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Cardiotonic Activity of 2,5-Dimethoxyphenylimidazo[2,1-*b*]-thiazoles+

Aldo Andreani, Mirella Rambaldi, Daniela Bonazzi

Istituto di Chimica Farmaceutica e Tossicologica, University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy

Rosaria Bossa and Iraklis Galatulas*

Dip. di Farmacologia, C., T. Medica, University of Milano, via Vanvitelli 32, 20129 Milano, Italy
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We report about the synthesis and the activities of imidazo[2,1-*b*]thiazoles and -thiazolines bearing a 2,5-dimethoxyphenylgroup at position 6. The inotropic activity was investigated in isolated guinea pig atria. Compound **10** shows a strong positive inotropic activity: it increases the myocardial contractility in normal and hypodynamic heart muscle.

Die cardiotonische Wirkung von 2,5-Dimethoxyphenylimidazo[2,1-*b*]thiazolen

In Fortsetzung unserer Bemühungen, neue positiv inotrope Substanzen zu erhalten, berichten wir über die Synthese und die cardiotonische Aktivität von Imidazo[2,1-*b*]thiazolen und -thiazolinen, die in 6-Stellung eine 2,5-Dimethoxyphenylgruppe tragen. Die inotrope Aktivität wurde am Vorhof isolierten des Meerschweinchenherzens getestet. Verbindung **10** zeigte eine stark positiv inotrope Wirkung: sie verstärkte die Kontraktionskraft sowohl des normalen als auch des insuffizienten Herzmuskels.

+ Dedicated to Professor *Teodoro Pozzo Balbi* on the occasion of his 70th birthday

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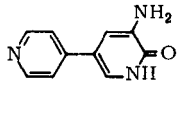
The treatment of cardiac failure is still one of the major therapeutic problems in clinical practice. Despite the development of potent arterial and venous vasodilators there remains a need for compounds with positive inotropic action. Digitalis is the standard inotropic agent for enhancement of myocardial contractility and improvement of heart function in congestive heart failure.

The primary limitation of digitalis is the narrow margin of safety; on the other hand the use of known sympathomimetic agents is limited due to positive chronotropic activity, arrhythmogenic properties and oral ineffectiveness.

The search for new orally active inotropic agents has led to the development of amrinone **(1)**[1], sulmazole **(2)**[2] and imidazolones **3**[3].



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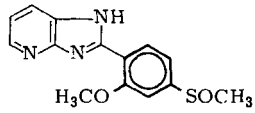

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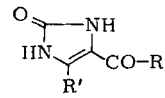

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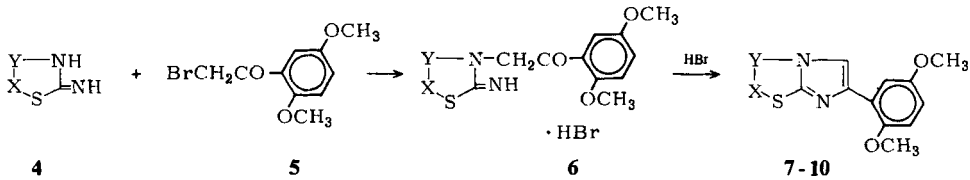
In pursuing our research on pharmacologically active imidazo[2,1-*b*]thiazoles and thiazolines we described the synthesis and cardiotonic activity of compounds related to sulmazole with the substitution of the imidazo[4,5-*b*]pyridine moiety by an imidazo[2,1-*b*]thiazole skeleton[4]. In this paper we report the synthesis and the inotropic activity of analogous imidazo[2,1-*b*]thiazoles and thiazolines bearing at position 6 a 2,5-dimethoxyphenyl group.

Chemistry

Compounds **7–10** were prepared according to the previously reported method[4]: the appropriate 2-amino-thiazole derivative **4** was reacted with α-bromo-2′, 5′-dimethoxyacetophenone **(5)** and the resulting salt **6**, treated with hydrobromic acid, gave the expected imidazo[2,1-*b*]thiazole derivatives **7–10**.



