED_{50}, mg/kg (fiducial limits)	
		3 h	4 h	3 h	4 h
5a	10	–29	–22	15.4	17.4
	20	–62	–51	(13.3–17.8)	(15.4–19.7)
	40	–90	–92		
5b	10	–42	–37	18.1	18.7
	20	–46	–52	(15.3–21.8)	(14.8–23.7)
	40	–78	–73		
5c	10	–28	–37	20.5	18.4
	20	–42	–40	(17.3–24.4)	(13.5–23.6)
	40	–76	–81		
5d	20	–23	–19	–	–
	40	–42	–44		
	60	–6	–3		
5e	20	–47	–34	–	–
	40	–52	–54		
	60	–54	–38		
5f	10	–40	–37	17.9	18.5
	20	–45	–48	(13.6–22.0)	(14.3–23.9)
	40	–76	–70		
5g	10	–29	–37	24.1	18.3
	20	–37	–44	(19.5–29.9)	(9.5–27.8)
	40	–68	–75		
6a	40	–59	–44	–	–
6b	40	–7	–6	–	–
6c	10	–29	–22	19.3	20.9
	20	–45	–51	(16.4–22.8)	(17.8–24.5)
	40	–78	–73		
6d	10	–17	–15	25.1	–
	20	–25	–18	(11.0–79.3)	
	40	–78	–73		
6e	20	–24	0	–	–
	40	–64	–63		
	60	–23	–19		
6g	40	–54	–63	–	–
7d	10	–12	–22	–	24 .2
	20	–12	–37		(20.5–28.6)
	40	–76	–71		
7e	20	–24	–19	–	–
	40	–54	–51		
	60	–41	–38		
IMA	5	–38	–35	7.0	6.7
	7.5	–49	–55	(4.5–10.8)	(4.8–8.7)
	10	–67	–79		

Table IV. Analgesic activity by the acetic acid writhing test in mice.

Compound	Dose mg/kg p.o.	% Decrease of mean no. of writhes in 25 min after treatment rel. to control
5a	40	–33
5b	40	–3
5c	40	–15
5d	40	–13
5f	40	–16
5g	40	–23
6a	40	–43
6c	40	–33
6d	40	–8
6g	40	–28
7d	40	–49
IMA	5	–56

different from that previously observed for 2-carboxylic and 2-acetic analogues. In fact, the analgesic activity was clearly prevailing over the antiinflammatory action in the series of imidazo[1,2-*a*]pyrimidine-2-carboxylic derivatives [2], whereas the imidazo[1,2-*a*]-pyrimidine-2-acetic derivatives showed low levels of both activities [3].

However, both series of compounds displayed weak, even if not negligible, ulcerogenic action at the gastrointestinal level and resulted completely devoid of inhibitory activity on prostaglandin biosynthesis in vitro [2, 3].

Table V. Incidence of gastrointestinal lesions in rats.

Compound	Dose mg/kg p.o.	Remarks at 6 h after treatment: % animals with	
		hyperaemia	ulcers
5a	100	30	20
5b	100	40	30
5c	100	40	30
5f	100	30	20
5g	100	50	40
6b	100	20	10
6c	100	30	10
7d	100	30	10
IMA	7.5	100	80

The third group of compounds described in the present paper were also tested in vitro for such inhibiting action. The most active compounds **5a**, **5b**, **5c**, **5f**, **5g**, **6c**, and the less active **5e**, **6g**, and **7e** were tested for their cyclooxygenase-inhibiting activity by measuring the rate of conversion of [1-^{14}C]arachidonic acid into PGE_2 in the microsomal fraction of mucosa preparations of rabbit distal colon after incubation with test compounds, following the method previously reported [2]. All compounds were found to be practically devoid of inhibitory activity, i.e. 0.9–9.5% relative to control, compared with 90–93% of indomethacin at the same concentration (10 μM).

