Eur J Med Chem (1992) 27, 167–170

Short communication

Synthesis and cardiotonic activity of pyridylmethylene-2-indolinones

A Andreani[1], M Rambaldi[1], A Locatelli[1], A Bongini[2], R Bossa[3], I Galatulas[3], M Ninci[3]

[1]*Dipartimento di Scienze Farmaceutiche, University of Bologna, Via Belmeloro 6, 40126 Bologna;*
[2]*Dipartimento di Chimica 'G Ciamician', University of Bologna, Via Selmi 2, 40126 Bologna;*
[3]*Dipartimento di Farmacologia, CTM, University of Milan, Via Vanvitelli 32, 20129 Milan, Italy*

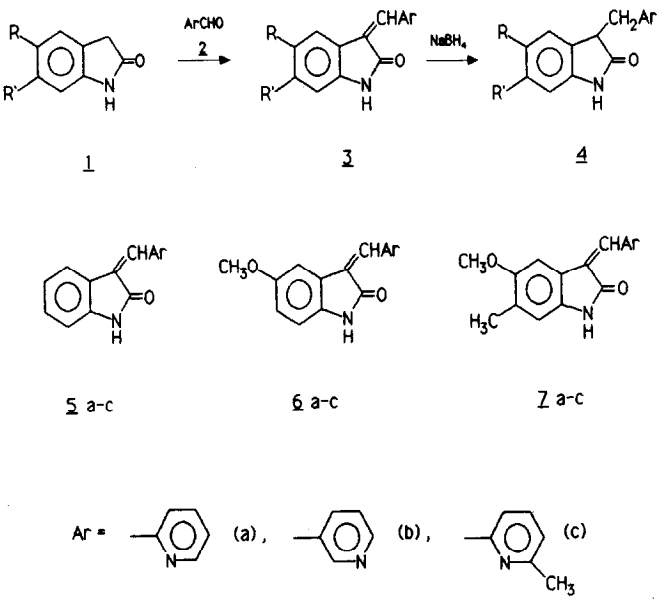
(Received 4 April 1991; accepted 8 July 1991)

Summary — The title compounds were prepared by reaction of 3 2-indolinones with 3 different pyridinecarboxaldehydes. In one case (**7b**) it was possible to isolate and characterize both the *E* and *Z* isomers. In the other cases (except **5b**) the E isomer was largely predominant or the only one present. The pharmacological activity of E-**7b** was not significantly different from that of *Z*-**7b**. Compound **6b**, arising from the reaction of 5-methoxy-2-indolinone with 3-pyridinecarboxaldehyde, was significantly more active than the other compounds prepared.

2-indolinones / pyridyl derivatives / *E–Z* isomerism / positive inotropic activity

Introduction

Our previous research on the positive inotropic activity of imidazo[2,1-*b*]thiazole derivatives [1–5] demonstrated that a dimethoxyphenyl group could be replaced by a pyridyl group without loss of activity or even with an improvement. This observation was recently confirmed by the Wellcome team in a series of isomazole analogues [6]. In our first paper devoted to the synthesis of 2-indolinones as potential cardiotonic agents [7] we wished to verify such a hypothesis and we described 2 series of compounds (**3**, **4**; see scheme 1) arising from 4 different indolinones **1** and 2 different aldehydes **2** (2,5-dimethoxybenzaldehyde and 4-pyridinecarboxaldehyde). The pharmacological test on isolated guinea pig atria showed that compounds **4** were devoid of positive inotropic activity and the most interesting compounds **3** were those bearing the 4-pyridylmethylene group. Compounds **3** bearing the dimethoxyphenyl group were active but, due to their poor solubility in the test medium, it was impossible to obtain quantitative data and to confirm the aforementioned hypothesis in this class of compounds.



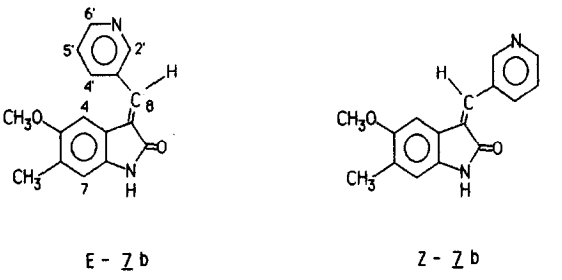
Scheme 1.