4 **5** **6** **7 - 10**

Results and Discussion

The inotropic activity of the compounds **7–10** (table 1) is summarized in table 2. As the compounds under test bear the same substituent at position 6, it is evident that the different

Table 1: *Compounds* **7–10**

Compound	X	Y	Formula (m.W.)	Calcd. / Found C	H	N	mp (°C)	Solvent	ν_{max}/cm^{-1}	^{1}H-NMR: δ (ppm)
7	CH	CH	$C_{13}H_{12}N_2O_2S$ (260.32)	60.0 / 59.9	4.65 / 4.70	10.8 / 10.6	111–113	EtOH	1495, 1265, 1160	3.72(3H,s,OCH_3);3.82(3H,s,OCH_3);6.80(1H,pseudo-q,arom.J=9Hz,J=2,5Hz);7.05(1H,d,arom.,J=9Hz);7.25(1H,d,H-2,J=4.5Hz);7.75(1H,d,arom.,J=2.5Hz);7.95(1H,d,H-3,J=4.5Hz);8.25(1H,s,H-5)
8	C–CH_3	CH	$C_{14}H_{14}N_2O_2S$ (274.34)	61.3 / 61.0	5.14 / 5.14	10.2 / 10.0	160–161	Pt.Et	1495, 1160, 1040	2.30(3H,d,CH_3,J=1.5Hz);3.70(3H,s,OCH_3);3.80(3H,s,OCH_3);6.78(1H,pseudo-q,arom.,J=9Hz,J=2.5Hz);7.0(1H,d,arom.,J=9Hz);7.65(1H,q,H-3,J=1.5Hz);7.72(1H,d,arom.,J=2.5Hz);8.12(1H,s,H-5)
9	CH	C–CH_3	$C_{14}H_{14}N_2O_2S$ (274.34)	61.3 / 61.5	5.14 / 5.10	10.2 / 10.3	141–142	EtOH	1495, 1270, 1040	2.35(3H,d,CH_3,J=1.5Hz);3.70(3H,s,OCH_3);3.84(3H,s,OCH_3);6.78(1H,pseudo-q,arom.,J=9Hz,J=2.5Hz);6.84(1H,q,H-2,J=1.5Hz);7.0(1H,d,arom.,J=9Hz);7.78(1H,d,arom.,J=2.5Hz);8.10(1H,s,H-5)
10	CH_2	CH_2	$C_{13}H_{14}N_2O_2S$ (262.33)	59.5 / 59.5	5.38 / 5.51	10.7 / 10.5	134–135	Pt.Et.	1495, 1265, 1235	3.65(3H,s,OCH_3);3.75(3H,s,OCH_3);3.80(2H,m,H-2);4.15(2H,m,H-3);6.70(1H,pseudo-q,arom.,J=9Hz,J=2.5Hz);6.95(1H,d,arom.,J=9Hz);7.58(1H,d,arom.,J=2.5Hz);7.68(1H,s,H-5)

Table 2: *Positive Inotropic Activity of Compounds* **7–10***

Compound	Maximum Increase in developed Tension (Changes in % from Control = 100)	Dose** µg/ml
7	216 ± 18	150
8	125 ± 9	150
9	180 ± 13	150
10	244 ± 15	150
Sulmazole***	175 ± 2,6	90

* In spontaneously beating guinea pig atria. Values are mean ± SEM of five preparations. Initial developed tension was g 0.38 ± 0.1 (mean ± SEM)

** Dose for inducing the maximum inotropic effect

*** In spontaneously beating rat atria (see[3c])

activity is related to the imidazo[2,1-*b*]thiazole moiety. The most active compound was the saturated derivative **10.** Of the other three compounds, the unsaturated and unsubstituted one **7** proved more active than the 3-methyl compound **9** which, in turn, was more active than the 2-methyl derivative **8.** These data perfectly agree with the results we recently published on analogous methoxyphenyl derivatives[4].

In isolated guinea pig atria at low Ca^{2+} concentrations compound **10** produced a marked inotropic activity similar to the effect of increasing Ca^{2+}. (fig. 1) As pointed out by

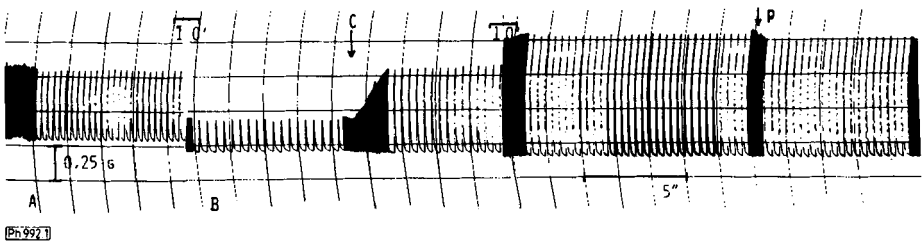


Fig. 1: Guinea pig atria incubated in normal Tyrode (A) and in Tyrode containing half of normal calcium concentration (B): effect of compound **10:** (C: 100 µg/ml) in hypodynamic condition. Lack of inhibition by propranolol (P: 20 µg/ml).

Fleckenstein et al.[6] a low calcium concentration produces a functional insufficiency of cardiac performance: it may therefore represent a means of simulating deficient or pathological situations in otherwise "intact" tissue. Moreover in isolated guinea pig atria compound **10** reversed the heart failure produced by propranolol, Mn^{2+}, and doxorubicin (fig. 2, 3, 4): this may suggest that compound **10** makes more Ca^{2+} available to the contractile mechanism.

