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Chiral resolution of the enantiomers of tetrahydronaphthalenic derivatives, new agonist and antagonist ligands for melatonin receptors, using high-performance liquid chromatography on cellulose chiral stationary phases

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Abstract

Analytical HPLC methods using derivatized cellulose chiral stationary phases were developed for the separation of the enantiomers of methoxy and ethyl tetrahydronaphthalenic derivatives, new agonist and antagonist ligands for melatonin receptors. The resolution were made using normal-phase methodology with a mobile phase consisting of *n*-hexane–alcohol (methanol, ethanol, 1-propanol or 2-propanol) in various percentage, and a silica-based cellulose tris-3,5-dimethylphenylcarbamate (Chiralcel OD-H), or tris-methylbenzoate (Chiralcel OJ). The mobile phase and the chiral stationary phase were varied to achieve the best resolution. The effects of concentration of alcohol, various aliphatic alcohols in the mobile phase were studied. The effects of substitution were analysed. Baseline separation ($R_s > 1.5$) was easily obtained in many cases.The resolution results were complementary between the two columns.

Keywords: Enantiomer separation; Tetrahydronaphthalenic derivatives; Melatonin

1. Introduction

The neurohormone melatonin (*N*-acetyl-5-methoxytryptamin) (Fig. 1) principally synthesized by the pineal gland and secreted into the general circulation during the night [1] plays a central role in the regulation of circadian and seasonal rhythms in vertebrates. Previous works have reported its potential usefullness in human in biological rhythm disorders and seasonal affective disorders [2–5]. Moreover melatonin could be implicated in various pathologies, stimulant action on the immunitary response [6], inhibition of the development of some human cancer and in melanoma [1,7]. Melatonin has also been described as a powerful antioxydant [8] and could be helpful against diseases due to oxydative stress like cardiovascular pathologies, Alzheimer's or Parkinson's disease, or cataract.

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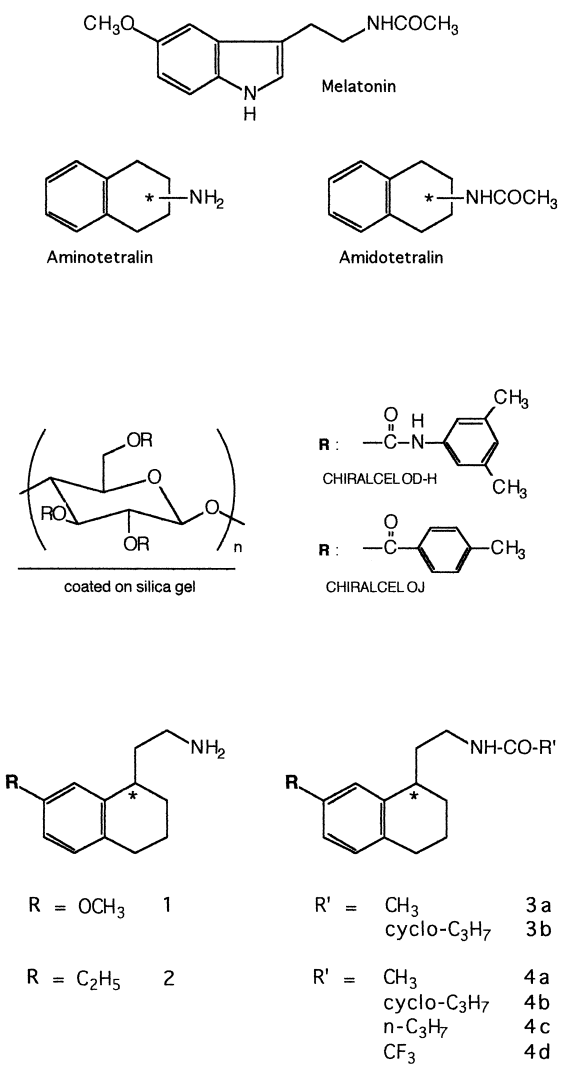

Fig. 1. Chemical structures of substrates 1, 2, 3 and 4. Structures of Chiralcel OD-H and OJ packings.

The very short biological half-life of melatonin, due to a rapid catabolism, and the lack of selectivity at its target sites limit their therapeutic use. Some of us recently described the synthesis, the pharmacological and biochemical studies of methoxy and ethyl tetrahydronaphthalenic derivatives (Fig. 1) [9] as potent and specific new agonist and antagonist melatoninergic ligands [10,11]. Agonist ligands decrease or suppress the forskolin induced cAMP production. Antagonist ligands has no activity alone, but are able to suppress melatonin activity. Some ligands, defined as forskolin potentialisators, induce an increase of cAMP. The racemate of the tetrahydronaphthalenic analog 3a of melatonin presents an affinity and an agonist activity similar to melatonin. None of the 7-ethyl ligands present agonist activity compounds 4a, 4 b, 4c are forskolin potentialisators and 4d antagonist (Fig. 1).