Therefore also in the present case the remarkable antiinflammatory activity shown by these compounds was found to be independent of the cyclooxygenase inhibition, so that further investigations will be necessary in order to understand the mode of action of these imidazo-derivatives.

5. Experimental protocols

5.1. Chemistry

Thin layer cromatography by precoated silica gel plates (Merck 60 F254) was used to control the course of reactions and purity of the products: all compounds were designated as pure when they showed a single spot after elution with a chloroform/methanol mixture (95:5); detection of components was made by UV light and/or treatment with iodine vapors. Preparative separations were performed in columns packed with silica gel from Farmitalia Carlo Erba (RS, Ø mm 0.05:0.20). Melting points were determined with a Kofler hot stage microscope and are uncorrected. Elemental analyses indicated by the symbols of the elements were within ± 0.4% of the theoretical values.

The ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AMX-500 spectrometer equipped with a Bruker X-32 computer; chemical shift values are reported in δ units (ppm) relative to tetramethylsilane used as internal standard. Commercially available solvents and chemicals were used, with the exception of 2-amino-4-ethoxy-6-methylpyrimidine **3g**, which was prepared following the method reported.

5.2. Ethyl 2,7-dimethyl-5-methoxyimidazo[1,2-a]pyrimidine-3-carboxylate ***5a***

A solution of 2-amino-4-methoxy-6-methylpyrimidine **3a** (4 g, 0.028 mol) in 100 mL of methanol was added with 5.8 mL (6.9 g, 0.042 mol) of ethyl 2-chloroacetoacetate **4** and than stirred and refluxed for 40 h. After cooling, the solution was evaporated under reduced pressure to dryness and the residue was treated with $NaHCO_3$ saturated aqueous solution. This alkaline mixture was extracted three times with chloroform, the organic extract was combined, dried on Na_2SO_4 to dryness in vacuo up to a small volume and cromathographed in a silica gel column, eluting with diethyl ether/petroleum ether 4:1. The required **5a** was obtained in 10% yield; m.p. 114–116 °C (from *n*-hexane). Anal. $C_{12}H_{15}N_3O_3$ (C, H, N).

5.3. Ethyl 2-methyl-5,7-dimethoxyimidazo[1,2-a]pyrimidine-3-carboxylate ***5b***

A solution of 2-amino-4,6-dimethoxypyrimidine **3b** (4.3 g, 0.028 mol) in 100 mL of methanol was added with 5.8 mL (6.9 g, 0.042 mol) of **4** and then stirred in an oil bath at 160 °C for 36 h. After cooling, the solution was worked up as described for **5a**, to obtain the required **5b** in 10% yield; m.p. 128–130 °C (from *n*-hexane). Anal. $C_{12}H_{15}N_3O_4$ (C, H, N).

5.4. Ethyl 2,5,7-trimethylimidazo[1,2-a]pyrimidine-3-carboxylate ***5c***

A solution of 2-amino-4,6-dimethylpyrimidine **3c** (6.5 g, 0.053 mol) in 100 mL of anhydrous ethanol was added with 12 mL (14.3 g, 0.087 mol) of **4** and then stirred and refluxed for 30 h. After cooling, the solution was worked up as described for **5a**, to obtain the required **5c** in 20% yield; m.p. 183–185 °C. (from *n*-hexane). Anal. $C_{12}H_{15}N_3O_2$ (C, H, N).

5.5. Ethyl 2-methylimidazo[1,2-a]pyrimidine-3-carboxylate ***5d***

A solution of 2-aminopyrimidine **3d** (4 g; 0.042 mol) in 100 mL of anhydrous ethanol was added with 8.7 mL (10.35 g, 0.064 mol) of **4** and then stirred and refluxed for 36 h. After cooling, the solution was worked up as described for **5a**, to obtain the required **5d** in 20% yield; m.p. 101–102 °C (from *n*-hexane). Anal. $C_{10}H_{11}N_3O_2$ (C, H, N).

