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Synthesis and cardiotonic activity of 2,5-dimethoxyphenylimidazo[2,1-*b*]thiazoles

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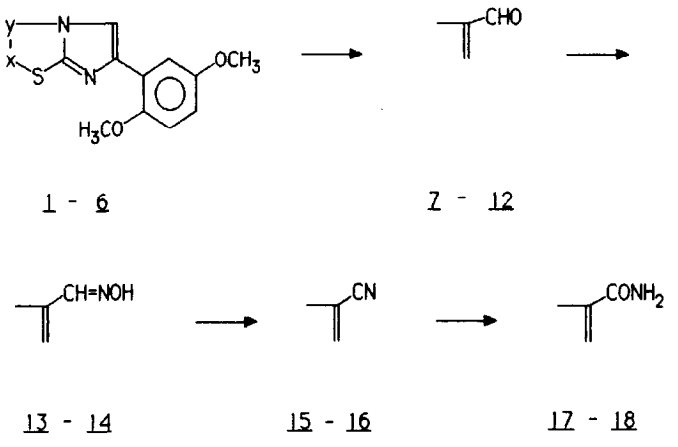
Introduction

In our previous papers on the synthesis of imidazo-[2,1-*b*]thiazoles with cardiotonic activity [1–5] we found that the most active compounds were those bearing a pyridyl group [2] or a 2,5-dimethoxyphenyl group [3] at the 6 position. In order to improve the pharmacological behaviour of the latter class (**1–4**, scheme 1 and table I), we prepared two new analogs (**5**, **6**) and a series of derivatives bearing a substituent at position 5. First of all we synthesized the formyl derivatives in order to develop a series of 5-carboxamides, as we had noticed that the activity of 6-phenylimidazo[2,1-*b*]thiazole-5-carboxamide [6] was higher than that of 6-phenylimidazo[2,1-*b*]thiazole



Scheme 1. x, y: see table I.

(unpublished results). However, before transforming all the seven aldehydes into the corresponding amides, we prepared two specimens only (**17**, **18**) which were subjected to the pharmacological test. As the positive inotropic activity of these derivatives turned out to be lower than that of the starting compounds (**1**, **2**), we decided not to complete this series but to test the available intermediates.

Chemistry

The imidazo[2,1-*b*]thiazoles **5**, **6** were prepared as usual [1–4], by treatment of 2-amino-4,5-dimethylthiazole (or 2-amino-5-chlorothiazole) with 2-bromo-2',5'-dimethoxyacetophenone. Compounds **1–6**, subjected to the Vilsmeier reaction, gave the corresponding aldehydes **7–12**, two of which (**7**, **8**) were converted into oximes (**13**, **14**), nitriles (**15**, **16**) and amides (**17**, **18**) by means of standard methods.

Pharmacological results

Table III reports the positive inotropic activity on spontaneously beating guinea pig atria of the newly synthesized compounds (**5–18**) in comparison with the most active 2,5-dimethoxyphenyl derivatives previously published [3]. The data clearly show that neither the different substituent at position 2,3 nor the substitution at position 5, gave an improvement with respect to **1** and **2**. Nevertheless the maximal effect of four compounds (**8**, **13–15**) was comparable to that of sulmazole used as a reference.

Table I. Compounds **1–18**.

Compd	*x y*	*Formula (Mw)*	*Mp/°C*	*IR: ν_{max}/cm^{-1}*
1	CH = CH		(3)	
2	CH_2-CH_2		(3)	
3	CCH_3 = CH		(3)	
4	CH = CCH_3		(3)	
5	CCH_3 = CCH_3	$C_{15}H_{16}N_2O_2S$ (288.4)	157–159	1600, 1245, 1210, 1040
6	CCl = CH	$C_{13}H_{11}ClN_2O_2S$ (294.8)	129–131	1495, 1270, 1165, 1050
7	CH = CH	$C_{14}H_{12}N_2O_3S$ (288.3)	120–124	1640, 1500, 1220, 1040
8	CH_2-CH_2	$C_{14}H_{14}N_2O_3S$ (290.3)	122–125	1655, 1500, 1225, 1045
9	CCH_3 = CH	$C_{15}H_{14}N_2O_3S$ (302.3)	117–120	1640, 1500, 1330, 1275
10	CH = CCH_3	$C_{15}H_{14}N_2O_3S$ (302.3)	188–189	1660, 1490, 1340, 1215
11	CCH_3 = CCH_3	$C_{16}H_{16}N_2O_3S$ (316.4)	130–133	1660, 1500, 1345, 1220
12	CCl = CH	$C_{14}H_{11}ClN_2O_3S$ (322.8)	132–133	1650, 1500, 1220, 1040
13	CH = CH	$C_{14}H_{13}N_3O_3S$ (303.3)	175–178	3120, 1275, 1215, 980
14	CH_2-CH_2	$C_{14}H_{15}N_3O_3S$ (305.3)	233–237	3140, 1270, 1215, 975
15	CH = CH	$C_{14}H_{11}N_3O_2S$ (285.3)	116–117	2205, 1375, 1360, 1215
16	CH_2-CH_2	$C_{14}H_{13}N_3O_2S$ (287.3)	131–134	2200, 1495, 1215, 1035
17	CH = CH	$C_{14}H_{13}N_3O_3S$ (303.3)	195–198	3400–3100, 1650, 1600, 1220
18	CH_2-CH_2	$C_{14}H_{15}N_3O_3S$ (305.3)	160–163	3500–3200, 1665, 1610, 1220