Chemistry

Based on the above observation, we decided to select the 3 indolinones which gave the highest activity (*ie* to exclude 5-hydroxy-2-indolinone) and to replace the 4-pyridyl group by 3 different pyridyls. Compounds **5–7** (see scheme 1) were prepared in the presence of piperidine and were expected to belong to the E-configuration, as the previously reported analogs [7].

When the 2-pyridyl ring was involved (**5–7a, c**), one isomer only was present; on the contrary, the reaction with 3-pyridinecarboxaldehyde gave the expected compounds as a mixture of 2 isomers (**5–7b**). We decided to isolate and characterize both isomers in one case only (**7b**) just determine whether the pharmacological behaviour was different. As the positive inotropic activity of *E*-**7b** was analogous to that of *Z*-**7b**, we did not consider it useful to isolate the 2 isomers in the case of **5b** and **6b**.

The 2 isomers **7b** (scheme 2) are different in their mp and spectra (IR, NMR: see tables I, II). The IR spectrum of the isomer melting at higher temperature shows 2 bands in the region 1150–1000 cm^{-1} (1115 and 1020) whereas the other one, in the same region, shows one band only (1085). The *E*-configuration was assigned to the former on the basis of its ^1H NMR spectrum, in fact the OCH_3 group (3.82 ppm) and the H-4 (7.40 ppm) are strongly deshielded by the neighbouring pyridine ring, in comparison to the corresponding protons of the *Z*-isomer (3.56 and 6.92 ppm, respectively), and the H-8 (7.78 ppm) is deshielded by the neighbouring carbonyl group (7.53 ppm in the *Z*-isomer); the fact that the H-4' (8.95 ppm) is strongly



Scheme 2.

Table I. 2-Indolinones **5–7**.

Compd	*Formula (mw)*	*Mp (°C)*	*IR: ν_{max}, cm^{-1}*	*MS: m/e (%)*
5a	$C_{14}H_{10}N_2O$ (222.2)	205–207[a]	3200-3100, 1705, 1615, 1330	222 (M^+ 85) 221 (100) 194 (64) 166 (8) 144 (60)
5b	$C_{14}H_{10}N_2O$ (222.2)	188–190[b]	3150-3050, 1710, 1610, 1315	222 (M^+ 100) 221 (55) 194 (21) 166 (6) 144 (21)
5c	$C_{15}H_{12}N_2O$ (236.3)	194–196	3200-3100, 1720, 1575, 1330	236 (M^+ 100) 235 (91) 208 (49) 144 (72)
6a	$C_{15}H_{12}N_2O_2$ (252.3)	192–194	3200-3100, 1715, 1315, 1265	252 (M^+ 100) 237 (9) 224 (22) 209 (25) 174 (47)
6b	$C_{15}H_{12}N_2O_2$ (252.3)	201–203	3150-3050, 1675, 1610, 1200	252 (M^+ 100) 237 (33) 209 (11) 181 (13) 174 (10)
6c	$C_{16}H_{14}N_2O_2$ (266.3)	196–199	3200-3100, 1685, 1605, 1315	266 (M^+ 100) 251 (9) 238 (14) 223 (23) 195 (11) 174 (51)
7a	$C_{16}H_{14}N_2O_2$ (266.3)	218–221	3200-3100, 1720, 1575, 1330	266 (M^+ 100) 251 (19) 234 (18) 236 (20) 223 (23) 188 (25)
E-7b	$C_{16}H_{14}N_2O_2$ (266.3)	207–210	3150-3050, 1690, 1115, 1020	266 (M^+ 100) 251 (53) 223 (7) 195 (5) 167 (3) 133 (5)
Z-7b	$C_{16}H_{14}N_2O_2$ (266.3)	188–190	3150-3050, 1690, 1200, 1085	266 (M^+ 100) 251 (60) 223 (11) 195 (8) 167 (6) 133 (5)
7c	$C_{17}H_{16}N_2O_2$ (280.3)	243–245	3200-3100, 1720, 1330, 1090	280 (M^+ 100) 265 (25) 252 (11) 237 (25) 209 (7) 188 (26)

[a]Lit 205–206°C [8]; 207–209°C dec [9]; [b]Lit 193–196°C [9].

