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Short communication

Synthesis and cardiotonic activity of imidazo[2,1-*b*]thiazoles bearing a lactam ring

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Summary — This paper describes the synthesis of 6-substituted imidazo[2,1-*b*]thiazoles with a lactam ring connected, by means of a methine group, to the 5-position. The pharmacological results show that interesting cardiotonic activity is obtained when the lactam ring is pseudothiohydantoin (**8**) or barbituric acid (**9**). Even the substituent at position 6 plays an important role in the pharmacological behavior of these derivatives. The following activity rank order was observed: phenyl > methyl > chlorine.

imidazo[2,1-*b*]thiazole / lactam / 2,5-dimethoxyphenyl / cardiotonic activity

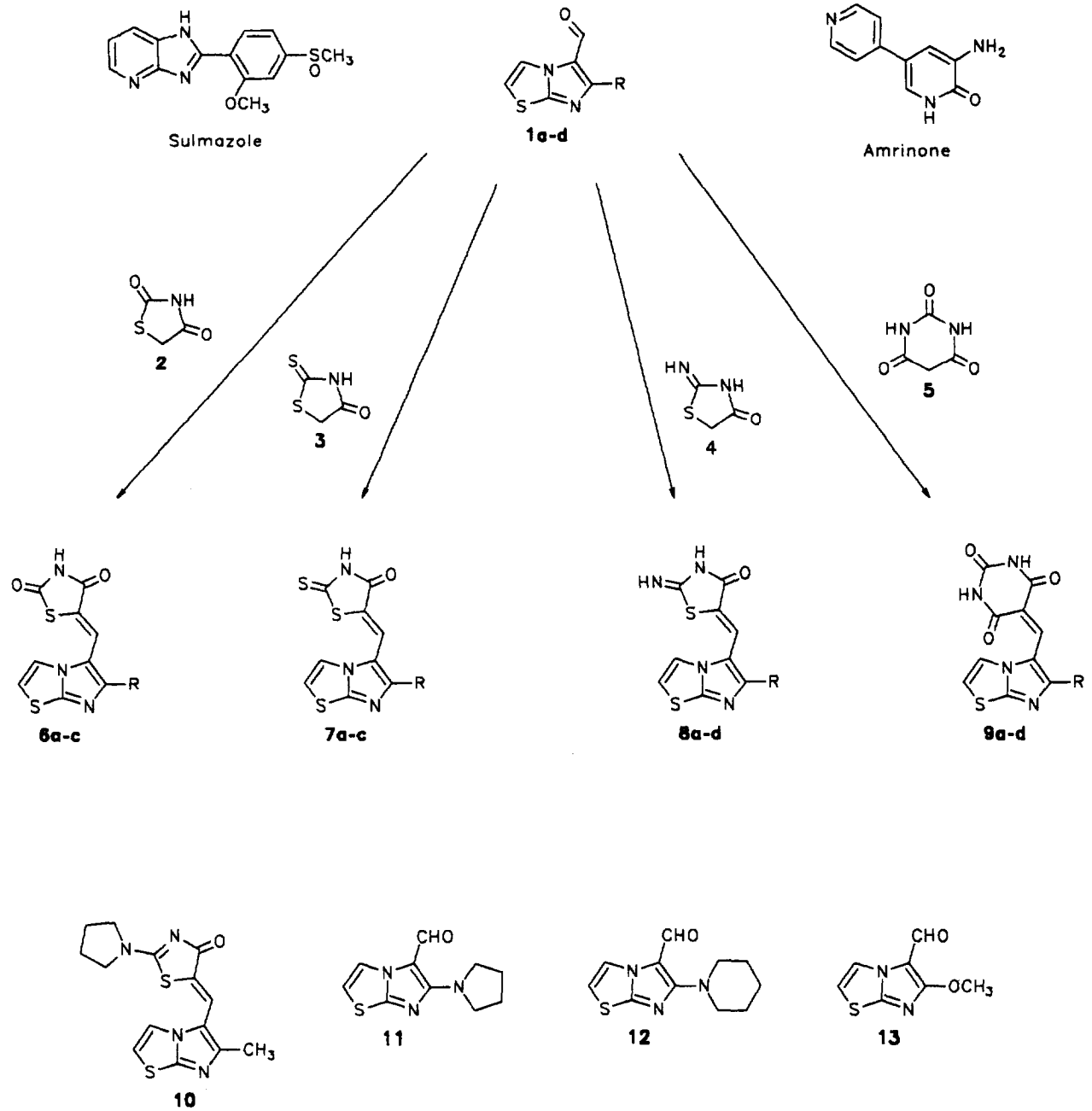
Introduction

In our first paper on positive inotropic agents [1], sulmazole (scheme 1) was taken as the reference for the synthesis of imidazo[2,1-*b*]thiazoles; to this project we dedicated six additional papers [2–7]. In another series of works [8–11] amrinone was taken as the reference for the synthesis of compounds containing a lactam ring. The present paper may be considered the intersection of the two previous projects, as the compounds here described are 6-substituted imidazo[2,1-*b*]thiazoles connected, by means of a methine group, to a lactam ring (scheme 1).

Chemistry

For the Knoevenagel reaction between the aldehyde (**1a–d**) and the lactam (**2–5**), five different methods were considered. These methods are reported in detail in the *Experimental protocols* and may be summarized as follows: 1: pyrrolidine with water separator; 2: acetic acid and sodium acetate; 3: piperidine; 4: sodium methoxide; 5: glycine. First of all we prepared and tested compounds **6a–c**–**9a–c**. As the pharmacological data indicated that compounds arising from thiazolidine-2,4-dione **2** (**6a–c**) and 2-thioxothiazolidine-4-one **3** (**7a–c**) were inactive, we decided to prepare the 2,5-dimethoxyphenyl derivatives only from 2-iminothiazolidine-4-one **4** (**8d**) and pyrimidine-2,4,6-trione **5** (**9d**); the 2,5-dimethoxyphenyl group, as shown in our previous papers [3, 6–8, 11], is a suitable pharmacophore in the design of new positive inotropic agents. As far as geometrical isomers are concerned, from every reaction we isolated one isomer only and we believe that these compounds belong to the configuration depicted in scheme 1 (ie, *Z*) for the same reasons we previously discussed for analogous derivatives [11].

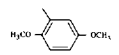
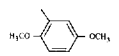
For compounds **6a–c** and **7a** we chose method 1. For compounds **7b,c**, **8b–d** and **9a–c** we employed method 2. An attempt to prepare **7b** with method 1 resulted in elimination of H_2S and formation of a compound which was characterized as **10**. This same compound was isolated in an attempt to prepare **8b** with method 1 (elimination of NH_3 instead of H_2S). Compound **9d** was prepared with method 3. An attempt to prepare compound **9d** with method 2 produced cleavage of the bond at position 5 with formation of 2,5-dimethoxyphenylimidazo[2,1-*b*]-thiazole [3]. The first four methods were unsuccessful for the synthesis of compound **8a**. With methods 1, 3 and 4 the only compounds isolated resulted from substitution of chlorine at position 6, with formation of **11**, **12** and **13** respectively, whereas, with method 2, only traces of reaction products were detected by TLC. Finally compound **8a** was obtained by means of method 5.



Scheme 1. (R see table I.)

The spectroscopic data of compounds **6–13** are in agreement with the assigned structures. All the compounds show C=O stretching bands (table I) and compounds **6–9** also show NH absorption bands. In the ^{1}H-NMR spectra (table II) the methine group is always a sharp singlet at ~8 ppm, whereas the NH groups are broad singlets in the region of 9 ppm (**8**), 11 ppm (**9**), 12 ppm (**6**) and 13 ppm (**7**). The imidazo[2,1-*b*]thiazole proton at position 2 ranges from 7.35–7.58 ppm, while the neighbouring proton

Table I. Compounds **6–13**.

