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Short communication

Potential anti-tumor agents XVI. Imidazo[2,1-*b*]thiazoles

Aldo ANDREANI[1], Mirella RAMBALDI[1], Franco ANDREANI[2], Rosaria BOSSA[3] and Iraklis GALATULAS[3]

[1] *Dipartimento di Scienze Farmaceutiche, University of Bologna, Via Belmeloro 6, 40126 Bologna,*
[2] *Dipartimento di Chimica Industriale e dei Materiali, University of Bologna, Viale del Risorgimento 4, 40136 Bologna, and*
[3] *Dipartimento di Farmacologia, C.T.M., University of Milano, Via Vanvitelli 32, 20129 Milano, Italy*

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Summary — A number of imidazo[2,1-*b*]thiazoles have been synthesized and tested in mice bearing Ehrlich ascites tumor cells. The nitrogen mustard **5** had a *T/C* of 140 at 8 mg/kg.

Résumé — **Agents potentiels anti-tumoraux XVI. Imidazo[2,1-*b*]thiazoles.** *Un certain nombre d'imidazo[2,1-b]thiazoles ont été synthétisés et essayés sur la Souris portant des cellules de tumeur ascitique d'Ehrlich. La moutarde à l'azote* **5** *a montré un* T/C *de 140 à 8 mg/kg.*

imidazo[2,1-*b*]thiazoles / anti-tumor activity

Introduction

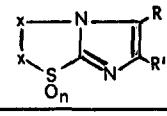
In the continuation of our research on new anti-tumor agents [1—5], we have further investigated the potential of imidazo[2,1-*b*]thiazole as a supporting moiety for a number of selected pharmacophoric functions. Since this heterocycle constitutes the main part of levamisole, a well-known immunomodulator [6], the possibility of reducing the harmful effects of the cytotoxic agents on the immune system could be seriously taken into account. In fact, the aim of this research was to discover a lead compound with a 2-fold action: first it could show anti-tumor activity and later, through one of its metabolites, it could restore the depressed immune system. With this in mind, a select number of substituted imidazo[2,1-*b*]thiazoles have been prepared (**1**—**14**: see Table I).

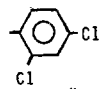
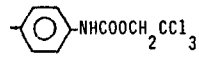
The first group of compounds consists of four chloroethylcarbamates (**1**—**4**) and one bis-chloroethylamino derivative (**5**) prepared as potential alkylating agents. Compound **6** is a thiosemicarbazone of an α-*N*-heterocyclic carboxaldehyde; many examples of the activity of this class of compounds have been reported in the literature, since Brockman *et al.* first discovered the anti-tumor activity of 2-formylpyridine thiosemicarbazone [7]. Compounds **7** and **8** bear a carboxylic group and a 2,4-dichlorophenyl group, as in the anti-tumor agent lonidamine [8]. In compound **9**, the same group present in lotifazole [9] has been introduced. The amidoximes **10** and **11** were designed according to a paper by Flora *et al.* [10], whereas the nitrovinyl derivatives **12**—**14** were prepared as potential cytotoxic agents [11].

