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Synthesis and cardiotonic activity of aryl- or pyridyl-substituted fused imidazoles

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Summary – The syntheses of 4 different fused imidazoles bearing a 2,5-dimethoxyphenyl group or a pyridyl group are reported. All the heterocycles, except **2a**, display positive inotropic activity. Some are approximately equipotent with sulmazole, and the imidazo[2,1-*b*]benzothiazole that bears a 4-pyridyl group is the most active of whole series.

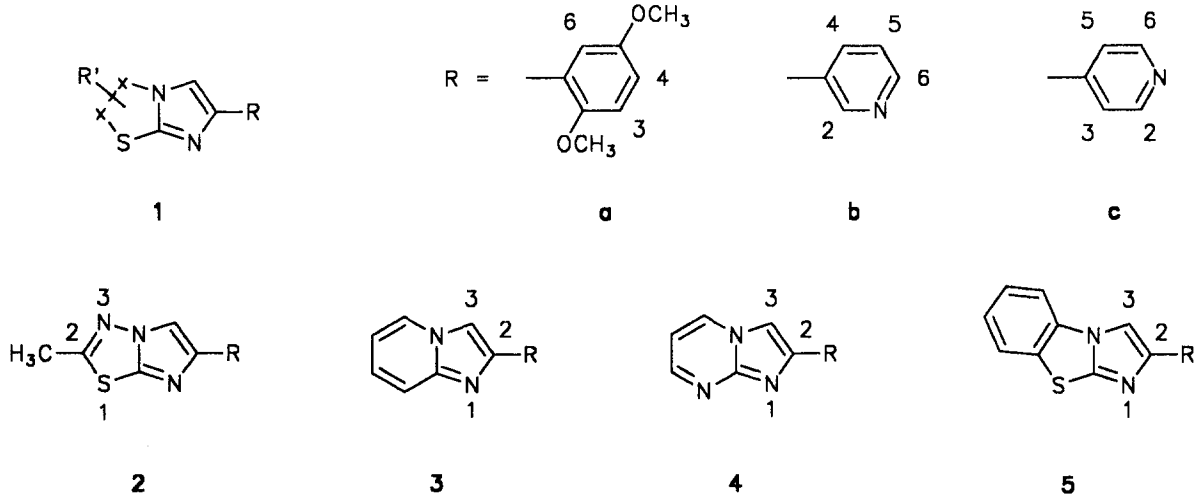
fused imidazoles / pyridyl group / 2,5-dimethoxyphenyl group / cardiotonic activity

Introduction

During the past few years we have investigated the positive inotropic activity of some heterocyclic compounds. Much effort worldwide in this field has been devoted to searching for drugs endowed with a more favourable therapeutic index than that of the cardiac glycosides.

From our investigations on the cardiotonic activity of imidazo[2,1-*b*]thiazoles [1–6], we found that the most active compounds are those bearing a 2,5-dimethoxyphenyl, a 3-pyridyl or a 4-pyridyl group at the 6 position (**1a–c**, see scheme 1).

Based on these results, we planned the synthesis of 4 different heterocycles fused with the same imidazole moiety: 2-methylimidazo[2,1-*b*]-1,3,4-thiadiazole **2**, imidazo[1,2-*a*]pyridine **3**, imidazo[1,2-*a*]-pyrimidine **4** and imidazo[2,1-*b*]benzothiazole **5**.



Scheme 1. In compound **1** x-x = R'C=CH (R' = H, CH_3) or CH_2-CH_2.

Table I. Compounds **2a–c** to **5a–c**.

Compound	*Formula (Mw)*	*Mp (°C)*	*Solvent*	ν_{max} *(cm^{-1})*
2a	$C_{13}H_{13}N_3O_2S$ (275.3)	137–140	EtOH	1500, 1245, 1210, 1055
2b	$C_{10}H_8N_4S$ (216.3)	187–189	Petroleum ether	1200, 1170, 1020, 740
2c	$C_{10}H_8N_4S$ (216.3)	200–203	Petroleum ether	1610, 1190, 1000, 830
3a	$C_{15}H_{14}N_2O_2$ (254.3)	113–115	Petroleum ether	1500, 1275, 1215, 1045
3b	$C_{12}H_9N_3$ (195.2)	114–115	Petroleum ether	1280, 1250, 945, 740
3c	$C_{12}H_9N_3$ (195.2)	169–171[a]	Petroleum ether	1605, 825, 745, 680
4a	$C_{14}H_{13}N_3O_2$ (255.3)	180–183	EtOH	1495, 1225, 1210, 1040
4b	$C_{11}H_8N_4$ (196.2)	206–210	Petroleum ether	1495, 1210, 785, 750
4c	$C_{11}H_8N_4$ (196.2)	240–244	Petroleum ether	1600, 1210, 800, 760
5a	$C_{17}H_{14}N_2O_2S$ (310.4)	151–154	EtOH	1485, 1280, 1040, 750
5b	$C_{14}H_9N_3S$ (251.3)	193–195	Petroleum ether	1595, 1270, 1225, 750
5c	$C_{14}H_9N_3S$ (251.3)	156–160	Petroleum ether	1600, 1325, 830, 740

[a]Lit [8] mp 168°C (MeOH).