Table II. ^1H NMR of compounds **5–7** and ^{13}C NMR of *E*-**7b** and *Z*-**7b**. s = singlet; d, t = doublet, triplet J = 5–8 Hz; d', t' = doublet, triplet J = 1–2 Hz.

Compound	*Isomer*	*∂ (ppm)*
5a	*E*	7.0 (m, H6 + H7) 7.4 (m, H5 + H5') 7.68 (s, H8) 7.9 (m, H3' + H4') 8.95 (d, H6') 9.10 (d, H4) 10.75 (s, NH)
5b	*Z*	6.9 (m, H6 + H7) 7.25 (t, H5) 7.37 (d, H4) 7.55 (dd, H5') 7.62 (s, H8) 8.11 (d, H4') 8.65 (d, H6') 8.87 (s, H2') 10.70 (s, NH)
5c	*E*	2.65 (s, CH_3) 7.0 (m, H6 + H7) 7.3 (m, H5 + H5') 7.60 (s, H8) 7.70 (d, H3') 7.85 (t, H4') 9.15 (d, H4) 10.70 (s, NH)
6a	*E*	3.80 (s, OCH_3) 6.9 (m, H6 + H7) 7.5 (m, H5') 7.62 (s, H8) 7.9 (m, H3' + H4') 8.90 (s, H4 + d, H6') 10.60 (s, NH)
6b	*E*	3.77 (s, OCH_3) 6.8 (m, H6 + H7) 7.45 (d', H4) 7.50 (dd, H5') 7.85 (s, H8) 8.60 (dd', H6') 8.95 (dt', H4') 9.3 (d', H2') 10.55 (s, NH)
6c	*E*	2.68 (s, CH_3) 3.82 (s, OCH_3) 6.9 (m, H6 + H7) 7.35 (d, H5') 7.58 (s, H8) 7.70 (d, H3') 7.85 (t, H4') 8.95 (d', H4) 10.50 (s, NH)
7a	*E*	2.20 (s, CH_3) 3.85 (s, OCH_3) 6.70 (s, H7) 7.4 (m, H5') 7.53 (s, H8) 7.85 (d, H3') 7.95 (t, H4') 8.90 (s, H4 + d, H6') 10.40 (s, NH)
7b	*E*	2.15 (s, CH_3) 3.82 (s, OCH_3) 6.65 (s, H7) 7.40 (s, H4) 7.50 (dd, H5') 7.78 (s, H8) 8.60 (dd', H6') 8.95 (dt', H4') 9.30 (d', H2') 10.48 (s, NH) 16.78 (CH_3) 55.95 (OCH_3) 103.53, 111.92, 123.32, 131.62, 137.88, 150.11, 152.42 (CH) 122.66, 127.94, 129.86, 130.31, 134.91, 152.91, 167.59 (C)
7b	*Z*	2.15 (s, CH_3) 3.56 (s, OCH_3) 6.70 (s, H7) 6.92 (s, H4) 7.53 (s, H8) 7.57 (dd, H5') 8.15 (d, H4') 8.65 (d, H6') 8.88 (s, H2') 10.40 (s, NH) 16.59 (CH_3) 55.25 (OCH_3) 105.11, 112.48, 123.60, 130.50, 136.37, 149.91, 150.06 (CH) 118.44, 128.20, 130.20, 130.78, 137.02, 152.04, 168.60 (C)
7c	*E*	2.20 (s, CH_3-6) 2.67 (s, CH_3-6') 3.88 (s, OCH_3) 6.70 (s, H7) 7.35 (d, H5') 7.45 (s, H8) 7.65 (d, H3') 7.85 (t, H4') 8.85 (s, H4) 10.35 (s, NH)

deshielded (8.15 ppm in the *Z*-isomer) can suggest a twisted orientation of the pyridyl group where the H-4' of the *Z*-isomer lies over the oxygen atom of the carbonyl group.

On the basis of the aforementioned NMR data of E-**7b** and Z-**7b** we have assigned the Z-configuration to compound **5b** and the *E*-configuration to all the others.

Pharmacological results

The positive inotropic activity of compounds **5–7** was tested on spontaneously beating guinea pig atria as reported in *Experimental protocols*. Table III clearly points out that the most favourable conditions are reached when the 5-methoxy-2-indolinone moiety is combined with the 3-pyridylmethylene group (**6b**). On the other hand, the unsubstituted 2-indolinone is the most versatile moiety as compound **5c** is the only one active among the 6-methyl-2-pyridyl derivatives. The activity of the E and Z isomers of compounds **7b** was not significantly different (the figures reported in table III refer to *E*-**7b**).