Compounds 1–4 have a chiral center and as stereoisomers often show different pharmacological activities, it seemed advisable to resolve the racemic mixtures to investigate the biological properties of each enantiomer (for example in those chemical series the stereoselective activity of the dopamine agonist 2-(*N*-propyl-*N*-2-thienylethylamino)-5-hydroxy-tetralin has been demonstrated [26]). As a first step to this a method has to be developed that would allow the chromatographic separation of these optical isomers. In order to obtain a more rapid method the direct resolution, without any pre-derivatization, of the enantiomeric components was studied. Separation of enantiomers by chiral HPLC is now well established with over 50 different chiral phases (CSP) commercially available. Among them cellulose and amylose esters and carbamates derivatives coated onto large pore silica gel backbone have proved to be extremely useful stationary phases for chiral resolution essentially used in normal-phase mode [12–19,33].

To the best of our knowledge only a limited amount of work using liquid chromatography for the analytical or preparative resolution of amino and/or amido tetralins (Fig. 1) has been published for compounds whose nitrogen atom is directly bonded onto the cycle. It is useful to mention the following described methods using polysaccharides-derived stationary phases. The chiral separations are mainly performed on Chiralcel OD for aminotetralins [22,26,27] and for amidotetralins [21,23,24] and on Chiralpak AD for amidotetralins [23,24] on an analytical scale with *n*-hexane–ethyl alcohol as mobile phase. Microcrystalline cellulose triacetate (CTA) has also been used for the preparative resolution of amidotetralins with 96% ethanol [24]. The enantiomeric purity of hydroxy aminotetralins was determined using a chiral crown ether coated on a silica gel column [31]. Analogous of aminotetralins (benzopyran derivatives) were resolved on Chiralcel OD and on Chiralpak AD using *n*-hexane–2-pro-

panol [25]. Chiral derivative agents (CDA) have also been employed with a silica normal achiral phase. Chiral aminotetralins, being derivatized with phenyl ethyl isocyanates or *O*-methyl mandelic acid to afford diastereomeric ureides [28] or amides [29] respectively, were resolved on an analytical scale [28] and on a preparative scale [26,27,29]. Chiral ion-pair chromatography, using *N*-benzoyloxycarbonylglycyl-L-proline as counter ion on a carbon column leads to the separation of aminotetralins [32]. But for compounds whose nitrogen atom is linked to the cycle through an alkyl chain, as in our own products, no literature data were available.

In the continuity of our work [20] on the enantioseparation of racemates with potent biological activity we examined in this study the direct separation of 1–4 on different chiral stationary phases of polysaccharide-derived types and particularly on (tris-3,5-dimethylphenylcarbamate) cellulose (Chiralcel OD-H) which shows a particularly high optical resolving ability among all the phenyl carbamate derivatives of cellulose developed so far [9]. Among the ester cellulose the (tris-methylbenzoate) cellulose (Chiralcel OJ) also found many applications but has never been used in the enantioseparation of tetralins. Preliminary works about 1–2 were undertaken on 150×4 mm I.D. Crownpack CR(+)(5 μm) column (Daicel Chemical Industries, Baker France). Mobile phase elution was made isocratically using perchloric acid (pH 2) and an organic modifier (methanol) was included in the mobile phase according to [30,31]. This leads to unsuccessful experiments, no resolution was observed whatever was the solvent used. No more success was obtained for compounds 1 and 2 on the described cellulose OD-H and OJ CSPs.

2. Experimental

2.1. Chromatography

Chiral chromatography was carried out on a Chiralcel OD-H column (tris-3,5-dimethylphenylcarbamate; 250×4.6 mm I.D.; 5 μm), and on a Chiralcel OJ (tris-methylbenzoate; 250×4.6 mm I.D.; 10 μm) (Daicel Chemical Industries, Baker France) using a gradient Waters 600E metering pump model equipped with a Waters 996 photodiode array spectrophotometer. Chromatographic data were collected and processed on a Digital computer running with Millenium 2010. The column eluate was monitored at 200; 210; 220; 230; 275 nm. The sample loop was 20 μl (Rheodyne 7125 injector). Mobile phase elution was made isocratically using *n*-hexane and a modifier (methanol, ethanol, 1-propanol or 2-propanol) at various percentage. The flow was 0.5 or 0.7 ml min^{-1}.

The peak of the solvent front was considered to be equal to the dead time (t_0) and was taken from each particular run. It was about 4.5 mm (0.7 ml min^{-1}) and 6.5 min (0.5 ml min^{-1}) for the Chiralcel OD-H and 4.8 min (0.7 ml min^{-1}) for the Chiralcel OJ. Retention times were mean values of two replicate determinations. All separations were carried out at 30°C unless noted otherwise to determine the temperature dependence of the optical resolution.