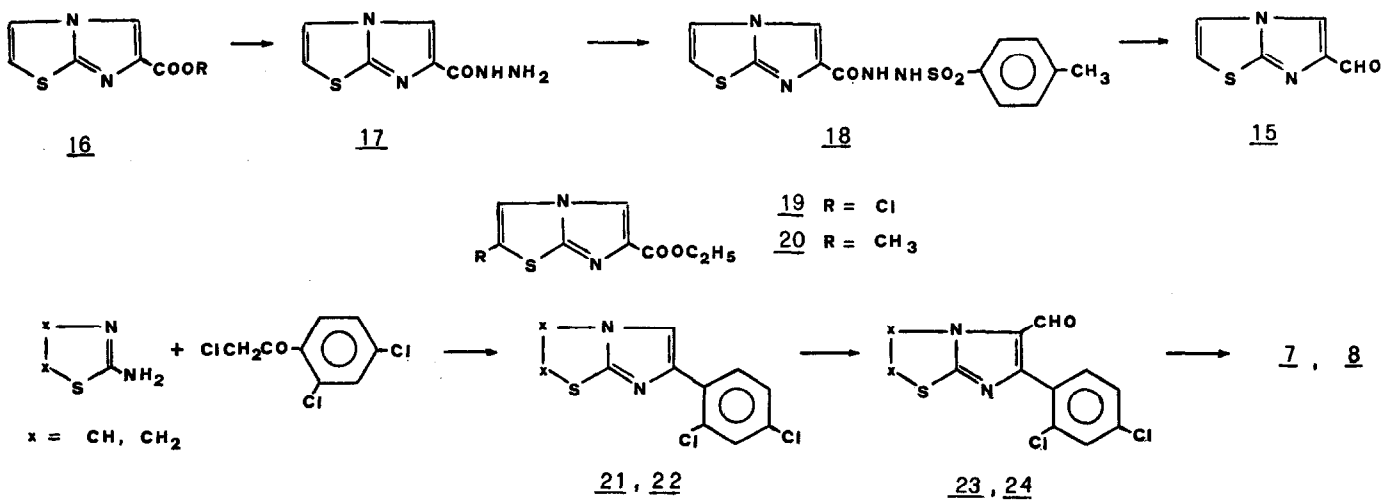
Chemistry

The chloroethyl carbamates **1**—**4** were prepared by reacting the corresponding hydroxymethyl derivatives [3] with 2-chloroethyl isocyanate. The bis-chloroethylamino derivative **5** was prepared by means of a Mannich reaction on the 6-chloroimidazo[2,1-*b*]thiazole [12]. The thiosemicarbazone **6** was obtained from the aldehyde **15** (see Scheme 1). In 1979, we reported an attempt to prepare compound **15** by oxidizing the 6-methylimidazo[2,1-*b*]-thiazole [13]. After other unsuccessful attempts, we were finally able to synthesize the aldehyde **15** by reducing the ester **16** [14, 15], using the method reported by McFadyen and Stevens and Mosettig [16, 17]. The synthesis of two analogs of **16** (**19** and **20**) is reported under Experimental protocols, whereas the corresponding aldehyde and thiosemicarbazones were not synthesized because of the inactivity of the only one prepared (**6**). The carboxylic acids **7** and **8** were prepared by oxidizing the corresponding 5-formyl derivatives **23** and **24** with $KMnO_4$, according to a method previously reported [18]: with this procedure, in the 2,3-dihydro derivatives, the oxidation of the formyl group takes place with the contemporaneous oxidation of the sulfur in position 1. Compound **9** was obtained from the 6-*p*-aminophenylimidazo[2,1-*b*]thiazoline which, in turn, was prepared from the corresponding nitro derivative [19]. The amidoximes **10**—**11** were prepared from the nitriles [20], whereas the starting material for the nitrovinyl derivatives **12**—**14** was, of course, the corresponding aldehyde [2].

Table I. Imidazo[2,1-*b*]thiazoles **1—14.**



Compound	n	x	R	R'	Formula (mw)	Anal.	Mp(°C)	Recrys.solvent
1	0	CH	$CH_2OCONHCH_2CH_2Cl$	-Cl	$C_9H_9Cl_2N_3O_2S$ (294.2)	C,H,N	98-100	EtOH
2	0	CH	"	$-C_6H_5$	$C_{15}H_{14}ClN_3O_2S$ (335.8)	"	140-141d	"
3	0	CH_2	"	-Cl	$C_9H_{11}Cl_2N_3O_2S$ (296.2)	"	95-97	"
4	0	CH_2	"	$-C_6H_5$	$C_{15}H_{16}ClN_3O_2S$ (337.8)	"	142-145d	"
5	0	CH_2	$CH_2N(CH_2CH_2Cl)_2$	-Cl	$C_{10}H_{14}Cl_3N_3S$ (314.7)	"	108-110	"
6	0	CH	H	$-CH=NNHCSNH_2$	$C_7H_7N_5S_2$ (225.3)	"	208-210d	MeOH/AcOEt
7	0	CH	COOH		$C_{12}H_6Cl_2N_2O_2S$ (313.2)	"	222-226d	EtOH
8	2	CH_2	"	"	$C_{12}H_8Cl_2N_2O_4S$ (347.2)	"	263-265d	"
9	0	CH_2	H		$C_{14}H_{12}Cl_3N_3O_2S$ (392.7)	"	195-200d	"
10	0	CH		-Cl	$C_6H_5ClN_4OS$ (216.6)	"	166-168d	"
11	0	CH_2	"	"	$C_6H_7ClN_4OS$ (218.7)	"	150-155d	"
12	0	CH_2	$CH=CHNO_2$	"	$C_7H_6ClN_3O_2S$ (231.7)	"	184-186	MeOH
13	0	CH_2	"	$-CH_3$	$C_8H_9N_3O_2S$ (211.2)	"	157-160	"
14	0	CH_2	"	$-C_6H_5$	$C_{13}H_{11}N_3O_2S$ (273.3)	"	185-188	"



Scheme 1.

