Notes

Potential Antitumor Agents. 24.[1] Synthesis and Pharmacological Behavior of Imidazo[2,1-*b*]thiazole Guanylhydrazones Bearing at Least One Chlorine

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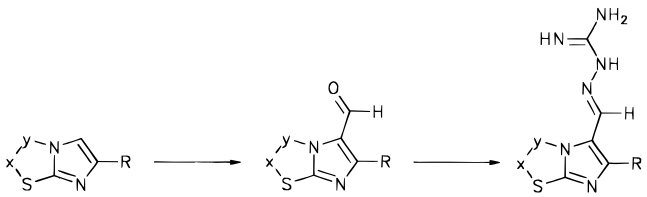
In connection with a previous research dealing with the antitumor activity of imidazo[2,1-*b*]-thiazole guanylhydrazones, this paper reports the synthesis of new derivatives which were tested for antitumor and positive inotropic activity. In most cases the cytotoxic data from the *in vitro* experiments (HeLa) were in agreement with the antitumor data *in vivo* (Ehrlich). The active compounds bear a phenyl ring at the 6 position. On the other hand, the most active cardiotonic agents were devoid of the phenyl ring.

In a previous paper of this series,[2] we briefly reviewed the pharmacological behavior of guanylhydrazones (in the meantime exhaustive reviews on the medicinal chemistry of amidines/imidates,[3] amidinohydrazones,[4,5] amidines/guanidines,[6] and thiosemicarbazones[7] have been published) and reported synthesis, configuration, and antitumor activity of a number of imidazo[2,1-*b*]-thiazole guanylhydrazones **3** (Scheme 1) where x = y = CH or CH_2.

Taking into account that some guanylhydrazones have been reported as cardiotonic agents,[8−10] we decided to test even the positive inotropic activity of our compounds. We demonstrated that a potent cardiotonic agent can antagonize[11] the cardiotoxicity of doxorubicin,[12−16] and we pointed out[17] that a molecule endowed with both antitumor and cardiotonic activity could be useful to potentiate the antitumor activity of doxorubicin (thus allowing the reduction of its dosage) and to counteract its harmful effects on the heart. While a search for such a molecule in the field of phenothiazine derivatives was unsuccessful,[17] we obtained the first encouraging result with some of the aforementioned[2] imidazo[2,1-*b*]thiazole guanylhydrazones. As a result of this research, we found that only compounds bearing a chlorine or a chlorophenyl group at position 6 could be useful for both the activities.[18]

In this paper we wish to describe a new series of compounds **3** with the imidazo[2,1-*b*]thiazole (x = CH) or thiazoline (x = CH_2) moiety bearing two or three chlorine atoms at the phenyl ring (**3a**−**d**, see Table 1) in order to study the influence of the substituents at the 6 position while maintaining, at the 2−3 positions, the same groups present in the previously described compounds.[2] Moreover we prepared a series of compounds **3** bearing different substituents at the 2−3 positions (**3e**−**l**) in order to see the influence of these groups while maintaining, at the 6 position, the same pharmacophores (Cl and 4-ClC_6H_4) present in the aforementioned antitumor agents.[2]

Scheme 1[a]



1 2 3

[a] For R, x, and y, see Table 1.

Chemistry

The guanylhydrazones **3a**−**l** were prepared by reaction of aminoguanidine with the appropriate aldehydes **2a**−**l**. Some of them are reported in the literature (see Table 1), and the others are described in the Experimental Section starting from the corresponding imidazo-[2,1-*b*]thiazoles **1**.

As we demonstrated for analogous guanylhydrazones, even compounds **3a**−**l** belong to the *E* configuration since they show the same spectroscopic features previously reported[2] and, in particular, (1) NOE (useful in the study of configuration) and (2) ^{1}H-NMR spectra of the hydrochlorides different from those of the bases (useful data in the determination of the tautomeric forms).

Pharmacological Results

Compounds **3a**−**l** were subjected to a cytotoxic test *in vitro* (HeLa cells), to an antitumor test *in vivo* (Ehrlich ascites in mice), and to a cardiotonic test on isolated guinea pig atria. From the results of these tests, reported in Table 3, it is evident that the phenyl ring (**3a**−**d,f,h,j,l**) is essential to the cytotoxic and antitumor activity since all the 6-chloro derivatives (**3e,g,i,k**) were inactive. The introduction of more than one chlorine on the phenyl ring (**3a**−**d**) does not bring an improvement in the antitumor activity compared to the monochlorophenyl derivatives previously tested.[2] Generally speaking, the compounds devoid of cytotoxic