The separation factor (α) was calculated as k_2'/k_1' and retention factors (k') as $k_1'=(t_1-t_0)/t_0$ and $k_2'=(t_2-t_0)/t_0$ where t_1, t_2 refer to the retention times of the first and second enantiomers respectively. The resolution factor (R_s) was calculated by the formula $R_s=2(t_2-t_1)/(w_1+w_2)$ where w_1 and w_2 are the peak widths for the first and second eluting enantiomer peaks respectively.

2.2. Reagents

The compounds 1–4 used in this study were synthesized as previously described [1]. The methanol, ethanol, 1-propanol, 2-propanol and *n*-hexane were HPLC grade from Merck or Baker. All the solutions were filtered (0.45 μm), degassed with a Waters in-line degasser apparatus. The mobile phases used were A: hexane–ethanol: 90–10; B: hexane–ethanol: 95/5; C: hexane–1-propanol: 90/10; D: hexane–1-propanol: 95/5; E: hexane–2-propanol: 90/10; F: hexane–2-propanol: 95/5; G: hexane–ethanol: 98/2; H: hexane–methanol: 98/2;. Compounds were chromatographed by dissolving them in the corresponding alcohol to a concentration of about 0.75 m*M* (which corresponds to 15 nmoles injected) and passed through a 0.45 μm membrane filter prior to loading the column.

3. Results and discussion

The results of the chiral separation of the 3, 4 racemates chromatographed are summarised in Table 1 for Chiralcel OD-H and Table 2 for Chiralcel OJ. Fig. 2 corresponding to compounds 3a, 3b and Fig. 3 corresponding to compounds 4a, 4b are examples typical of the separations achieved on Chiralcel OD-H (Eluents E or F). The UV spectra are shown in Figs. 2 and 3 for the two eluted peaks as expected, the UV absorbance of the separate enantiomers were identical and are, of course, very similar for compounds 3 and 4. The maximum wavelengths are respectively (200.6, 278.6 nm for 3a, 3b) and (200.6, 276.2 nm for 4a, 4b). Fig. 4 illustrates the results obtained for the separations of compounds 3a, 3b (Eluent G) on Chiralcel OJ.

The retention factors (k') enantioselectivity factor (α) and resolution (R_s) of every solute may be regulated over a wide range by the addition of an alcohol. The influence of the percentage of ethanol, 1-propanol or 2-propanol and the nature of the alcohol in the mobile phase was thoroughly studied.

Most striking is the influence of the kind of alcohol in the mobile phase. The retention times and retention factors k' decrease on changing the mobile

Table 1
HPLC resolution: retention times (t, min) retention factors (k') enantioselectivity factor (α) and resolution (R_s) of 3, 4 Chiralcel OD-H

Compound	Eluent	T°C	t_1	k'_1	α	R_s
3a	A	30	9.42	1.13	1.22	1.04
	B	30	17.27	2.78	1.17	1.42
	C	30	12.90	1.91	1.20	1.84
	E	20	18.30	3.02	1.25	1.98
	E	30	18.23	2.88	1.22	1.86
	E	40	17.56	2.85	1.20	1.80
	E	30	25.53	2.87	1.22	2.05 (0.5 ml min^{-1})
	F	30	41.87	7.90	1.23	2.16
	F	30	58.94	7.94	1.23	2.92 (0.5 ml min^{-1})
3b	A	30	11.26	1.52	1	++
	B	30	20.39	3.41	1.04	0.60
	C	30	15.45	2.44	1	++
	E	30	22.95	4.18	1	++
	F	30	50.11	10.01	1.07	0.70
4a	A	30	6.69	0.51	1	++
	B	30	10.68	1.32	1[a]	++
	C	30	7.42	0.67	1.24	1.09
	E	20	8.96	0.96	1.39	1.43
	E	30	9.05	0.99	1.35	1.23
	E	40	9.20	1.00	1.31	1.03
	E	30	13.11	1.02	1.35	1.38 (0.5 ml min^{-1})
	F	30	18.03	2.94	1.42	1.92
	F	30	24.27	2.64	1.43	1.93 (0.5 ml min^{-1})
4b	A	30	7.28	0.64	1	++
	B	30	10.97	1.39	1	++
	E	30	11.31	1.50	1.08[a]	<0.50
	F	30	21.73	3.71	1.12	0.60
4c	E	30	8.44	0.86	1.15[a]	<0.50
	F	30	14.39	2.15	1.22[a]	0.78
4d	E	30	6.17	0.37	1[a]	++
	F	30	7.90	0.71	1[a]	++

++ Unresolved; Concentration ca. 0.75 m*M*.
[a] Overlapping.
Eluents A: hexane–ethanol: 90/10; B: hexane–ethanol: 95/5; C: hexane–1-propanol: 90/10; D: hexane–1-propanol: 95/5; E: hexane–2-propanol: 90/10; F: hexane–2-propanol: 95/5; G: hexane–ethanol: 98/2; H: hexane–methanol: 98/2.
The flow-rate was 0.7 ml min^{-1} unless noted otherwise