Pharmacological results

Compounds **1**—**14** were tested in mice bearing Ehrlich ascites tumor cells (see Experimental protocols). The nitrogen mustard **5** is the only compound that showed significant anti-tumor activity: the *T/C* was 140 at the dose of 8 mg/kg and 130 at 1.6 mg/kg.

It is interesting to point out the particular behavior of the amidoximes **10** and **11** in this test: at a single dose of 5—10 mg/kg, i.p., the animals showed strong, tonic-clonic convulsions followed by death. An excessive central nervous system stimulation had even been reported for the amidoximes described in the paper we previously cited [10]. A study of the pharmacological profile of these two derivatives is in progress, in order to evaluate their usefulness in the test of new anti-convulsant agents.

Experimental protocols

Chemistry

The melting points are uncorrected. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. Baker-flex plates (silica gel IB2-F) were used for TLC: the eluent was a mixture of petroleum ether/acetone in various proportions. Unless otherwise noted, the IR were recorded in nujol on a Perkin—Elmer 298. The ^{1}H NMR were recorded on a Varian EM-390 (90 MHz) using tetramethylsilane as the internal standard; the solvent was $CDCl_3$ for compounds **12**—**14** and DMSO-d_6 for all the others.

Synthesis of the chloroethyl carbamates 1—4
10 mmol of the 6-substituted 5-hydroxymethylimidazo[2,1-*b*]thiazole [3] were dissolved in tetrahydrofuran (THF) (30—100 ml) and treated with 10 mmol of triethylamine and 18 mmol of 2-chloroethyl isocyanate. The reaction mixture was refluxed for 3—8 h (according to a thin—layer chromatography (TLC) test), evaporated under reduced pressure and crystallized. The expected product was obtained with a yield of 70—80% (see Tables I, II).

2,3-Dihydro-5-bischloroethylaminomethyl-6-chloroimidazo[2,1-b]thiazole 5
2,3-Dihydro-6-chloroimidazo[2,1-*b*]thiazole [12] (20 mmol), dissolved in 25 ml of CH_3OH, was treated with CH_3COOH (4 ml), 40% HCHO (2 ml) and bis(2-chloroethyl)amine hydrochloride (23 mmol). The mixture was refluxed for 7 h and methanol was eliminated under reduced pressure; water was added and the resulting precipitate was collected and crystallized (35% yield) (see Tables I, II).

Synthesis of the esters 16 [14, 15], 19 and 20
The appropriate 2-aminothiazole (0.05 mol), dissolved in 25 ml of THF, was treated dropwise (4 h *ca.*), under vigorous stirring, with a solution of ethyl bromopyruvate (0.05 mol) in THF (50 ml). The reaction mixture was refluxed for 1 h and THF was eliminated under reduced pressure. The residue was dissolved in 100 ml of $CHCl_3$, washed with N NaOH (3×20 ml), with N HCl and finally with H_2O. After treatment with Na_2SO_4 and evaporation of the solvent, the ester was crystallized with a yield of 30—33%.
2-Chloroimidazo[2,1-b]thiazole-6-carboxylic acid ethylester 19. Anal. $C_8H_7ClN_2O_2S$ (230.7): C, H, N. mp: 210—212°C (AcOEt). ν_{max} (cm^{-1}): 1720, 1210, 990, 755. δ (ppm): 1.27 (3H, t, CH_3, J = 7 Hz); 4.28 (2H, q, CH_2, J = 7 Hz); 8.30 (1H, s, th); 8.41 (1H, s, im).
2-Methylimidazo[2,1-b]thiazole-6-carboxylic acid ethylester 20. Anal. $C_9H_{10}N_2O_2S$ (210.3): C, H, N. mp: 189—191°C (AcOEt). ν_{max} (cm^{-1}): 1710, 1510, 1200, 1125. δ (ppm): 1.37 (3H, t, CH_2CH_3, J = 7 Hz); 2.47 (3H, d, CH_3-2, J = 1.5 Hz); 4.35 (2H, q, CH_2CH_3, J = 7 Hz); 7.78 (1H, q, th, J = 1.5 Hz); 8.38 (1H, s, im).