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Table 1. Guanylhydrazones **3a**−**l**

compd	x	y	R	starting compd 1	starting compd 2	formula (MW)	mp, °C
3a	CH	CH	2,4-$Cl_2C_6H_3$	**1a**[a]	**2a**[a]	$C_{13}H_{10}Cl_2N_6S\cdot 2HCl\cdot H_2O$ (444.2)	298−302 dec
3b	CH	CH	2,3,4-$Cl_3C_6H_2$	**1b**	**2b**	$C_{13}H_9Cl_3N_6S\cdot 2HCl\cdot H_2O$ (478.6)	308−310 dec
3c	CH_2	CH_2	2,4-$Cl_2C_6H_3$	**1c**[a]	**2c**[a]	$C_{13}H_{12}Cl_2N_6S\cdot 2HCl\cdot H_2O$ (446.2)	265−270 dec
3d	CH_2	CH_2	2,3,4-$Cl_3C_6H_2$	**1d**	**2d**	$C_{13}H_{11}Cl_3N_6S\cdot 2HCl\cdot H_2O$ (480.6)	215−220 dec
3e	CCH_3	CH	Cl	**1e**[b]	**2e**[b]	$C_8H_9ClN_6S\cdot HCl\cdot 2H_2O$ (329.2)	168−170 dec
3f	CCH_3	CH	4-ClC_6H_4	**1f**[c]	**2f**[b]	$C_{14}H_{13}ClN_6S\cdot HCl\cdot 2H_2O$ (405.3)	298−300 dec
3g	CH	CCH_3	Cl	**1g**[d]	**2g**	$C_8H_9ClN_6S\cdot 2HCl\cdot H_2O$ (347.6)	205−207 dec
3h	CH	CCH_3	4-ClC_6H_4	**1h**[e]	**2h**	$C_{14}H_{13}ClN_6S\cdot 2HCl\cdot H_2O$ (423.7)	244−246 dec
3i	CCH_3	CCH_3	Cl	**1i**[f]	**2i**	$C_9H_{11}ClN_6S\cdot HCl\cdot H_2O$ (325.2)	210−215 dec
3j	CCH_3	CCH_3	4-ClC_6H_4	**1j**	**2j**	$C_{15}H_{15}ClN_6S\cdot 2HCl\cdot H_2O$ (437.8)	258−260
3k	CCl	CH	Cl	**1k**[f]	**2k**	$C_7H_6Cl_2N_6S\cdot HCl\cdot H_2O$ (331.6)	195−198 dec
3l	CCl	CH	4-ClC_6H_4	**1l**	**2l**	$C_{13}H_{10}Cl_2N_6S\cdot 2HCl\cdot H_2O$ (444.2)	310−313 dec

[a] Reference 19. [b] Reference 20. [c] Reference 21. [d] Reference 22. [e] Reference 23. [f] Reference 24.

Table 2. IR and ^{1}H-NMR Data of the Guanylhydrazones **3a**−**l** as Hydrochlorides

compd	IR:[a] ν_{max}, cm^{-1}	^{1}H-NMR:[b] δ, ppm
3a	1680, 1630, 1490, 1165	7.59 (1H, d, th, J = 4.4), 7.60 (2H, s, ar), 7.85 (1H, s, ar), 8.07 (1H, s CH), 8.73 (1H, d, th, J = 4.4)
3b	1680, 1605, 1160, 840	7.58 (1H, d, ar, J = 8.4), 7.59 (1H, d, th, J = 4.5), 7.80 (1H, d, ar, J = 8.4), 8.07 (1H, s, CH), 8.73 (1H, d, th, J = 4.4)
3c	1680, 1610, 1160, 1105	4.04 (2H, t, thn, J = 7.4), 4.66 (2H, t, thn, J = 7.4), 7.50 (1H, d, ar, J = 8), 7.55 (1H, dd, ar, J = 2, 8), 7.79 (1H, d, ar), 7.88 (1H, s, CH)
3d	1675, 1620, 1500, 1170	4.04 (2H, t, thn, J = 7.4), 4.66 (2H, t, thn, J = 7.4), 7.49 (1H, d, ar, J = 8.4), 7.77 (1H, d, ar, J = 8.4), 7.90 (1H, s, CH)
3e	1670, 1620, 1245, 1155	2.50 (3H, d, CH_3, J = 1.5), 8.26 (1H, s, CH), 8.43 (1H, q, th, J = 1.5)
3f	1680, 1625, 1600, 1165	2.50 (3H, d, CH_3, J = 1.5), 7.53 (2H, d, ar, J = 8), 7.69 (2H, d, ar, J = 8), 8.43 (1H, q, th, J = 1.5), 8.46 (1H, s, CH)
3g	1675, 1630, 1500, 1340	2.58 (3H, d, CH_3, J = 1.5), 7.13 (1H, q, th, J = 1.5), 8.50 (1H, s, CH)
3h	1675, 1620, 1515, 1190	2.57 (3H, d, CH_3, J = 1.5), 7.10 (1H, q, th, J = 1.5), 7.54 (2H, d, ar, J = 8), 7.72 (2H, d, ar, J = 8), 8.50 (1H, s, CH)
3i	1670, 1610, 1265, 1130	2.35 (3H, s, CH_3), 2.48 (3H, s, CH_3), 8.50 (1H, s, CH)
3j	1680, 1600, 1510, 1090	2.38 (3H, s, CH_3), 2.47 (3H, s, CH_3), 7.52 (2H, d, ar, J = 8), 7.71 (2H, d, ar, J = 8), 8.51 (1H, s, CH)
3k	1675, 1620, 1240, 1150	8.30 (1H, s, CH), 8.90 (1H, s th)
3l	1680, 1600, 1490, 1165	7.56 (2H, d, ar, J = 8), 7.71 (2H, d, ar, J = 8), 8.48 (1H, s, CH), 8.90 (1H, s, th)