Table 2
HPLC resolution: retention times (t, min) retention factors (k') enantioselectivity factor (α) and resolution (R_s) of 3, 4 Chiralcel OJ

Compound	Eluent	T°C	t_1	k'_1	α	R_s
3a	A	30	9.94	1.08	1.19	1.03
	B	30	18.48	2.79	1.20	1.39
	C	30	11.53	1.44	1	++
	D	30	23.24	3.87	1	++
	E	30	16.98	2.39	1.10	0.54
	F	30	37.98	6.94	1.11	0.89
	G	30	49.34	9.06	1.19	1.63
	H	30	41.15	7.99	1.19	1.60
3b	A	30	10.29	1.15	1.67	3.97
	B	30	19.20	2.96	1.66	4.85
	C	30	12.39	1.61	1.12	0.77
	D	30	25.20	4.27	1.09	0.65
	E	30	17.06	2.60	1.27	1.88
	F	30	37.78	6.94	1.29	2.39
	G	30	48.15	8.76	1.60	5.00
	H	30	32.19	6.09	1.79	5.88
4a	A	30	6.65	0.39	1	++
	B	30	9.76	1.01	1	++
	E	30	8.73	0.85	1	++
	F	30	15.76	2.30	1	++
	G	30	19.86	2.97	1.09[a]	<0.5
4b	A	30	6.86	0.42	1	++
	B	30	10.16	1.08	1	++
	E	30	9.15	0.93	1	++
	F	30	16.13	2.36	1	++
	G	30	19.56	2.95	1.08[a]	<0.5

++ Unresolved; Concentration ca 0.75 m*M*.
[a] Overlapping.
Eluents A: hexane–ethanol: 90/10; B: hexane–ethanol: 95/5; C: hexane–1-propanol: 90/10; D: hexane–1-propanol: 95/5; E: hexane–2-propanol: 90/10; F: hexane–2-propanol: 95/5; G: hexane–ethanol: 98/2; H: hexane–methanol: 98/2.
The flow-rate was 0.7 ml min^{-1} unless noted otherwise.

phase modifier from 2-propanol (eluents E,F) to 1-propanol (eluents C,D) and to ethanol (eluents A,B) as expected from the higher polarity of the ethanol [18,19]. On Chiralcel OD-H for example for 3a the parameters (k' α, R_s) were (1.13, 1.22, 1.04); (1.91, 1.20, 1.84) and (2.88, 1.22, 1.86) with eluent A, C, and E respectively at a flow-rate of 0.7 ml min^{-1}. But on Chiralcel OJ for example for 3b the parameters (k', α, R_s) were (1.15, 1.67, 3.97) (1.61, 1.12, 0.77) and (2.60, 1.27, 1.88) with eluent A, C and E respectively at a flow-rate of 0.7 ml min^{-1}. The separation is in opposite way between the two columns and this could be correlated to the recognition mechanism of the enantioseparation. This one involves hydrogen bonding, dipole–dipole interaction, π–π interaction and inclusion into the chiral groove [14]. In OD-H CSP the carbamate residue appears to be important to induce efficient chiral discrimination because the carbonyl oxygen and the NH groups interact through H bondings with the corresponding groups on the analyte molecule [21,22]. Stonger solvents, as alcohols, compete more effectively for the chiral sites than the analyte. The enantiomeric resolution increased as the size of the alcohol increased with isopropanol giving the maximum resolution. This might be due to the decrease in the capacity of larger alcohols to compete for hydrogen bonding sites because of steric hindrance [17]. In OJ CSP the best results are obtained with lower alcohols (methanol and ethanol added to the mobile phase). Partial resolution or total loss of resolution are observed when using 1-propanol or 2-propanol. This suggests that hydrogen bonding interactions are probably not the predominant type but separations might involve more π–π interactions between the aromatic moiety of the analyte and the stationary phase. For this reason we investigate, on Chiralcel OJ, the eluents G, H to enhance the separation for the two compounds 3a, 3b. With Eluent H the parameters (k', α, R_s) for 3b are (6.09; 1.79; 5.88) which becomes very interesting for preparative mode.

It can be seen that decrease in the concentration of polar modifier (ethanol eluents A,B or 2-propanol eluents E,F) in the mobile phase increases (k', R_s), parameters in a general manner both for 3 and 4 on Chiralcel OD-H and OJ columns [15,18]. It must be remarked that the enantioselectivity factor (α) largely increases when the percentage of polar modifier decreases on Chiralcel OD-H column to the difference of Chiralcel OJ column where a remains slightly constant [22,25].