Imidazo[2,1-b]thiazole-6-carboxylic acid hydrazide 17
The ester **16** (10 mmol) was suspended, under stirring, in 15 ml of water and refluxed for 5 h with 40 mmol of hydrazine hydrate. The crude hydrazide was collected, washed with water and dried (82% yield). Anal. $C_6H_6N_4OS$ (182.2): C, H, N. mp: 228—230°C. ν_{max} (cm^{-1}): 3250, 1655, 1545, 1245. δ (ppm): 4.41 (2H, s, NH_2); 7.37 (1H, d, th, J = 4.5 Hz); 7.98 (1H, d, th, J = 4.5 Hz); 8.24 (1H, s, im); 9.36 (1H, s, NH).

Imidazo[2,1-b]thiazole-6-carboxylic acid tosylhydrazide 18
The hydrazide **17** (15 mmol) was stirred in 30 ml of anhydrous pyridine

Table II. IR and ^{1}H NMR of compounds **1**—**14**.

Compound	$\nu_{max.}$ (cm^{-1})	δ (ppm): th = thiazole thn = thiazoline im = imidazole
1	3210,1710,1240,970	3.35(2H,m,CH_2) 3.62(2H,m,CH_2) 5.30(2H,s,CH_2O) 7.48(1H,d,th,J=4.5Hz) 7.60(1H,t,NH) 8.03(1H,d,th,J=4.5Hz)
2	3200,1710,1550,1250	3.35(2H,m,CH_2) 3.62(2H,m,CH_2) 5.40(2H,s,CH_2O) 7.35(1H,d,th,J=4.5Hz) 7.65(5H,m,ar.+1H,NH) 8.05(1H,d,th,J=4.5Hz)
3	3300,1700,1550,1265	3.30(2H,m,CH_2) 3.60(2H,m,CH_2) 3.90(2H,m,thn) 4.25(2H,m,thn) 4.98(2H,s,CH_2O) 7.58(1H,t,NH)
4	3180,1705,1545,1250	3.30(2H,m,CH_2) 3.60(2H,m,CH_2) 3.90(2H,m,thn) 4.28(2H,m,thn) 5.10(2H,s,CH_2O) 7.50(5H,m,ar.+1H,NH)
5	1220,1105,720,640	2.80(4H,t,2xCH_2,J=6.5Hz) 3.60(4H,t,2xCH_2,J=6.5Hz) 3.65(2H,s,CH_2) 3.85(2H,m,thn) 4.25(2H,m,thn)
6	3120,1605,1315,1160	7.38(1H,s,CH) 7.52(1H,d,th,J=4.5Hz) 8.12(1H,d,th,J=4.5Hz) 8.20(2H,broad,NH_2) 8.31(1H,s,im) 12.75(1H,s,NH)
7	3200-2200,1710,1235,1115	7.55(2H,s,ar.) 7.60(1H,d,th,J=4.5Hz) 7.73(1H,s,ar.) 8.28(1H,d,th,J=4.5Hz)
8	3100-2200,1725,1330,1125	4.30(2H,m,thn) 4.88(2H,m,thn) 7.57(2H,s,ar.) 7.78(1H,s,ar.)
9	3370,1720,1530,1220	4.03(2H,m,thn)4.38(2H,m,thn)5.15(2H,s,CH_2)7.80(2H,d,ar.,J=10Hz)7.90(1H,s,im)8.0(2H,d,ar.,J=10Hz)10.50(1H,s,NH)
10	3440,1640,1230,940	5.80(2H,s,NH_2) 7.50(1H,d,th,J=4.5Hz) 8.10(1H,d,th,J=4.5Hz) 10.05(1H,s,NOH)
11	3460,1630,1235,935	3.85(2H,m,thn) 4.30(2H,m,thn) 5.65(2H,s,NH_2) 9.90(1H,s,NOH)
12	1625,1320,1230,955	3.94(2H,m,thn) 4.37(2H,m,thn) 7.58(1H,d,CH,J=14Hz) 7.90(1H,d,CH,J=14Hz)
13	1600,1295,1240,1200	2.38(3H,s,CH_3) 3.92(2H,m,thn) 4.35(2H,m,thn) 7.30(1H,d,CH,J=14Hz) 7.98(1H,d,CH,J=14Hz)
14	1605,1300,1230,955	3.98(2H,m,thn) 4.42(2H,m,thn) 7.38(1H,d,CH,J=14Hz) 7.55(5H,m,ar.) 8.14(1H,d,CH,J=14Hz)