[a] The NH group give broad bands in the range 3600−2300 cm^{-1}. [b] The NH groups give a broad signal at ∼8 ppm (3H) and a singlet at ∼12 ppm (1H). Abbreviations: th = thiazole, thn = thiazoline, ar = aromatic.

Table 3. Pharmacological Activity of Compounds **3a**−**l**

compd	HeLa IC_{50} (μg)	Ehrlich % T/C	Ehrlich mg/kg ip	E_{max} (mean of 3−4 atria) % Δ from base line value = 100[a]	E_{max} (mean of 3−4 atria) conctn to obtain E_{max} (μg)	EC_{50}	Δ rate (%)
3a	2.5	146	25	100 ± 0			
3b	2	180	12.5	100 ± 0			
3c	5	200	50	119 ± 3	20	6	−30
3d	2.5	166	50	111 ± 4	20	9	−13
3e	>10	106	50	146 ± 3	16	4	−21
3f	1.5	166	6.25	106 ± 3	10	0.5	−11
3g	>10	106	50	134 ± 3	16	3	−26
3h	2	133	25	115 ± 0	16	4	−29
3i	>10	100	50	137 ± 3	8	3	−20
3j	2	140	12.5	118 ± 2	20	9	−17
3k	>10	120	100	135 ± 1	16	3	−34
3l	0.6	166	12.5	100 ± 0			
5-fluorouracil	6	180	100				
doxorubicin	0.005	200	1				
sulmazole				163 ± 9	350	15	

[a] Initial contractile force: 0.4 ± 0.1 g.

and antitumor activity (**3e,g,i,k**) were the most active cardiotonic agents even though a negative chronotropic effect was observed in all the experiments (see Table 3). The simultaneous presence of both antitumor and borderline positive inotropic activity was confirmed in compounds **3c,j**.

As far as the substituents at the 2−3 positions are concerned, it is interesting to point out that, contrary to the unsubstituted compounds previously described,[2,18] in the analogs bearing one or two substituents (**3e**−**l**) a separation between the two activities was observed. The chlorophenyl derivatives (**3f,h,j,l**) showed mainly cytotoxic (HeLa) and antitumor (Ehrlich) activity, whereas the chloro derivatives (**3e,g,i,k**) showed cardiotonic activity only.

Experimental Section

Chemistry. The melting points are uncorrected. Elemental analyses (C, H, N) were within ±0.4% of the theoretical values. Bakerflex plates (silica gel IB2-F) were used for TLC; the eluent was a mixture of petroleum ether (60−80 °C)/acetone in the proportion of 50/50 (containing 0.1% of concentrated NH_4OH for the guanylhydrazones which were analyzed as free bases). The IR spectra were recorded in Nujol on a Perkin-Elmer 298 spectrometer; the ^{1}H-NMR spectra were

recorded in DMSO-d_6 ($CDCl_3$ for compound **2b** only) on a Varian Gemini spectrometer (300 MHz), and J values are reported in hertz (Hz).

Synthesis of the Imidazo[2,1-*b*]thiazoles 1. The appropriate 2-aminothiazole or thiazoline (20 mmol) was dissolved in acetone (100 mL) and treated with the equivalent of the appropriate 2-bromoacetophenone. The mixture was refluxed for 6−8 h, and the resulting salt was collected by filtration, washed with acetone, and refluxed for 2 h with 500 mL of 1 N HBr. Before complete cooling, the resulting solution was cautiously basified with 20% NH_4OH, in order to precipitate the crude compound **1** which was crystallized from ethanol with a yield of 50−60%.