A small amount of diethyl amine was used as a modifier to the mobile phase but it did not influence the chromatographic parameters dramatically.

The Chiralcel OD-H column gives better results compared to Chiralcel OJ for 3a and 4a. The retention times of the two resolved peaks, in same eluting conditions, for the two CSPs are quite similar but a high decrease in enantioselectivity factor (α) and resolution (R_s) is observed. For example with 3a the parameters (k', α, R_s) were (7.90, 1.23, 2.16) and

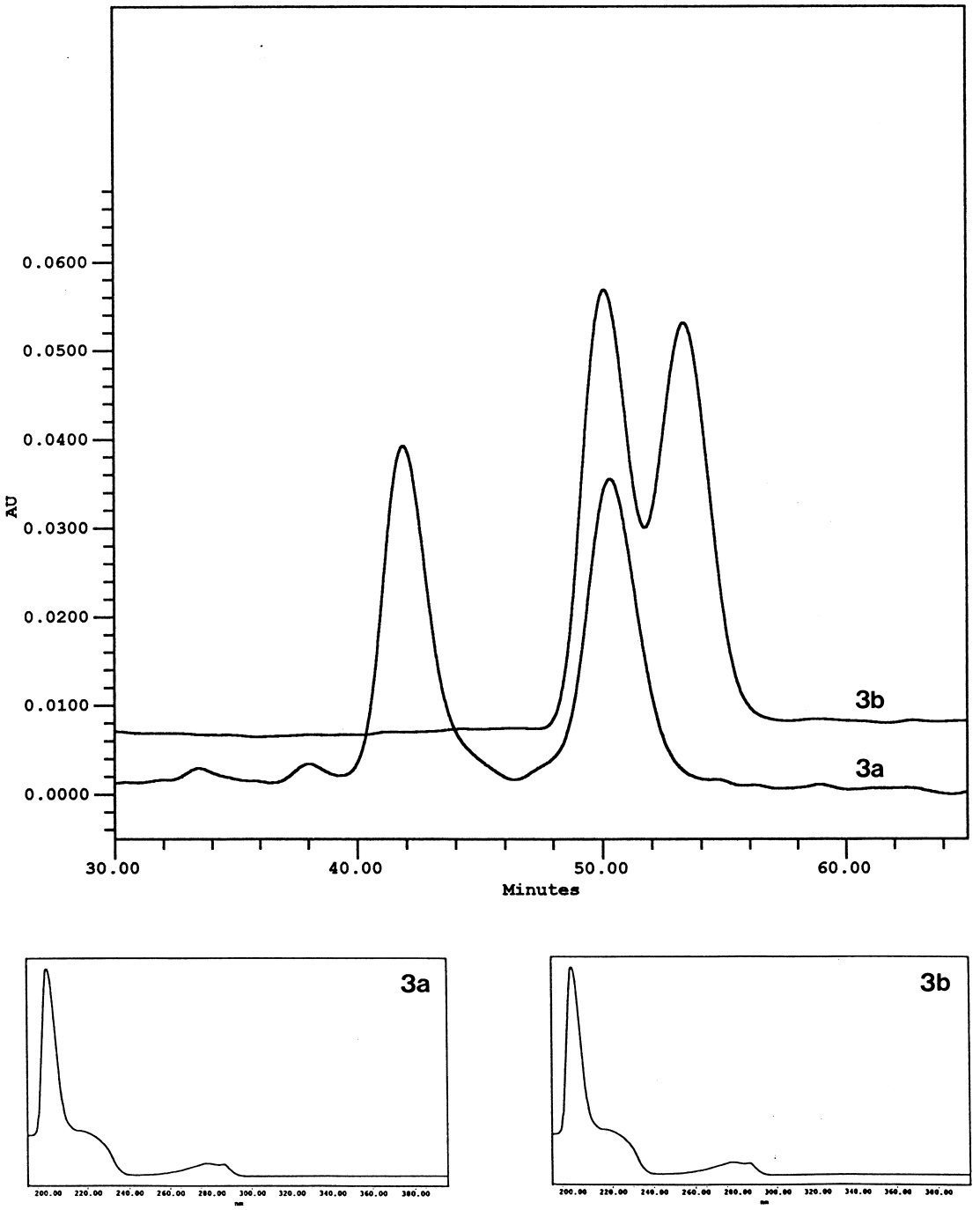

Fig. 2. Chromatograms (λ=200 nm) and UV spectra obtained for compounds 3a and 3b (Eluent F; 0.7 ml min^{-1}; Chiralcel OD-H).

