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Direct enantiomeric separation of mianserin and 6-azamianserin derivatives using chiral stationary phases

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Abstract

The direct enantiomeric separation of mianserin and 6-azamianserin and some of their derivatives, respectively, by means of HPLC using two different chiral selectors was investigated. For the cellulose-based Chiralcel OD column, a strong dependence of the lipophilicity of the compounds tested on the retention behaviour was observed. To some extent, this was also found for the enantiomeric separation on the amylose-based Chiralpak AD column. In some cases a complementary behaviour of these two phases was observed: racemic mixtures that could not be separated by one column could be resolved by the other one. © 1998 Elsevier Science Ltd

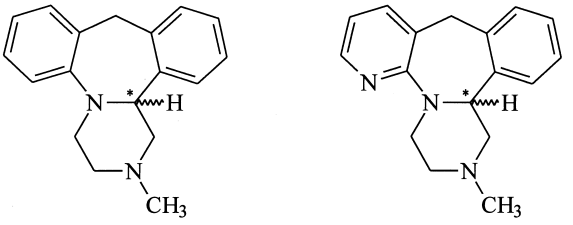
Keywords: Enantiomer separation; Chiral stationary phases, LC; Mianserin; 6-Azamianserin

1. Introduction

In recent years the importance of developing methods for the analysis of chiral compounds has increased in various fields, such as pharmaceuticals and agrochemicals, as well as in asymmetric synthesis. From the analytical tools available, direct high-performance liquid chromatography (HPLC) on chiral stationary phases (CSPs) has become a reliable method for the separation and determination of optical isomers. Several chiral selectors are presently marketed [1–3], with new selectors being introduced every year [4–6].

The tetracyclic compounds mianserin (**1**, Tolvon®) and 6-azamianserin (**2**, Mirtazapine®) are known to possess antidepressant activity [7–9], Fig. 1. This feature has been ascribed to their interaction with 5-HT receptors [10], as well as with presynaptic α-adrenoceptors. In addition, their noradrenaline uptake-inhibiting properties may be of importance for their clinical effects [11].

The α_2-blocking effect [12] and the affinities for



1 **2**

Fig. 1. Structures of (±)-mianserin (**1**) and (±)-6-azamianserin (**2**).

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5-HT_{1C} and 5-HT_2 receptors of **1** reside in the *S*-(+)-enantiomer [7,10]. In contrast, the enantioselectivity for 5-HT_3 receptors was reversed [10]. Similar results were found for **2** with regard to the blockade of the α_2-adrenoceptors, whereas the affinities for serotonergic receptors were shown to be considerably lower, as compared to mianserin [8,13]. Both compounds had negligible affinity for dopamine D_2 receptors [13].

The main metabolites of mianserin found in urine appear to be the N-desmethyl, 8-hydroxy- and N-oxide derivatives of mianserin [14]. It has been reported that the *R*-form is preferentially N-demethylated, while the *S*-form preferentially undergoes hydroxylation [15]. After administration of mianserin enantiomers to rats, the 8-OH metabolites have been found to be sulfate conjugates and free phenolic metabolites [16].

In order to make a mianserin derivative with a better metabolic stability than that of (+)- or (−)-mianserin, a triflate group was introduced in the molecule in the 8-position (see Fig. 2). The triflate group is known to be a biochemically and chemically stable functionality and is able to prevent aromatic ring oxidation and subsequent conjugation, thereby increasing the metabolic stability [17,18]. For comparison, the 8-triflate derivative of 6-azamianserin was also synthesized. Additionally, the effect of a nitro group as electron-withdrawing substituent, and of a hydroxy group as electron-donating substituent in the 8-position of either compound on the chiral separation was investigated.

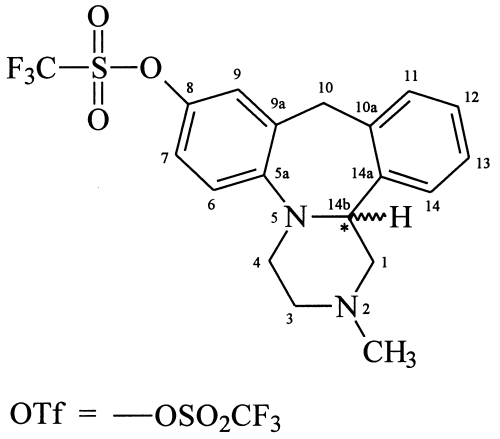

Fig. 2. Structure of (±)-8-OTf-mianserin (the asterisk marks the chiral center).