Table II. ^{1}H-NMR spectra of compounds **5–18** in DMSO–d_6 (A) or $CDCl_3$ (B). it: imidazothiazole, thn: thiazoline.

Compd	*Solv*	*∂ (ppm), J (Hz)*
5	A	2.32 (3H, s, CH_3) 2.34 (3H, s, CH_3) 3.76 (3H, s, OCH_3) 3.93 (3H, s, OCH_3) 6.83 (1H, dd, ar, J = 3, J = 9) 7.05 (1H, d, ar, J = 9) 7.81 (1H, d, ar, J = 3) 8.05 (1H, s, it)
6	A	3.75 (3H, s, OCH_3) 3.88 (3H, s, OCH_3) 6.84 (1H, dd, ar, J = 3, J = 9) 7.04 (1H, d, ar, J = 9) 7.67 (1H, d, ar, J = 3) 8.20 (1H, s, it) 8.27 (1H, s, it)
7	A	3.73 (3H, s, OCH_3) 3.77 (3H, s, OCH_3) 7.2 (3H, m, ar) 7.60 (1H, d, it, J = 4.4) 8.38 (1H, d, it, J = 4.4) 9.72 (1H, s, CHO)
8	A	3.71 (3H, s, OCH_3) 3.77 (3H, s, OCH_3) 4.0 (2H, m, thn) 4.5 (2H, m, thn) 7.1 (3H, m, ar) 9.58 (1H, s, CHO)
9	B	2.51 (3H, s, CH_3) 3.80 (3H, s, OCH_3) 3.83 (3H, s, OCH_3) 6.9 (2H, s, ar) 7.2 (1H, s, ar) 8.10 (1H, s, it) 9.73 (1H, s, CHO)
10	A	2.70 (3H, d, CH_3, J = 1.4) 3.70 (3H, s, OCH_3) 3.75 (3H, s, OCH_3) 7.1 (3H, m, ar) 7.11 (1H, q, it, J = 1.4) 9.39 (1H, s, CHO)
11	A	2.39 (3H, s, CH_3) 2.64 (3H, s, CH_3) 3.70 (3H, s, OCH_3) 3.75 (3H, s, OCH_3) 7.1 (3H, m, ar) 9.36 (1H, s, CHO)
12	A	3.73 (3H, s, OCH_3) 3.75 (3H, s, OCH_3) 7.1 (3H, m, ar) 8.59 (1H, s, it) 9.67 (1H, s, CHO)
13	A	3.72 (3H, s, OCH_3) 3.78 (3H, s, OCH_3) 7.1 (3H, m, ar) 7.48 (1H, d, it, J = 4.4) 8.07 (1H, s, CH) 8.12 (1H, d, it, J = 4.4) 11.20 (1H, s, NOH)
14	A	3.70 (3H, s, OCH_3) 3.75 (3H, s, OCH_3) 4.0 (2H, m, thn) 4.4 (2H, m, thn) 7.0 (3H, m, ar) 7.88 (1H, s, CH) 11.20 (1H, s, NOH)
15	A	3.79 (3H, s, OCH_3) 3.88 (3H, s, OCH_3) 7.3 (3H, m, ar) 7.65 (1H, d, it, J = 4.4) 8.21 (1H, d, it, J = 4.4)
16	A	3.72 (3H, s, OCH_3) 3.80 (3H, s, OCH_3) 4.0 (2H, m, thn) 4.4 (2H, m, thn) 7.2 (3H, m, ar)
17[a]	A	3.70 (3H, s, OCH_3) 3.74 (3H, s, OCH_3) 6.99 (1H, dd, ar, J = 3, J = 9) 7.04 (1H, d, ar, J = 3) 7.09 (1H, d, ar, J = 9) 7.42 (1H, d, it, J = 4.4) 8.20 (1H, d, it, J = 4.4)
18[a]	A	3.70 (3H, s, OCH_3) 3.73 (3H, s, OCH_3) 4.0 (2H, m, thn) 4.4 (2H, m, thn) 7.0 (3H, m, ar)

[a]The NH_2 group gives a broad signal in the range 6–8 ppm.