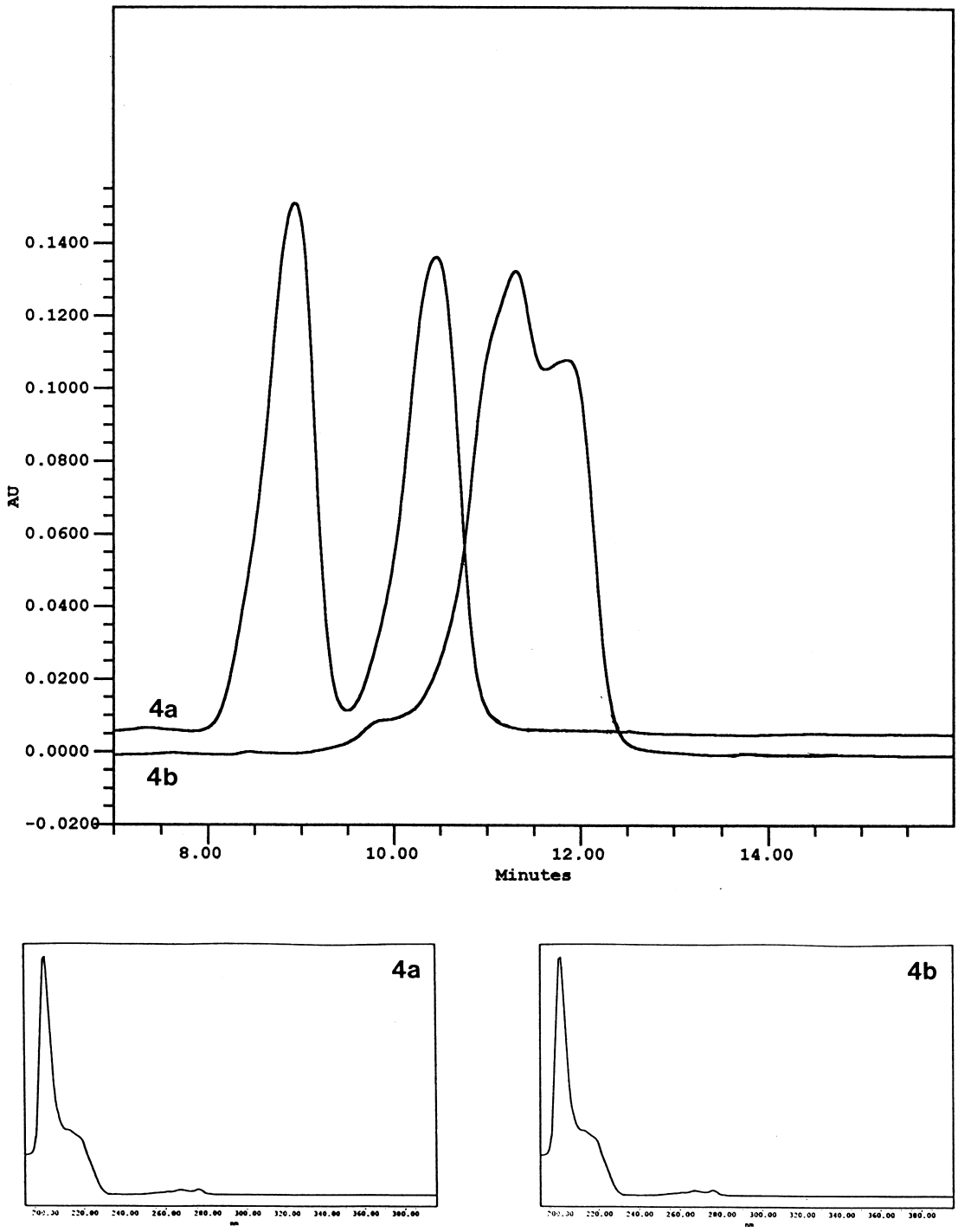

Fig. 3. Chromatograms (λ=200 nm) and UV spectra obtained for compounds 4a and 4b (Eluent E; 0.7 ml min^{-1}; Chiralcel OD-H).