Chemistry

Compounds **2a–c** to **5a–c** were prepared according to the same procedure employed for the synthesis of the imidazo[2,1-*b*]thiazoles **1** [1–6], *ie* by reaction of the appropriate 2-amino heterocycle with 2-bromo-2',5'-dimethoxyacetophenone or bromoacetylpyridines. The spectroscopic data of all the compounds are in agreement with the assigned structures (tables I, II). In the ^{1}H-NMR spectra, the deshielding effect of the neighbouring substituent on the only imidazole hydrogen of compounds **2a–c** to **5a–c** follows the order: 4-pyridyl > 3-pyridyl > dimethoxyphenyl. The

Table II. ^{1}H-NMR of compounds **2a–c** to **5a–c**[a].

Compound	*δ (ppm); J (Hz) in DMSO-d_6*
2a	2.72 (3H, s, CH_3) 3.75 (3H, s, OCH_3) 3.88(3H, s, OCH_3) 6.83 (1H, dd, ar4, J=3, J=9) 7.01 (1H, d, ar3, J=9) 7.69 (1H, d, ar6, J=3) 8.37 (1H, s, im)
2b	2.74 (3H, s, CH_3) 7.43 (1H, dd, py5) 8.19 (1H, d, py6) 8.47 (1H, d, py4) 8.75 (1H, s, im) 9.08 (1H, s, py2)
2c	2.74 (3H, s, CH_3) 7.80 (2H, d, py3,5) 8.57 (2H, d, py2,6) 8.88 (1H, s, im)
3a	3.79 (3H, s, OCH_3) 3.92 (3H, s, OCH_3) 6.86 (1H, t, het, J=8) 6.88 (1H, dd, ar4, J=3, J=9) 7.06 (1H, d, ar3, J=9) 7.24 (1H, t, het, J=8) 7.58 (1H, d, het, J=8) 7.88(1H, d, ar6, J=3) 8.41 (1H, s, im) 8.57 (1H, d, het, J=8)
3b	6.94 (1H, t, het) 7.29 (1H, t, het) 7.49 (1H, dd, py5) 7.63 (1H, d, het) 8.32 (1H, dt, py6) 8.53 (1H, s, im) 8.54 (1H, dd, py4) 8.57 (1H, d, het) 9.18 (1H, d, py2)
3c	6.94 (1H, t, het) 7.29 (1H, t, het) 7.63 (1H, d, het) 7.91 (2H, d, py3,5) 8.56 (1H, d, het) 8.61 (2H, d, py2,6) 8.62 (1H, s, im)
4a	3.80 (3H, s, OCH_3) 3.92 (3H, s, OCH_3) 6.91 (1H, dd, ar4, J=3, J=9) 7.04 (1H, dd, het, J=4, J=7) 7.08 (1H, d, ar3, J=9) 7.88 (1H, d, ar6, J=3) 8.39 (1H, s, im) 8.53 (1H, dd, het, J=2, J=4) 8.98 (1H, dd, het, J=2, J=7)
4b	7.09 (1H, dd, het) 7.50 (1H, dd, py5) 8.35 (1H, dt, py6) 8.49 (1H, s, im) 8.56 (2H: 1H, dd, het + 1H, dd, py4) 8.99 (1H, dd, het) 9.21 (1H, d, py2)
4c	7.11 (1H, dd, het) 7.96 (2H, d, py3,5) 8.60 (1H, s, im) 8.61 (1H, dd, het) 8.66 (2H, d, py2,6) 9.01 (1H, dd, het)
5a	3.77 (3H, s, OCH_3) 3.94 (3H, s, OCH_3) 6.84 (1H, dd, ar4, J=3, J=9) 7.04 (1H, d, ar3, J=9) 7.42 (1H, t, het, J=8) 7.55 (1H, t, het, J=8) 7.74 (1H, d, ar6, J=3) 8.02 (1H, d, het, J=8) 8.14 (1H, d, het, J=8) 8.68 (1H, s, im)
5b	7.46 (2H: 1H, dd, het + 1H, dd, py5) 7.59 (1H, t, het) 7.98 (1H, d, het) 8.05 (1H, d, het) 8.20 (1H, dt, py6) 8.50 (1H, dd, py4) 8.92 (1H, s, im) 9.08 (1H, d, py2)
5c	7.46 (1H, t, het) 7.59 (1H, t, het) 7.80 (2H, d, py3,5) 8.00 (1H, d, het) 8.05 (1H, d, het) 8.61 (2H, d, py2,6) 9.05 (1H, s, im)