There have been reports about the enantiomeric separation of mianserin and its metabolites using cyclodextrins as chiral selectors in HPLC or in capillary electrophoresis [15,19]. In this paper the direct enantiomeric separation of mianserin and 6-azamianserin derivatives by means of analytical HPLC on a cellulose- and an amylose-based chiral stationary phase is reported, and an attempt is made to relate the observed separations to the lipophilicity (log *P* values) of the respective substances.

2. Experimental

2.1. Chemicals

The HCl salts of racemic mianserin and 6-azamianserin, as well as 8-hydroxy 6-azamianserin were kindly provided by Organon (Oss, The Netherlands). The triflate and nitro derivatives of either compound, as well as the 8-hydroxy mianserin, were synthesized in our Department of Medicinal Chemistry. A more detailed description of the synthetic procedures will appear elsewhere [20].

Ethanol LiChrosolv, gradient grade, and 2-propanol, extra pure, were obtained from E. Merck (Darmstadt, Germany). *n*-Hexane was purchased from Labscan (Dublin, Ireland), and triethylamine from Janssen Pharmaceutica (Beerse, Belgium).

2.2. Apparatus and columns

Chromatography was performed using a SP 8800 ternary HPLC pump (Spectra-Physics, Santa Clara, CA, USA) as solvent delivery system, which was connected to a WISP 710 A autosampler (Water Associates Inc., Milford, MA, USA) and a Spectroflow 757 absorption detector (Kratos Analytical Instruments, Ramsey, NJ, USA). Chromatograms were evaluated with a Shimadzu C-R3A integrator (Shimadzu, Tokyo, Japan).

The chiral columns used (25×0.46 cm I.D. Chiralcel OD and Chiralpak AD, respectively) were obtained via J.T. Baker (Deventer, The Netherlands) from Daicel Chemical Industries (Tokyo, Japan).

2.3. HPLC conditions

Analyses were carried out at room temperature (22°C). For UV detection the wavelength was set to 250 nm. Depending on the retention time of the second eluted enantiomer, the flow-rate was set to 0.5 or 1.0 ml/min, respectively.

About 2 mg sample was dissolved in 1 ml ethanol, gradient grade, and diluted with 4 ml of the eluent. Per run, 20 μl of this solution was injected.

The eluent mixture contained either 95% *n*-hexane and 5% ethanol (A) or 90% *n*-hexane and 10% 2-propanol (B). In both cases, 0.1% triethylamine was added to the eluent to prevent peak tailing. The eluents were prepared fresh every day and filtered before use through a 0.45-μm membrane filter (Schleicher & Schuell, Dassel, Germany).

Chromatographic data were calculated as follows: $\alpha = k_2'/k_1'$, $k_2 = (t_2 - t_0)/t_0$, $R_S = (t_2 - t_1)/[0.8496 (\text{height}_1/\text{area}_1 + \text{height}_2/\text{area}_2)]$. The peak of the solvent front was considered to be equal to the dead time and was taken from each particular run. It was about 3.5 min at a flow-rate of 1 ml/min.

The theoretical octanol–water partition coefficients for the various compounds were calculated with the PALLAS 1.2 program (CompuDrug, Budapest, Hungary), which utilizes the method presented by Rekker et al. [21] where the hydrophobic contributions of the molecular fragments are added.

3. Results and discussion

3.1. Mianserin and its derivatives

The chromatographic data of the separation of mianserin and its derivatives on the chiral columns are given in Table 1. Under the conditions chosen, the enantiomers of mianserin could be baseline separated on both types of CSP in a short time. The introduction of a hydroxy group in the 8-position led to a decrease in selectivity, probably due to the interactions of the hydroxy substituent with the supporting silica gel (to be noted: the carbamate derivatives of cellulose and amylose are coated onto the silica surface).

In contrast to the 8-OH-mianserin, the substitution of the parent compound with a triflate group in the 8-position led to a strongly improved separation on the cellulose selector, as compared to mianserin itself. Such a substitution affects the enantioseparation in two ways. On the one hand, it causes the less and more optimal presentation of the respective triflate mianserin enantiomers towards the chiral selector, which is reflected in their lower and higher capacity factors, respectively, as compared to the capacity factors of the least and most retained enantiomers of mianserin. On the other hand, the relatively enhanced π-acidity of the substituted aromatic ring in the mianserin molecule, caused by

Table 1
Chromatographic data of mianserin and its derivatives obtained on the analytical Chiralcel OD (CC-OD) and Chiralpak AD (CP-AD) columns