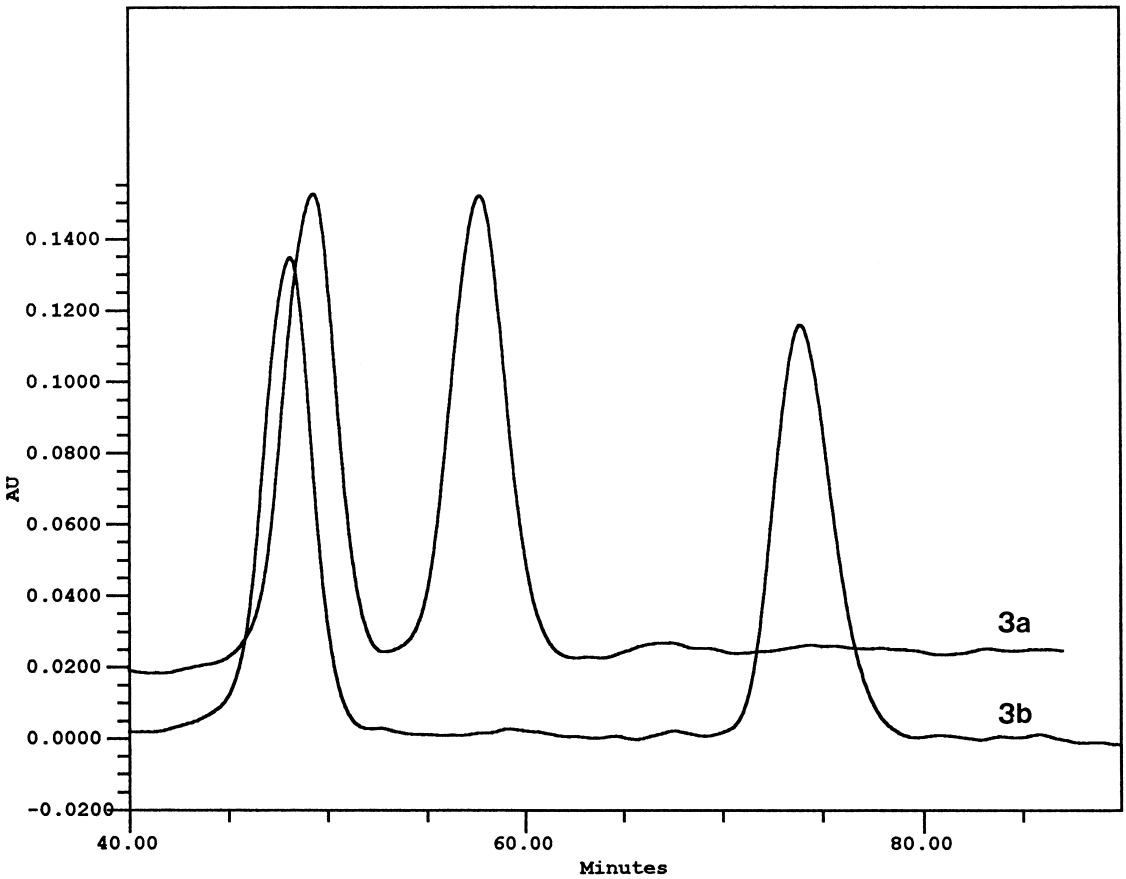

Fig. 4. Chromatograms (λ=200 nm) for compounds 3a and 3b (Eluent G; 0.7 ml min^{-1}; Chiralcel OJ).

(6.94, 1.11, 0.89) with Chiralcel OD-H and Chiralcel OJ phases respectively (0.7 ml min^{-1}; Eluent F). The Chiralcel OJ column gives better results compared to Chiralcel OD-H for 3b. The retention times of the two resolved peaks, in same eluting conditions are quite similar but a high increase in enantioselectivity factor (α) and resolution (R_s) is observed. For example with 3b the parameters (k', α, R_s) were (10.01, 1.07, 0.70) and (6.94, 1.29, 2.39) with Chiralcel OD-H and Chiralcel OJ phases respectively (0.7 ml min^{-1}; Eluent F).

From these data it is clear that the resolution abilities of the two columns are quite different OJ seems to be not well adapted for the enantioseparation of compounds 4 to the difference of OD-H even if, in this series, baseline separation (R_s>1.5) is only obtained for 4a.

Increasing the bulkiness of the acyl substituent led on a significant decrease in the enantioselectivity and in the resolution on Chiralcel OD-H phase but a significant increase in the enantioselectivity and in the resolution on Chiralcel OJ phase. For example with 3a, 3b the parameters (k', α, R_s) were: (7.90, 1.23, 2.16) and (10.01, 1.07, 0.70) (Chiralcel OD-H; Eluent F) or (9.06, 1.19, 1.63) and (8.76, 1.60, 5,00) (Chiralcel OJ; Eluent G). This remark is illustrated in the chromatograms (Figs. 2 and 3) [21–23,25]. In same eluting conditions we note a marked difference in the enantioseparation between 3a and 4a. This may be due to the presence of the methoxy group which may induce a supplementary H bonding with the CSP.

Also the temperature of the surrounding of the chiral column has been partly investigated with

compounds 3a, 4a as a potentional factor affecting the enantioselectivity [22]. It was found that lower temperature improved the separation on Chiralcel OD-H by the retention factor increased for 3a and decreased for 4a [21–23,25].

The resolution results of compounds described above indicated that the two columns, Chiralcel OD-H and OJ perform in a complementary fashion. The Chiralcel OD-H phase provided more baseline separations of the compounds 3, 4 than Chiralcel OJ. The good separation of optical isomers of 3 and 4 (i) makes this chromatographic method suitable for quantify optical purity and for studies in pharmacological distribution on one hand and (ii) opens the way, for some of them, to the rapid preparative HPLC isolation of individual enantiomers on the other hand.