Table III. Positive inotropic activity of compounds **1–18**.

Compd	EC_{50} (μM)	E_{max} *% Δ from baseline value = 0*[a]	E_{max} *Concentration to obtain* E_{max} (μM)
1	[b]	116 ± 18	576
2	[b]	144 ± 15	547
3	[b]	25 ± 9	547
4	[b]	80 ± 13	572
5	[c]	44 ± 16	173
6	–	NS[d]	–
7	42.3	23 ± 11	277
8	147	66 ± 26	689
9	–	NS	–
10	–	NS	–
11	–	NS	–
12	–	NS	–
13	44.5	63 ± 21	330
14	85.2	87 ± 8	524
15	81.7	65 ± 24	175
16	[c]	26 ± 9	174
17	236	47 ± 11	1300
18	555	18 ± 8	1300
Sulmazole	14.6	63 ± 9	348

[a]Initial contractile force = 0.57 ± 0.18 g; [b]not calculated; E_{max} taken from [3]; [c]due to the poor solubility in the test medium, the activity was fleeting and it was impossible to obtain this datum; [d]not significant.

Experimental protocols

Chemistry

The melting points are uncorrected. 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/acetone in various proportions or toluene/-$CHCl_3$/CH_3OH, 50/40/10. The IR were recorded in nujol on a Perkin-Elmer 298. The ^{1}H-NMR were recorded on a Varian Gemini (300 MHz) or on a Varian EM 390 (90 MHz) using TMS as internal standard

2,3-Dimethyl-6-(2,5-dimethoxyphenyl)imidazo[2,1-b]thiazole ***5*** *and 2-chloro-6-(2,5-dimethoxyphenyl)imidazo[2,1-b]thiazole* ***6***

30 mmol of 2-amino-4,5-dimethylthiazole (or 2-amino-5-chlorothiazole) were dissolved in acetone (100 ml) and treated with 9 g (35 mmol) of 2-bromo-2',5'-dimethoxyacetophenone. The mixture was refluxed for 6 h. The intermediate salt was collected by filtration, washed with acetone and refluxed for 2 h with 200 ml of 2 N HBr. The solution was treated with 20% NH_4OH until basic and the resulting precipitate was collected and crystallized from ethanol with a yield of 50% (**5**) and 70% (**6**).

Aldehydes 7–12

50 mmol of the appropriate imidazo[2,1-*b*]thiazole (**1–6**) were treated with 11.8 g (150 mmol) of pyridine and $CHCl_3$ (100 ml). The resulting solution was cooled and added dropwise at 5–10°C to a stirred solution of the Vilsmeier reagent, prepared under cooling from 23 g (150 mmol) of $POCl_3$ and 11 g (150 mmol) of DMF in 10 ml of $CHCl_3$. The reaction mixture was refluxed for 1–14 h (according to a TLC test), concentrated under reduced pressure and poured onto ice. The resulting precipitate was collected and crystallized from ethanol with a yield of 70–85%.

Oximes ***13, 14***

10 mmol of the aldehyde **7** (or **8**) were dissolved in ethanol (100 ml) and refluxed for 20 min with 0.8 g (11.5 mmol) of hydroxylamine hydrochloride dissolved in 10 ml of H_2O. The resulting salt gave the free base by treatment with 10% NH_4OH: it was crystallized from ethanol with a yield of 80%.

Nitriles ***15, 16***

10 mmol of the oxime **13** (or **14**) were added portionwise, under stirring, to 25 ml of $SOCl_2$. After 15 min reflux, the excess $SOCl_2$ was evaporated under reduced pressure and the residue poured onto ice: the crude product was recovered by filtration and crystallized from ethanol (yield 90%).

Amides ***17, 18***

10 mmol of the nitrile **15** (or **16**) were added portionwise to 15 ml of stirred H_2SO_4. The reaction mixture was heated at 80°C for 8 h and poured onto ice, then 20% NH_4OH was added until pH 6 was reached. The crude amide thus obtained was crystallized from ethanol with a yield of 60%.

Pharmacology

The experiments were carried out on spontaneously beating isolated atria of guinea pig (350–650 g body weight). The preparations were 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 10–1000 μM 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 [7] which were determined in 4 to 6 atria.

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