6-(2,3,4-Trichlorophenyl)imidazo[2,1-*b*]thiazole (1b): $C_{11}H_5Cl_3N_2S$ (303.6); mp 202−205 °C; ν_{max} 1550, 1520, 1200, 640 cm^{-1}; δ (ppm) 7.36 (1H, d, th, J = 4.4), 7.72 (1H, d, ar, J = 8.8), 7.98 (1H, d, th, J = 4.4), 8.14 (1H, d, ar, J = 8.8), 8.52 (1H, s, H-5).

6-(2,3,4-Trichlorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (1d): $C_{11}H_7Cl_3N_2S$ (305.6); mp 175−177 °C; ν_{max} 1530, 1355, 1210, 830 cm^{-1}; δ (ppm) 3.93 (2H, t, thn, J = 7.4), 4.27 (2H, t, thn, J = 7.4), 7.63 (1H, d, ar, J = 8.8), 8.02 (1H, d, ar, J = 8.8), 8.02 (1H, s, H-5).

6-(4-Chlorophenyl)-2,3-dimethylimidazo[2,1-*b*]thiazole (1j): $C_{13}H_{11}ClN_2S$ (262.8); mp 190−194 °C dec; ν_{max} 1535, 1085, 825, 725 cm^{-1}; δ (ppm) 2.32 (3H, s, CH_3), 2.33 (3H, s, CH_3), 7.43 (2H, d, ar, J = 8), 7.83 (2H, d, ar, J = 8), 8.22 (1H, s, H-5).

2-Chloro-6-(4-chlorophenyl)imidazo[2,1-*b*]thiazole (1l): $C_{11}H_6Cl_2N_2S$ (269.1); mp 220−225 °C dec; ν_{max} 1535, 1185, 1090, 1000, 830, 730 cm^{-1}; δ (ppm) 7.47 (2H, d, ar, J = 8), 7.87 (2H, d, ar, J = 8), 8.31 (1H, s, th), 8.34 (1H, s, H-5).

Synthesis of the Aldehydes 2. The Vilsmeier reagent was prepared at 0−5 °C by dropping $POCl_3$ (20 mmol) into a stirred solution of DMF (25 mmol) in $CHCl_3$ (5 mL). Compound **1** (10 mmol) in $CHCl_3$ (60 mL) was added dropwise to the Vilsmeier reagent while maintaining stirring and cooling. The reaction mixture was kept for 3 h at room temperature and under reflux for 8 h. Chloroform was removed under reduced pressure, and the resulting oil was poured onto ice. The crude aldehyde **2** thus obtained was collected by filtration and crystallized from ethanol with a yield of 60−70%.

6-(2,3,4-Trichlorophenyl)imidazo[2,1-*b*]thiazole-5-carboxaldehyde (2b): $C_{12}H_5Cl_3N_2OS$ (331.6); mp 255−258 °C; ν_{max} 1655, 1320, 1265, 1180 cm^{-1}; δ (ppm) 7.15 (1H, d, th, J = 4.4), 7.45 (1H, d, ar, J = 8.4), 7.55 (1H, d, ar, J = 8.4), 8.39 (1H, d, th, J = 4.4), 9.64 (1H, s, CHO).

6-(2,3,4-Trichlorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole-5-carboxaldehyde (2d): $C_{12}H_7Cl_3N_2OS$ (333.6); mp 209−212 °C dec; ν_{max} 1650, 1310, 1295, 1180 cm^{-1}; δ (ppm) 4.06 (2H, t, thn, J = 7.4), 4.52 (2H, t, thn, J = 7.4), 7.58 (1H, d, ar, J = 8.4), 7.77 (1H, d, ar, J = 8.4), 9.39 (1H, s, CHO).

6-Chloro-3-methylimidazo[2,1-*b*]thiazole-5-carboxaldehyde (2g): $C_7H_5ClN_2OS$ (200.6); mp 153−155 °C dec; ν_{max} 1660, 1350, 1315, 1270 cm^{-1}; δ (ppm) 2.68 (3H, s, CH_3), 7.21 (1H, s, th), 9.73 (1H, s, CHO).

6-(4-Chlorophenyl)-3-methylimidazo[2,1-*b*]thiazole-5-carboxaldehyde (2h): $C_{13}H_9ClN_2OS$ (276.7); mp 197−200 °C; ν_{max} 1665, 1400, 1340, 830 cm^{-1}; δ (ppm) 2.72 (3H, s, CH_3), 7.15 (1H, s, th), 7.57 (2H, d, ar, J = 8), 7.84 (2H, d, ar, J = 8), 9.73 (1H, s, CHO).