References

[1] A. Miles, D.R.S. Philbrick, C. Thomson, in: Melatonin, Clinical Perspective, Oxford Medical Publications Oxford University Press, 1988.
[2] D. Dawson, N. Encel, J. Pineal. Res. 15 (1993) 1.
[3] E.J.W. Van Someren, M. Mirmiran, D.F. Swaab, Behav. Brain Res. 57 (1993) 235.
[4] D.S. Schlager, Am. J. Psychiatry 151 (1993) 1383.
[5] L. Wetterberg, J. Intern. Med. 235 (1994) 5.
[6] N.E. Rosenthal, C. Brown, D.A. Oren, G. Galetto, P.J. Schwartz, J.D. Malley, Photochem. Photobiol. 59 (1994) 314.
[7] P. Lissoni, S. Barni, M. Cazzaniga, A. Ardizzoia, F. Rovelli, F. Brivio, G. Tancini, Oncology 51 (1994) 344.
[8] R.J. Reiter, D. Melchiori, E. Sewerynek, B. Poeggeler, L. Sarlowwalden, J. I Chuang, G.G. Ortiz, Acunascastroviejo, D.J. Pineal. Res. 18 (1995) 1.
[9] E. Fourmaintraux, P. Depreux, D. Lesieur, B. Guardiola-Lemaitre, C. Bennejean, P. Delagrange, H.E. Howell, Bioorg. Med. Chem. 6 (1998) 9.
[10] P.J. Morgan, L.M. Williams, G. Davidson, W. Lawson, H.E. Howell, J. Mol. Endocrinol. 1 (1989) 1.
[11] P.J. Morgan, M. Lawson, G. Davidson, H.E. Howell, J. Mol. Endocrinol. 5 (1989) 3.
[12] A. Shibukawa and T. Nakagawa, Chiral separations by HPLC, AM. Krstulovic, Ed., Ellis Horwood Ltd., 1989, p. 477.
[13] K. Oguni, H. Oda, A. Ichida, J. Chromatogr. A 694 (1995) 91.
[14] Y. Okamoto, Y. Kaida, J. Chromatogr. A 666 (1994) 403.
[15] G. Liu, D.M. Goodall, A.T. Hunter, P.R. Massey, Chirality 6 (1994) 290.
[16] H.Y. Aboul-Enein, S.A. Bakr, P.J. Nicholls, J. Liq. Chromatogr. 17 (1994) 1105.
[17] K.M. Kirkland, J. Chromatogr. A 718 (1995) 9.
[18] Instruction Manual for Chiralcel OD-H, Daicel Chemical Industries, Baker France Instruction Manual for Chiralcel OJ, Daicel Chemical Industries, Baker France.
[19] A. Kunath, F. Theil, J. Wagner, J. Chromatogr. A 684 (1994) 162.
[20] C. Vaccher, M.P. Vaccher, J.P. Bonte, J. Chromatogr. A 771 (1996) 343.
[21] U. Selditz, S. Copinga, J.P. Franke, H. Wikstrom, R.A. DeZeeuw, Chirality 8 (1996) 574.
[22] D.T. Witte, J.P. Franke, F.J. Bruggeman, D. Dijkstra, R.A. DeZeouw, Chirality 4 (1992) 389.
[23] D.T. Witte, F.J. Bruggeman, J.P. Franke, S. Copinga, J.M. Jansen, R.A. De Zeeuw, Chirality 5 (1993) 545.
[24] J.M. Jansen, S. Copinga, G. Gruppen, R. Isaksson, D.T. Witte, C.J. Grol, Chirality 6 (1994) 596.
[25] S. Caccamese, G. Principato, M.C. Viaud, G. Guillaumet, J. Chromatogr. A 704 (1995) 83.
[26] D.T. Witte, J.P. Franke, P.J. Swart, R.A. DeZeeuw, Chirality 4 (1992) 62.
[27] S. Chumpradit, M.P. Kung, H.F. Kung, J. Med. Chem. 36 (1993) 4308.
[28] I. Rondelli, R. Corsaletti, E. Rendeti, D. Acerbi, M. Delcanale, G. Amari, P. Ventura, Chirality 8 (1996) 381.
[29] H. Wilkström, B. Andersson, D. Sanchez, P. Lindberg, L.E. Arvidsson, A.M. Johansson, J.L.G. Nilsson, K. Svensson, S. Hjorth, A. Carlsson, J. Med. Chem. 30 (1987) 602.
[30] C. Vaccher, P. Berthelot, N. Flouquet, M.P. Vaccher, M. Debaert, J. Chromatogr. A 732 (1996) 239.
[31] P. Castelnovo, Chirality 5 (1993) 181.
[32] A. Karlsson, L. Bjork, C. Petterson, N. Anden, U. Hacksell, Chirality 2 (1990) 90.
[33] Y. Okamoto, E. Yashima, Angew. Chem. Int. Ed. 37 (1998) 1020.