[a]Abbreviations: ar: aromatic; im: imidazole; py: pyridine; het: heterocycle fused with imidazole (pyridine, pyrimidine, benzothiazole).

methoxy groups are in the range 3.7–3.9 ppm and the 4-pyridyl derivatives show the expected simpler coupling pattern compared with the 3-pyridyl derivatives.

Pharmacological results

The positive inotropic activity of compounds **2a–c** to **5a–c** was tested on spontaneously beating guinea-pig

Table III. Positive inotropic activity of compounds **2a–c** to **5a–c**.

Compound	EC_{50} *(μmol)*	E_{max}*(mean of 3-4 atria)*[a]	
		%Δ from baseline value = 0[b]	*Concentration to obtain* E_{max} *(μmol)*
2a	–	Not significant	–
2b	82	68 ± 6	900
2c	607	53 ± 23	1800
3a	58	52 ± 17	300
3b	269	64 ± 28	1000
3c	132	86 ± 1	400
4a	36	96 ± 1	150
4b	13	75 ± 5	400
4c	293	39 ± 8	2000
5a	13	85 ± 12	120
5b	25	55 ± 12	60
5c	26	120 ± 7	15
Sulmazole	15	63 ± 9	350

[a]Chronotropic effect was not significant (± 9%); [b]initial contractile force: 0.4 ± 0.1 g.

atria in comparison with sulmazole and the results obtained are reported in table III. With the exception of compound **2a**, all the others were significantly active. The inotropic activity of the imidazo[1,2-*a*]-pyrimidines **4** is not surprising in view of similar activities displayed by analogues of **4a** [7]. As expected from our previous results [1–6], the 3 selected pharmacophores (2,5-dimethoxyphenyl, 3-pyridyl and 4-pyridyl groups) confirm their usefulness in the design of new cardiotonic agents but do not show the same potency rank order when the supporting moiety is changed (2-methylimidazo[2,1-*b*]-1,3,4-thiadiazole, imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine and imidazo[2,1-*b*]benzothiazole). This behaviour is more evident for the 2,5-dimethoxyphenyl than for the 3-pyridyl group (since the first yielded the only inactive compound (**2a**) and 2 compounds that were more active than sulmazole (**4a**, **5a**)), but it becomes particularly evident for the 4-pyridyl group, which produced the less active derivatives when connected with 2-methylimidazo[2,1-*b*]-1,3,4-thiadiazole **2c** and with imidazo[1,2-*a*]pyrimidine **4c**. On the other hand the 4-pyridyl group furnished the 'most active' compound of the whole series when connected with imidazo-[2,1-*b*]benzothiazole **5c**.

Experimental protocols

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/acetone in various proportions. The IR spectra were recorded in nujol on a Perkin–Elmer 298. The ^{1}H-NMR spectra were recorded on a Varian Gemini 300, using TMS as the internal standard.

The 2-amino heterocycles and 2-bromo-2',5'-dimethoxyacetophenone are commercially available whereas the bromoacetylpyridines were prepared according to the literature [9, 10].

*Synthesis of compounds **2a–c** to **5a–c***

A 30 mmol portion of the appropriate 2-amino heterocycle (2-amino-5-methyl-1,3,4-thiadiazole, 2-aminopyridine, 2-aminopyrimidine or 2-aminobenzothiazole) was dissolved in 100 ml acetone and treated with the equivalent of the appropriate bromoketone (2-bromo-2',5'-dimethoxyacetophenone, 2-bromo-1-pyridin-3-ylethanone or 2-bromo-1-pyridin-4-ylethanone). The reaction mixture was refluxed for 1–5 h (according to a TLC test) and, after cooling, the resulting precipitate was collected, washed with acetone and treated with 200 ml 1 N HCl. The mixture was refluxed for 1 h after complete solution of the salt. Before cooling, the solution was cautiously basified under stirring with 20% NH_4OH in order to precipitate the expected compound as a free base. It was then collected, washed with water and crystallized according to table I. The yield was 60–70% for the dimethoxyphenyl derivatives **2a–5a** and 20–30% for the pyridyl derivatives **2b–c** to **5b–c**.

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