6-Chloro-2,3-dimethylimidazo[2,1-*b*]thiazole-5-carboxaldehyde (2i): $C_8H_7ClN_2OS$ (214.7); mp 130−134 °C; ν_{max} 1670, 1300, 1270, 855 cm^{-1}; δ (ppm) 2.37 (3H, s, CH_3), 2.60 (3H, s, CH_3), 9.72 (1H, s, CHO).

6-(4-Chlorophenyl)-2,3-dimethylimidazo[2,1-*b*]thiazole-5-carboxaldehyde (2j): $C_{14}H_{11}ClN_2OS$ (290.8); mp 210−214 °C; ν_{max} 1665, 1340, 1320, 1090 cm^{-1}; δ (ppm) 2.40 (3H, s, CH_3), 2.65 (3H, s, CH_3), 7.57 (2H, d, ar, J = 8), 7.83 (2H, d, ar, J = 8), 9.71 (1H, s, CHO).

2,6-Dichloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde (2k): $C_6H_2Cl_2N_2OS$ (221.1); mp 180−183 °C; ν_{max} 1650, 1500, 1295, 1255 cm^{-1}; δ (ppm) 8.64 (1H, s, th), 9.75 (1H, s, CHO).

2-Chloro-6-(4-chlorophenyl)imidazo[2,1-*b*]thiazole-5-carboxaldehyde (2l): $C_{12}H_6Cl_2N_2OS$ (297.2); mp 178−180 °C dec; ν_{max} 1650, 1400, 1340, 1315 cm^{-1}; δ (ppm) 7.58 (2H, d, ar, J = 8), 7.91 (2H, d, ar, J = 8), 8.65 (1H, s, th), 9.89 (1H, s, CHO).

Synthesis of the Guanylhydrazones 3. The appropriate aldehyde **2** (5 mmol) was dissolved in 150 mL of ethanol and treated with 5 mmol of aminoguanidine hydrochloride, prepared in turn from an ethanol suspension of aminoguanidine bicarbonate and excess of 37% hydrochloric acid. The reaction mixture was refluxed for 30 min, and the resulting precipitate was collected by filtration with a yield of 80−90% (see Tables 1 and 2).

Pharmacology. (a) *In Vitro* Antitumor Activity. Stock cultures of HeLa cells were plated on Falcon plastic dishes (150 cells/plate) in MEM (minimum essential medium; Whittaker-M.A. Bioproducts) and incubated at 37 °C in 5% CO_2. The compounds under test, dissolved in DMSO (1−10 μL/mL), were added directly to the growth medium after 48 h; the amount of DMSO, previously used in analogous experiments, did not affect cell growth. At the end of the drug exposure period (48 h), the growth medium was removed and a new medium was added. Colonies that contained more than 50 cells were counted after 7 days of incubation, and IC_{50} values were calculated. Compounds displaying $IC_{50} < 4$ μg/mL are considered significantly active.

(b) *In Vivo* Antitumor Activity. One group of animals included 10 female Swiss mice (average weight 24 ± 1 g) which were implanted with 10^6 Ehrlich ascites tumor cells from donor mice. After 24 h each group was treated ip with a single dose (100 mg/kg) of the test compound dissolved in DMSO (0.05 mL/mouse); the amount of DMSO, previously used in analogous experiments, did not affect tumor growth. If the dose was toxic or active, the test was repeated at halved doses (range 100−3.125 mg/kg). Deaths were recorded for a period of 40 days. The activity was measured as the ratio of the mean survival time of the test animals to that of the control (10 mice receiving vehicle only) expressed as a percentage (% T/C). Significant activity is achieved as 25% increase in the life span (T/C ≥ 125).

(c) Positive Inotropic Activity. The experiments were carried out on spontaneously beating guinea pig (300−450 g of body weight) atria. The preparation was suspended at 37 °C in a 20 mL bath of Tyrode solution (composition in g/L: NaCl, 8.0; $NaHCO_3$, 1.0; KCl, 0.2; NaH_2PO_4, 0.005; $MgCl_2$, 0.1; $CaCl_2$, 0.2; glucose, 1.0). An initial tension of 1 g was applied to the preparation. Isometric contractions were recorded by a strain gauge transducer connected to a recording microdynamometer. After taking basal responses, the test compounds were added to the preparation at 5−800 μmol on a cumulative basis, and the responses were recorded. The contact time for each dose was 5 min. Concentrations producing 50% of the maximal effect (EC_{50}) were calculated from concentration−response curves.[25]

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