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. The IR were recorded in Nujol on a Perkin–Elmer 298. The NMR were recorded in DMSO–d_6 on a Varian Gemini 300 MHz or on a Varian EM-390 (90 MHz) using tetramethylsilane as the internal standard. The EI-MS were recorded at 70 eV on a VG 7070E.

2-Indolinone and the pyridinecarboxaldehydes are commercially available (Aldrich), whereas 5-methoxy-2-indolinone [10] and 5-methoxy-6-methyl-2-indolinone [11] were prepared according to the literature.

Table III. Positive inotropic activity of compounds **5–7**.

Compd	EC_{50} (μM)	E_{max} % Δ *from baseline value = 0*[a]	E_{max} *Concentration to obtain* E_{max} (μM)
5a	36.4	45 ± 10.7	225
5b	37.8	66 ± 18.0	360
5c	52.5	33 ± 9.4	338
6a	29.3	54 ± 22.2	198
6b	27.7	73 ± 24.1	198
6c	–	NS[b]	–
7a	–	NS	–
7b	40.5	47 ± 14.3	188
7c	–	NS	–
Sulmazole	14.6	63 ± 9.5	348

[a]Initial contractile force = 0.56 ± 0.17 g. [b]Not significant.

Synthesis of compounds 5–7

The appropriate 2-indolinone (60 mmol) was dissolved in methanol (100–200 ml) and treated with 2-pyridinecarboxaldehyde (or 3-pyridinecarboxaldehyde or 6-methyl-2-pyridinecarboxaldehyde: 70 mmol) and piperidine (3 ml). The reaction mixture was refluxed for 2 h, cooled and, if necessary, concentrated under reduced pressure. The resulting precipitate was collected and crystallized from methanol. The yield was ≈ 90% for compounds **5a–c** and ≈ 70% for the others. In the case of compound **7b**, the first crop was a mixture of the 2 isomers which, after 3 crystallizations from methanol gave a pure sample of the *E*-isomer, whereas the second crop was almost pure *Z*-isomer which was crystallized from methanol just once.

Pharmacology

The experiments were carried out on spontaneously beating isolated guinea pig atria (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 [12] which were determined in 4 to 6 atria.

References

1 Andreani A, Rambaldi M, Bonazzi D, Lelli G, Bossa R, Galatulas I (1984) *Eur J Med Chem* 19, 219–222
2 Andreani A, Rambaldi M, Andreani F, Bossa R, Galatulas I (1985) *Eur J Med Chem* 20, 93–94
3 Andreani A, Rambaldi M, Bonazzi D, Bossa R, Galatulas I (1985) *Arch Pharm* 318, 1003–1008
4 Andreani A, Rambaldi M, Andreani F, Bossa R, Galatulas I (1986) *Eur J Med Chem* 21, 55–58
5 Andreani A, Rambaldi M, Mascellani G, Bossa R, Galatulas I (1986) *Eur J Med Chem* 21, 451–453
6 Barraclough P, Black JW, Cambridge D, Demaine DA, Gerskowitch VP, Giles H, Hill AP, Hull RAD, Lyer R, King WR, Livingstone DJ, Nobbs MS, Randall P, Shah GP, Whiting MV (1990) *Arch Pharm* 323, 507–512
7 Andreani A, Rambaldi M, Locatelli A, Bossa R, Galatulas I, Ninci M (1990) *Eur J Med Chem* 25, 187–190
8 Elliott IW, Rivers P (1964) *J Org Chem* 29, 2438–2440
9 Walker GN, Smith RT, Weaver BN (1965) *J Med Chem* 8, 626–637
10 Koelsch CF (1944) *J Am Chem Soc* 66, 2019–2020
11 Andreani A, Rambaldi M, Bonazzi D, Greci L, Andreani F (1979) *Il Farmaco Ed Sci* 34, 132–138
12 Brunkhorst D, v der Leyen H, Meyer W, Schmidt-Schumacher C, Scholz H (1988) *Arzneim Forsch* 38, 1293–1298