Compound	*R*	*Formula*	*Mw*	*Method*	*Mp (°C)*	*Solvent*	$\nu_{max}(cm^{-1})$[a]
6a	-Cl	$C_9H_4ClN_3O_2S_2$	285.7	1	265–268 dec	–	1735, 1690, 1605, 1245
6b	$-CH_3$	$C_{10}H_7N_3O_2S_2$	265.3	1	295–297 dec	EtOH	1750, 1710, 1600, 1300
6c	$-C_6H_5$	$C_{15}H_9N_3O_2S_2$	327.3	1	312–315 dec	EtOH	1725, 1685, 1600, 1290
7a	-Cl	$C_9H_4ClN_3OS_3$	301.8	1	270–275 dec	–	1710, 1595, 1255, 1195
7b	$-CH_3$	$C_{10}H_7N_3OS_3$	281.4	2	305–309 dec	–	1690, 1590, 1270, 1180
7c	$-C_6H_5$	$C_{15}H_9N_3OS_3$	343.4	2	312–315 dec	–	1685, 1590, 1260, 1200
8a	-Cl	$C_9H_5ClN_4OS_2$	284.7	5	287–292 dec	EtOH	1660, 1600, 1530, 1240
8b	$-CH_3$	$C_{10}H_8N_4OS_2$	264.3	2	260–265 dec	EtOH	1655, 1600, 1520, 1235
8c	$-C_6H_5$	$C_{15}H_{10}N_4OS_2$	326.4	2	278–280 dec	EtOH	1675, 1625, 1595, 1545
8d		$C_{17}H_{14}N_4O_3S_2$	386.4	2	240–245 dec	EtOH	1680, 1605, 1525, 1220
9a	-Cl	$C_{10}H_5ClN_4O_3S$	296.7	2	> 315	AcOH	1755, 1690, 1665, 1575
9b	$-CH_3$	$C_{11}H_8N_4O_3S$	276.3	2	> 315	DMF	1740, 1685, 1660, 1570
9c	$-C_6H_5$	$C_{16}H_{10}N_4O_3S$	338.3	2	> 315	–	1745, 1695, 1640, 1550
9d		$C_{18}H_{14}N_4O_5S$	398.4	3	270–275 dec	–	1740, 1690, 1635, 1550
10	–	$C_{14}H_{14}N_4OS_2$	318.4	1	286–288 dec	EtOH	1670, 1600, 1560, 1230
11	–	$C_{10}H_{11}N_3OS$	221.3	1	231–235 dec	–	1675, 1610, 1570, 1240
12	–	$C_{11}H_{13}N_3OS$	235.3	3	241–244 dec	EtOH	1680, 1540, 1335, 1240
13	–	$C_7H_6N_2O_2S$	182.2	4	127–130	EtOH	1640, 1525, 1320, 1280

[a]The NH groups are in the range 3300–2500 cm^{-1}.

(position 3) is in the region of 8.02–8.36 ppm, except in the four compounds **9** (7.58–7.64 ppm) where it is shielded by the pyrimidine ring.

The following mass spectra were also recorded: **6a**: 285 ($M^{\ddagger}$, 30), 250 (M–Cl, 27), 216 (40), 214 (100); **6b**: 265 ($M^{\ddagger}$, 84), 221 (M–CO_2, 83), 194 (89), 193 (100); **7a**: 301 ($M^{\ddagger}$, 5), 266 (M–Cl, 5), 214 (17), 180 (8), 76 (100); **7b**: 281 ($M^{\ddagger}$, 88), 194 (98), 193 (100); **8a**: 284 ($M^{\ddagger}$, 14), 249 (M–Cl, 32), 214 (55), 180 (27), 76 (100), 60 (86); **9b**: 276 ($M^{\ddagger}$, 100), 261 (M–CH_3, 11), 259 (17), 161 (14), 85 (10), 58 (17); **10**: 318 ($M^{\ddagger}$, 43), 222 (15), 196 (12), 195 (15), 194 (100), 193 (74).

Pharmacological results

Compounds **1–10** were tested in spontaneously-beating guinea-pig atria according to the procedures described in the *Experimental protocols*. Table III shows the results obtained in comparison with sulmazole. As we mentioned above, compounds **6a–c** and **7a–c** were inactive whereas the by-product **10** and all the compounds arising from 2-iminothiazolidine-4-one (**8a–d**) and from pyrimidine-2,4,6-trione (**9a–d**) showed positive inotropic activity. As far as the effect of the substituent at the 6-position is concerned, chlorine is the least suitable, while

Table II. ^{1}H-NMR of compounds **6–13**.