Column	Eluent	Chrom. data	Mian	8-OH-mian	8-NO_2-mian	8-OTf-mian
CC–OD	A	α	1.35	1.08	1.24	3.63
		k_2'	0.77	4.56	1.91	1.52
		R_S	2.58	1.03	2.73	5.12
	B	α	1.26	1.15	1.47	5.09
		k_2'	0.97	3.15	2.51	2.72
		R_S	1.65	1.37	4.17	13.36
CP–AD	A	α	2.68	1.00	2.94	2.71
		k_2'	1.04	3.59	4.25	1.11
		R_S	6.87	0.00	14.57	7.14
	B	α	2.36	1.24	3.47	3.44
		k_2'	0.94	3.65	4.33	1.47
		R_S	5.54	2.29	17.64	9.52

[a]95% *n*-hexane, 5% ethanol, 0.1% TEA.
[b]90% *n*-hexane, 10% 2-propanol, 0.1% TEA.

the electron-withdrawing properties of the triflate group, allows much stronger π–π interactions of this analyte with the π-basic carbamate residues of the cellulose-based CSP than expected for the non-substituted mianserin. The combination of these two effects is supposed to result in a more stable transient diastereomeric complex between the chiral selector and the most retained enantiomer of 8-triflate mianserin than between the chiral selector and the most retained enantiomer of mianserin.

Regarding the amylose selector, it can be noted that the improvement of the selectivity is, firstly, not as high as that observed for the cellulose phase and, secondly, dependent on the eluent composition.

The fact, that the mianserin triflate enantiomers can be separated on both polysaccharide stationary phases in a short time with excellent chromatographic characteristics is quite interesting, because this is not in line with earlier findings, which indicated a complementary selectivity of the cellulose- and amylose-based stationary phases for another series of basic compounds: compounds that could not be separated on one of the CSPs could often be separated on the other one [22].

On both columns and with both eluent mixtures, the (*R*)-(−)-enantiomer of the triflate compound eluted first. The elution order was determined by collecting the peaks and measuring the optical rotation of the solutions obtained, as described elsewhere [20].

The substitution of mianserin with a nitro group as electron-withdrawing substituent in the 8-position showed some interesting results too. With eluent mixture A, the selectivity of the Chiralcel OD column for this analyte decreased, whereas it slightly increased with eluent B, as compared to mianserin. However, there is a quite remarkable change in the separation behavior to be seen on the Chiralpak AD column. With eluent mixture A, the selectivity factor, and especially the resolution, are higher than those obtained for the parent compound. This is in contrast to the results of 8-triflate mianserin, the other derivative with an electron-withdrawing substituent. Here, the separation behaviour on the Chiralcel OD column is improved enormously with both eluent mixtures, as compared to mianserin, whereas on the Chiralpak AD column there is only a slight increase in selectivity to be seen for eluent A, and a somewhat higher one for eluent mixture B, but not as dramatic as seen with the cellulose-based CSP. These findings may indicate that, besides the electronic properties of the derivatives, the steric features also play an important role in the chiral recognition mechanism of these analytes.

For a better explanation of the above findings, we investigated the relationship between the octanol–water coefficient $\log P$, which is a measure of the lipophilicity of a compound, and the α values of the respective analytes. A similar relationship between a lipophilicity parameter and retention data was also investigated by Roussel and co-workers for a set of related atropisomers [23,24]. They reported a linear correlation between the lipophilicity parameter $\log k'w$ (determined by HPLC) and the capacity factors of the (+)-isomers of a set of N-arylthiazolin-2-(thi)-ones on cellulose-based chiral stationary phases, which was dependent on the position of the substituents. The vertical deviation of the (−)-isomer from the lipophilicity line in these plots should then reflect the chiral discrimination, the latter being attributed to other effects than sheer lipophilicity interactions with the CSP. Roussel et al. used their approach in a series of related substances in which the position of the substituent varied. In our studies, we applied the partition coefficient $\log P_{calc.}$, calculated by means of the PALLAS 1.2 program [25], to evaluate the impact of the nature of the substituent present in the same position on the retention behaviour and the enantioselectivity. The chromatographic data presented in Table 1 were therefore related to the calculated $\log P$ values of mianserin and its derivatives, listed in Table 2.