and treated portionwise with an equivalent of *p*-toluenesulfonyl chloride. Stirring was maintained for 4 h at room temperature and the reaction mixture was then poured into 250 ml of 2 N HCl. The crude hydrazide thus obtained was collected and washed with water (89% yield): it was pure enough for the subsequent step. Anal. $C_{13}H_{12}N_4O_3S_2$ (336.4): C, H, N. mp: 176—178°C (dil. EtOH). ν_{max} (cm^{-1}): 3140, 1660, 1545, 1160. δ (ppm): 2.34 (3H, s, CH_3); 7.36 (2H, d, ar, J = 8 Hz); 7.42 (1H, d, th, J = 4.5 Hz); 7.76 (2H, d, ar, J = 8 Hz); 7.97 (1H, d, th, J = 4.5 Hz); 8.25 (1H, s, im); 9.85 (1H, s, NH); 10.15 (1H, s, NH).

*6-Formylimidazo[2,1-*b*]thiazole* **15**
The tosylhydrazide **18** (10 mmol) was heated under stirring in 30 ml of ethylene glycol. When the temperature of 130°C was reached, anhydrous K_2CO_3 (30 mmol) was added portionwise. After 5 min at 130—140°C, the mixture was poured into water and extracted with chloroform. The crude aldehyde thus obtained was crystallized (46% yield) and analyzed. Anal. $C_6H_4N_2OS$ (152.2): C, H, N. mp: 147—150°C (AcOEt). ν_{max} (cm^{-1}): 1680, 1515, 1155, 675 (KBr). δ (ppm): 7.52 (1H, d, th, J = 4.5 Hz); 8.08 (1H, d, th, J = 4.5 Hz); 8.60 (1H, s, im); 9.95 (1H, s, CHO).

*6-Formylimidazo[2,1-*b*]thiazole thiosemicarbazone* **6**
The aldehyde **15** (4 mmol) in 70 ml of CH_3OH and 0.5 ml of CH_3COOH, was treated with an equivalent of thiosemicarbazide and refluxed for 5 h. The precipitate produced after cooling was collected and crystallized (see Tables I, II).

*6-(2,4-Dichlorophenyl)imidazo[2,1-*b*]thiazole* **21** *and 2,3-dihydro-6-(2,4-dichlorophenyl)imidazo[2,1-*b*]thiazole* **22**
30 mmol of 2-aminothiazole (or 2-amino-2-thiazoline) were dissolved in 150 ml of acetone, treated with the equivalent of 2,2',4'-trichloroacetophenone and refluxed for 48 **(21)** or 1 h **(22)**. The precipitate was collected and refluxed for 2 h with 200 ml of 2 N HCl. The solution of the hydrochloride thus formed was basified with 20% NH_4OH. The crude base was collected, washed with water and crystallized.
21. (30% yield) Anal. $C_{11}H_6Cl_2N_2S$ (269.1): C, H, N. mp: 182—185°C (EtOH). ν_{max} (cm^{-1}): 1530, 1190, 1030, 720. δ (ppm): 7.37 (1H, d, th, J = 4.5 Hz); 7.52 (1H, dd, ar, J = 9 Hz, J = 2 Hz); 7.69 (1H, d, ar, J = 2 Hz); 8.0 (1H, d, th, J = 4.5 Hz); 8.23 (1H, d, ar, J = 9 Hz); 8.48 (1H, s, im).
22. (40% yield) Anal. $C_{11}H_8Cl_2N_2S$ (271.2): C, H, N. mp: 118—120°C (EtOH). ν_{max} (cm^{-1}): 1535, 1190, 1030, 760. δ (ppm): 3.92 (2H, m, thn); 4.27 (2H, m, thn); 7.44 (1H, dd, ar, J = 9 Hz, J = 2 Hz); 7.59 (1H, d, ar, J = 2 Hz); 7.93 (1H, s, im); 8.10 (1H, d, ar, J = 9 Hz).