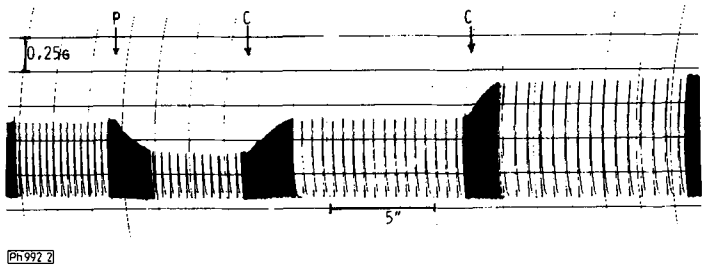


Fig. 2: Effect of compound **10** (C: 100 + 100 μg/ml) on propranolol (P: 20 μg/ml)-induced negative inotropic response in isolated guinea pig atria.

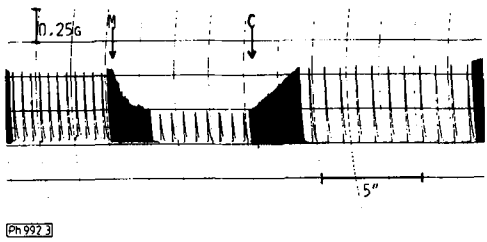


Fig. 3: Effect of compound **10** (C: 100 μg/ml) on Mn^{++} (M: $MnCl_2 \cdot 4H_2O$ 100 μg/ml)-induced negative inotropic response in isolated guinea pig atria.

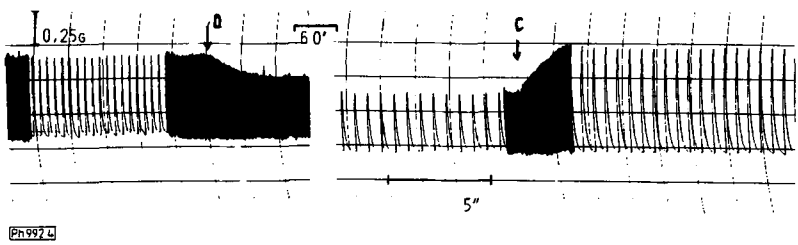


Fig. 4: Effect of compound **10** (C: 100 μg/ml) on doxorubicin (D: 100 μg/ml)-induced negative inotropic response in isolated guinea pig atria.

Experimental Part

Chemistry: MP: Electrothermal apparatus, uncorr. *TLC:* Bakerflex plates (Silica -gel IB2-F). Petroleum ether (bp 60–80°)/acetone mixtures in various proportions as eluents. *IR spectra:* Perkin-Elmer 298 in Nujol. *^{1}H-NMR spectra:* 90 MHz spectrometer Varian EM 390 in DMSO-d_6, TMS int. stand.

Synthesis of compounds **7–10**

Compounds **4** were commercially available products except 2-amino-5-methyl-thiazole which was prepared from thiourea and α-bromo-propionaldehyde[5]. The 2-amino-thiazole derivative **4** (30 mmoles) was dissolved in 100 ml of acetone (compounds **7, 9, 10**) or chloroform (compound **8**) and treated with 7.8 g of **5**. The reaction mixture was refluxed for 10 min; the intermediate salt **6** was separated ($\nu_{C=O} \simeq 1680\ cm^{-1}$) and treated with 250 ml of 2N-HBr. After 1 h reflux the solution was cooled and basified with 15 % NH_4OH: the resulting crude product (**7**, **10**) was collected and crystallized (see table 1) with a yield of ca. 80 %.

Pharmacology

Guinea pigs (300–400 g) were sacrificed by cervical dislocation. The atria were separated from the rest of the heart and mounted vertically in 20 ml of tissue bath containing Tyrode solution of the following composition: (g/l) NaCl 8.0, $NaHCO_3$ 1.0, KCl 0.2, NaH_2PO_4 0.05, $MgCl_2$ 0.1, $CaCl_2$ 0.2, glucose 1.0. The solution was bubbled with a mixture of oxygen-carbon dioxide (95/5) and maintained at 37°C.

Isometric contraction was recorded by a strain gauge transducer connected to a recording microdynamometer (Basile DY1; resting tension 1g). After stabilization (usually 30–40 min) the compound was added to the bath. All compounds were dissolved in DMSO (2 %). At the concentration used for solubilization of compounds DMSO produces no appreciable inotropic effects. In some experiences hypodynamia was induced by 50 % reduction in the calcium content of Tyrode's solution or by adding a myocardial depressant dose of propranolol, $MnCl_2$, or doxorubicin.

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