Compound	*δ (ppm) J (Hz in DMSO–d_6)* [a]
6a	7.53 (1H, d, th-2, J = 4.5), 7.83 (1H, s, -CH=), 8.20 (1H, d, th-3, J = 4.5)
6b	2.34 (3H, s, CH_3), 7.37 (1H, d, th-2, J = 4.5), 7.87 (1H, s, -CH=), 8.05 (1H, d, th-3, J = 4.5)
6c	7.43 (3H, m, ar), 7.46 (1H, d, th-2, J = 4.4), 7.57 (2H, m, ar), 8.03 (1H, s, -CH=), 8.17 (1H, d, th-3, J = 4.4)
7a	7.55 (1H, d, th-2, J = 4.5), 7.71 (1H, s, -CH=), 8.28 (1H, d, th-3, J = 4.5)
7b	2.38 (3H, s, CH_3), 7.40 (1H, d, th-2, J = 4.5), 7.71 (1H, s, -CH=), 8.11 (1H, d, th-3, J = 4.5)
7c	7.46 (3H, m, ar), 7.50 (1H, d, th-2, J = 4.6), 7.58 (2H, m, ar), 7.91 (1H, s, -CH=), 8.26 (1H, d, th-3, J = 4.6)
8a	7.51 (1H, d, th-2, J = 4.5), 7.62 (1H, s, -CH=), 8.17 (1H, d, th-3, J = 4.5)
8b	2.34 (3H, s, CH_3), 7.35 (1H, d, th-2, J = 4.5), 7.65 (1H, s, -CH=), 8.02 (1H, d, th-3, J = 4.5)
8c	7.41 (3H, m, ar), 7.43 (1H, d, th-2, J = 4.4), 7.60 (2H, m, ar), 7.80 (1H, s, -CH=), 8.09 (1H, d, th-3, J = 4.4)
8d	3.59 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 7.00 (3H, m, ar), 7.41 (1H, d, th-2, J = 4.5), 7.76 (1H, s, -CH=), 8.16 (1H, d, th-3, J = 4.5)
9a	7.58 (1H, d, th-2, J = 4.4), 7.64 (1H, d, th-3, J = 4.4), 8.05 (1H, s, -CH=)
9b	2.50 (3H, s, CH_3), 7.43 (1H, d, th-2, J = 4.4), 7.58 (1H, d, th-3, J = 4.4), 8.19 (1H, s, -CH=)
9c	7.48 (1H, d, th-2, J = 4.5), 7.56 (3H, m, ar), 7.62 (1H, d, th-3, J = 4.5), 7.66 (2H, m, ar), 8.03 (1H, s, -CH=)
9d	3.68 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 7.10 (3H, m, ar), 7.48 (1H, d, th-2, J = 4.4), 7.59 (1H, d, th-3, J = 4.4), 8.07 (1H, s, -CH=)
10	2.01 (4H, qui, pyr), 2.36 (3H, s, CH_3), 3.57 (2H, t, pyr), 3.69 (2H, t, pyr), 7.37 (1H, d, th-2, J = 4.5), 7.68 (1H, s, -CH=), 8.05 (1H, d, th-3, J = 4.5)
11	1.99 (4H, qui, pyr), 3.58 (2H, t, pyr), 3.69 (2H, t, pyr), 7.51 (1H, d, th-2, J = 4.5), 7.64 (1H, s, CHO), 8.19 (1H, d, th-3, J = 4.5)
12	1.65 (6H, m, pip), 3.56 (2H, t, pip), 3.88 (2H, t, pip), 7.51 (1H, d, th-2, J = 4.5), 7.64 (1H, s, CHO), 8.19 (1H, d, th-3, J = 4.5)
13	4.05 (3H, s, OCH_3), 7.48 (1H, d, th-2, J = 4.3), 8.22 (1H, d, th-3, J = 4.3), 9.51 (1H, s, CHO)

[a]th = imidazo[2,1-*b*]thiazole, ar = aromatic, pyr = pyrrolidine, pip = piperidine. For the NH groups see text.

the methyl group is associated to compound **8b** which was interesting but less active than compounds bearing the phenyl group (**8c**, **9c**). The introduction of methoxy groups at the 2,5-positions produced less potent compounds **8d**, **9d** in comparison to the unsubstituted 6-phenyl derivatives **8c**, **9c** and, contrary to our previous series of imidazo[2,1-*b*]thiazoles [3], did not afford a significant improvement in activity.

Table III. Positive inotropic activity of compounds **8–10**.