*5-Formyl-6-(2,4-dichlorophenyl)imidazo[2,1-*b*]thiazole* **23** *and 2,3-dihydro-5-formyl-6-(2,4-dichlorophenyl)imidazo[2,1-*b*]thiazole* **24**
The Vilsmeier reagent was prepared, under cooling and stirring, by dropping 50 mmol of $POCl_3$ onto the equivalent of dimethylformamide (DMF). The temperature was maintained between 5 and 10°C and a solution of compound **21** or **22** (10 mmol in 50 ml of $CHCl_3$ and 3 ml of pyridine) was added dropwise. After 1 h at room temperature, the reaction mixture was refluxed for 9 h; $CHCl_3$ was eliminated under reduced pressure and the residue was poured onto ice. The precipitate thus formed was collected and crystallized.
23. (90% yield) Anal. $C_{12}H_6Cl_2N_2OS$ (297.2): C, H, N. mp: 178—180°C (EtOH). ν_{max} (cm^{-1}): 1635, 1320, 1250, 785. δ (ppm): 7.60 (1H, dd, ar, J = 9 Hz, J = 2 Hz); 7.70 (1H, d, th, J = 4.5 Hz); 7.78 (1H, d, ar, J = 9 Hz); 7.88 (1H, d, ar, J = 2 Hz); 8.46 (1H, d, th, J = 4.5 Hz); 9.67 (1H, s, CHO).
24. (64% yield) Anal. $C_{12}H_8Cl_2N_2OS$ (299.2): C, H, N. mp: 155—157°C (EtOH). ν_{max} (cm^{-1}): 1645, 1360, 1320, 1130. δ (ppm): 4.07 (2H, m, thn); 4.56 (2H, m, thn); 7.60 (2H, m, ar); 7.80 (1H, m, ar); 9.47 (1H, s, CHO).

*6-(2,4-Dichlorophenyl)imidazo[2,1-*b*]thiazole-5-carboxylic acid* **7** *and 2,3-dihydro-6-(2,4-dichlorophenyl)imidazo[2,1-*b*]thiazole-1,1-dioxide-5-carboxylic acid* **8**
15 mmol of the aldehyde **23** (or **24**) were dissolved in 500 ml of acetone and treated with a solution of $KMnO_4$ (70 mmol) in 100 ml of water. The mixture was stirred at room temperature for 15 h, destained with 4% H_2O_2 and filtered. Acetone was eliminated from the filtrate and the resulting solution acidified with 2 N HCl. The crude acid thus obtained was crystallized with a yield of 38% **(7)** and 77% **(8)** (see Tables I, II).

*2,3-Dihydro-6-(*p*-trichloroethoxycarboxamido)phenylimidazo[2,1-*b*]thiazole* **9**
3 mmol of 2,3-dihydro-6-*p*-aminophenylimidazo[2,1-*b*]thiazole **(19)**, dissolved in 15 ml of pyridine, were treated dropwise, under stirring, with 3.2 mmol of 2,2,2-trichloroethyl chloroformate. The reaction mixture was stirred at room temperature for 30 min and poured into water. The resulting precipitate was purified by crystallization (65% yield) (see Tables I, II).

Synthesis of the amidoximes **10** *and* **11**
10 mmol of 5-cyano-6-chloroimidazo[2,1-*b*]thiazole or thiazoline **(20)** were dissolved in 100 ml of EtOH and treated with a solution of NH_2OH (prepared from 15 mmol of $NH_2OH{\cdot}HCl$, 10 ml of water and Na_2CO_3 until basic). The mixture was refluxed for 2 h and evaporated under reduced pressure; water was added and the precipitate was crystallized with a yield of 45 **(10)** and 52% **(11)** (see Tables I, II).

Synthesis of the nitrovinyl derivatives **12—14**
The appropriate aldehyde **(2)** (8 mmol) was treated with 100 mmol of CH_3NO_2 and 10 mmol of CH_3COONH_4. After 30 min at 100°C, the mixture was evaporated and the residue crystallized with a yield of 30—35% (see Tables I, II).

Pharmacology

Eight female Swiss mice (average weight 21±1 g) were implanted with 10^6 Ehrlich ascites tumor cells from donor mice. After 24 h, the animals were treated i.p. with a single dose (200 mg/kg) of the test compound **(1—14)** dissolved in dimethyl sulfoxide (DMSO): the amount of DMSO, previously used in analogous experiments, did not affect tumor growth. If the dose proved to be toxic or active, the test was repeated at lower doses with other groups of eight mice. Deaths were recorded for a period of 60 days. The activity was measured as the ratio of the mean survival time of the test animals to that of the control (10 mice) expressed as a percentage (% *T/C*). Significant activity is considered as 25% increase in the life span ($T/C \geqslant 125$).

Acknowledgments

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