5.6. Ethyl 2,7-dimethylimidazo[1,2-a]pyrimidine-3-carboxylate ***5e*** *and ethyl 2,5-dimethylimidazo[1,2-a]pyrimidine-3-carboxylate* ***5f***

A solution of 2-amino-4-methylpyrimidine **3e** (4 g, 0.041 mol) in 100 mL of anhydrous ethanol was added with 8.6 mL (10.2 g, 0.063 mol) of **4** and then stirred and refluxed for 20 h. After cooling, the solution was evaporated under reduced pressure to dryness and the residue was treated with a $NaHCO_3$-saturated aqueous solution. This alkaline mixture was extracted three times with chloroform, the organic extracts were combined, dried on Na_2SO_4, concentrated in vacuo up to a small volume and chromatographed in a silica gel column, eluting with chloroform/*n*-hexane 4:1. By means of this procedure the compound **5e** was obtained in 18% yield; m.p. 148–150 °C (from *n*-hexane). TLC $R_f = 0.59$. Anal. $C_{11}H_{13}N_3O_2$ (C, H, N).

The above chromatographic procedure allowed us to isolate also **5f** in 2% yield; m.p. 137–139 °C (from *n*-hexane). TLC $R_f = 0.54$. Anal. $C_{11}H_{13}N_3O_2$ (C, H, N).

5.7. Ethyl 2,7-dimethyl-5-ethoxyimidazo[1,2-a]pyrimidine-3-carboxylate ***5g***

A solution of 2.5 g (0.1 mol) of sodium in 200 mL of anhydrous ethanol was added with 14 g (0.1 mol) of 2-amino-4-chloro-6-methylpyrimidine. The mixture was stirred and refluxed for 4 h. After cooling, the ethanol was removed in vacuo, and the crude product was crystallized from water, obtaining 2-amino-4-ethoxy-6-methylpyrimidine **3g** in 98% yield (from ethanol). Anal. $C_7H_{11}N_3O$ (C, H, N).

A solution of **3g** (7.4 g, 0.047 mol) in 100 mL of anhydrous ethanol was added with 10 mL (11.9 g, 0.073 mol) of **4** and then stirred and refluxed for 45 h. After cooling the solution was worked up as described for **5a**, to obtain the required **5g** in 10% yield; m.p. 103–105 °C (from *n*-hexane). Anal. $C_{13}H_{17}N_3O_3$ (C, H, N).

5.8. 2,7-Dimethyl-5-methoxyimidazo[1,2-a]pyrimidine-3-carboxylic acid ***6a***

A solution of 1 g of ester **5a** in 30 mL of ethanol and 6 mL of 4 N KOH solution was refluxed for 1.5 h. After cooling, ethanol was evaporated and the residual aqueous solution was acidified with 10% aqueous HCl to pH 4. The precipitate was filtered and recrystallized from ethanol to obtain **6a** in 90% yield; m.p. > 200 °C dec. Anal. $C_{10}H_{11}N_3O_3$ (C, H, N).

5.9. 2-Methyl-5,7-dimethoxyimidazo[1,2-a]pyrimidine-3-carboxylic acid ***6b***

A solution of 1 g of ester **5b** in 20 mL of methanol and 10 mL of 4 N KOH was refluxed for 4 h. The same procedure as described for **6a** afforded **6b** in 50% yield; m.p. > 200 °C dec. Anal. $C_{10}H_{11}N_3O_4$ (C, H, N).

5.10. 2,5,7-Trimethylimidazo[1,2-a]pyrimidine-3-carboxylic acid ***6c***

Starting from 1 g of ester **5c**, the same procedure as described for **6a** afforded **6c** in 85% yield; m.p. > 200 °C dec. Anal. $C_{10}H_{11}N_3O_2$ (C, H, N).

5.11. 2-Methylimidazo[1,2-a]pyrimidine-3-carboxylic acid ***6d***

Starting from 1 g of ester **5d**, the same procedure as described for **6a** afforded **6d** in 75% yield; m.p. > 200 °C dec. Anal. $C_8H_7N_3O_2$ (C, H, N).