Compound	EC_{50} (*μmol*)	E_{max} *(mean of 3 or 4 atria)*[a]	
		% Δ from baseline value = 0[b]	*Concentration to obtain E_{max} (μmol)*
8a	–	20 ± 1	28
8b	13	42 ± 5	60
8c	7	54 ± 7	24
8d	49	54 ± 8	207
9a	–	17 ± 7	27
9b	9	28 ± 6	22
9c	16	61 ± 5	47
9d	45	65 ± 12	201
10	9	23 ± 4	50
Sulmazole	15	63 ± 9	350

[a]Chronotropic effect was not significant (±15%). [b]Initial contractile force = 0.65 ± 0.15 g.

Experimental protocols

Chemistry

The melting points are uncorrected. Analyses (C, H, N) were within ±0.4% of the theoretical values. TLC was performed on Bakerflex plates (Silica gel IB2-F); the eluent was a mixture of petroleum ether (bp 60–80 °C) and acetone in various proportions. Kieselgel 60 (Merck) was used for column chromatography. The IR spectra were recorded in Nujol on a Perkin-Elmer 683. The ^{1}H-NMR spectra were recorded on a Varian Gemini (300 MHz), using TMS as the internal standard. The EI-MS were recorded at 70 eV on a VG 7070E. The starting aldehydes **1a–d** were prepared according to the literature [6, 12, 13] and the lactams were commercially available: thiazolidine-2,4-dione **2**, 2-thioxothiazolidine-4-one (rhodanine) **3**, 2-iminothiazolidine-4-one (pseudothiohydantoin) **4** and pyrimidine-2,4,6-trione (barbituric acid) **5**.

The Knoevenagel reaction between the aldehyde and the lactam was performed with one or more of the following methods until the expected compound was isolated. This means that we did not test all the methods for all the reactions; ie, the yields could be improved.

*Method 1: preparation of **6a–c, 7a, 10** and **11***
The aldehyde (16 mmol) was treated with pyrrolidine (18 mmol) in toluene (150 mL) and refluxed for 1 h under a water separator (Dean–Stark trap). The lactam (16 mmol) was then added to the solution of the enamine thus formed and the mixture was refluxed for 4 h. After cooling, the resulting precipitate was collected by filtration. The yields for compounds **6a–c** and **7a** were 35–40%; for compound **10** it was 20% and for **11** it was 10%.

*Method 2: preparation of **7b,c, 8b–d, 9a–c***
The aldehyde (15 mmol) was treated with 14.5 mmol of the lactam, 30 mmol of anhydrous sodium acetate and 130 mL of acetic acid. The reaction mixture was refluxed for 0.5–12 h, according to a TLC test. Acetic acid was removed under reduced pressure and the residue was poured into ice water. The resulting precipitate was recovered by filtration with a yield of 50–60% (**7b,c, 8b**) and 80–90% (**9a–c**); compounds **8c,d** purified by column chromatography, were obtained with a yield of 10–15%.

*Method 3: preparation of **9d, 12***
The lactam (10 mmol) was dissolved in methanol (100 mL) and treated with the aldehyde (10 mmol) and piperidine (2 mL). The reaction mixture was refluxed for 5 h, cooled and concentrated under reduced pressure. The resulting precipitate was collected by filtration. In the reaction with barbituric acid for the synthesis of **9d**, a piperidine salt was obtained which was dissolved in methanol and treated with 2N HCl [11]: the resulting precipitate was compound **9d** in almost quantitative yields. Compound **12** was separated by column chromatography with a yield of 15%.

*Method 4: preparation of **13***
The aldehyde (12 mmol) was dissolved in methanol and treated dropwise with the solution of the lactam in sodium methoxide (from 24 mmol of sodium and 70 mL of methanol). The reaction mixture was refluxed for 6 h, cooled and evaporated under reduced pressure. The residue was treated with water and the resulting precipitate was collected. Compound **13** was obtained with a yield of 50%.

*Method 5: preparation of **8a***
The aldehyde was added to a solution of glycine (10 mmol) and anhydrous potassium carbonate (5 mmol) in water (20 mL); the resulting mixture was added to the lactam (10 mmol) and refluxed under stirring for 4 h. After cooling, the product was recovered by filtration. Compound **8a** was separated by column chromatography with a yield of 20%.

Pharmacology

The experiments were carried out on spontaneously-beating guinea-pig (400–600 g 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 5–300 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 [14].

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