5.12. 2,7-Dimethylimidazo[1,2-a]pyrimidine-3-carboxylic acid ***6e***

Starting from 1 g of ester **5e**, the same procedure as described for **6a** afforded **6e** in 75% yield, m.p. > 200 °C dec. Anal. $C_9H_9N_3O_2$ (C, H, N).

5.13. 2,7-Dimethyl-5-ethoxyimidazo[1,2-a]pyrimidine-3-carboxylic acid ***6g***

A solution of 1 g of ester **5g** in 10 mL of 5 N HCl solution was refluxed for 4 h. After cooling, the solution was added with $NaHCO_3$ up to pH 4. The precipitate was filtered and recrystallized from ethanol to obtain **6g** in 30% yield; m.p. > 200 °C dec. Anal. $C_{11}H_{13}N_3O_3$ (C, H, N).

5.14. 2-Methylimidazo[1,2-a]pyrimidine-3-carboxamide ***7d***

A solution of 1 g of acid **6d** in 20 mL of $SOCl_2$ was refluxed and stirred for 3 h. After cooling, the solution was evaporated under reduced pressure to dryness and the residue was dissolved in $CHCl_3$ and treated with gaseous NH_3 for 2 h. The required product **7d** was obtained as a precipitate which was collected, dried and recrystallized from ethanol to obtain **7d** in 25% yield; m.p. > 200 °C dec. Anal. $C_8H_8N_4O$ (C, H, N).

5.15. 2,7-Dimethylimidazo[1,2-a]pyrimidine-3-carboxamide ***7e***

Starting from 1 g of acid **6e**, the same procedure described for **7d** afforded **7e** in 20% yield, m.p. > 200 °C dec. Anal. $C_9H_{10}N_4O$ (C, H, N).

Acknowledgements

The NMR spectra were performed at the 'Centro di Ricerca Interdipartimentale di Analisi Strumentale', Università di

Napoli Federico II. The assistance of the Staff was highly appreciated. This research has been financially supported by the National Research Council (CNR – Rome) and the Italian Ministry of University and Scientific and Technological Research (MURST – Rome).

References

[1] Abignente E., Actual. Chim. Thér. 18 (1991) 193–214.
[2] Abignente E., Sacchi A., Laneri S., Rossi F., D'Amico M., Berrino L., Calderaro V., Parrillo C., Eur. J. Med. Chem. 29 (1994) 279–286.
[3] Sacchi A., Laneri S., Arena F., Luraschi E., Abignente E., D'Amico M., Berrino L., Rossi F., Eur. J. Med. Chem. 32 (1997) 677–682.
[4] Hand E.S., Paudler W.W., Org. Magn. Res. 14 (1980) 52–54.
[5] Abignente E., Arena F., De Caprariis P., Patscot R., Marmo E., Lampa E., Rossi F., Eur. J. Med. Chem. 20 (1985) 79–85.
[6] Abignente E., De Caprariis P., Fattorusso E., Mayol L., J. Heterocycl. Chem. 26 (1989) 1875–1880.
[7] Rimoli M.G., Avallone L., De Caprariis P., Luraschi E., Abignente E., Filippelli W., Berrino L., Rossi F., Eur. J. Med. Chem. 32 (1997) 195–203.
[8] Pugmire R.J., Smith J.C., Grant D.M., Stanovnik B., Tisler M., Vercek B., J. Heterocycl. Chem. 24 (1987) 805–809.
[9] Winter C.A., Risley E.A., Nuss G.W., Proc. Soc. Exp. Biol. Med. 111 (1962) 544–547.
[10] Davies J.E., Kellet D.N., Pennington J.C., Arch. Int. Pharmacodyn. Ther. 221 (1976) 274–282.
[11] Calderaro V., Parrillo C., Giovane A., Greco R., Matera M.G., Berrino L., Rossi F., J. Pharmacol. Exp. Ther. 263 (1992) 579–587.