The study revealed two findings: firstly, in accordance with Roussel's results, an almost linear relationship between the lipophilicity parameter and the retention parameters of the first eluted enantiomers of the mianserin derivatives was found ($r=-0.999$ for Chiralcel OD, $n=3$; $r=-0.999$ for Chiralpak AD, $n=3$), as pictured in Fig. 3, yet the non-substi-

Table 2
Log *P* values of mianserin and its derivatives as calculated by means of the PALLAS program [25]

	Mianserin	8-OH-mian	8-NO_2-mian	8-OTf-mian
$\log P_{calc.}$	3.05	2.49	3.12	3.87

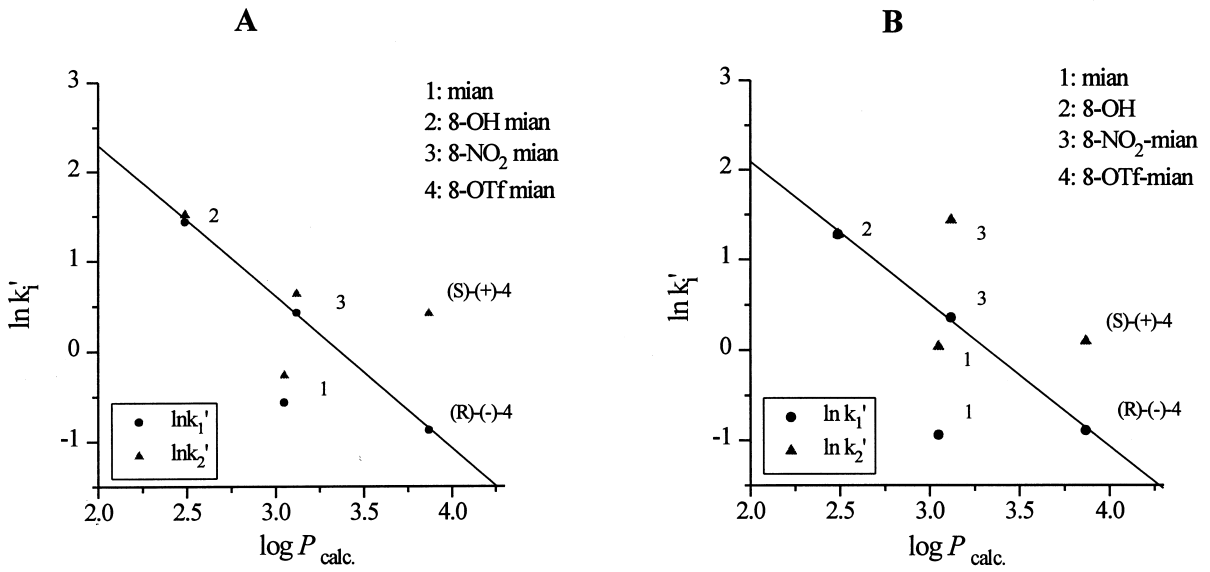

Fig. 3. Plots of $\ln k_i'$ vs. $\log P_{calc.}$ for mianserin and derivatives on the basis of retention parameters obtained on Chiralcel OD (A) and Chiralpak AD (B), respectively. HPLC conditions: 5% ethanol in *n*-hexane, 0.1% TEA, 1.0 ml/min, 250 nm.

tuted mianserin itself deviated significantly from the trend. The imaginary curves of the second eluted enantiomers in Fig. 3A and Fig. 3B are also interesting. Whereas the shape of the $\ln k_2'$ curve for the Chiralcel OD column is concave relative to the *x*-axis, it is convex for the curve observed on the Chiralpak AD column.

The second important finding of our investigation concerns the relation between the lipophilicity and the selectivity parameters: the higher the value of log *P*, the higher the selectivity (see Fig. 4). Hereby, it is obvious from Fig. 4A and Fig. 4B, that the two CSPs exhibit a complementary behaviour. However, the 8-nitro derivative of mianserin seems to be a minor deviation.

Although the nitro group has a strong electron-withdrawing impact on the aromatic ring system, the calculated log *P* value of 8-NO_2 mianserin is close to that of mianserin (Table 2). Therefore, one would expect from the postulated trend above, that the selectivity factor α is in the same order as that of mianserin. In the case of the Chiralcel OD column, this trend was generally confirmed by the results, although the selectivity factors with 2-propanol in *n*-hexane were slightly higher, and with ethanol in *n*-hexane slightly lower than those of mianserin. This behaviour may be explained by the influence of the organic modifier on the chiral recognition process. Firstly, different solvation mechanisms on the enantiomers can occur for different modifiers, as was discussed by Pirkle and Welch [26] and by Cantrell et al. [27]. Secondly, the competition between the modifier and the analyte molecules for the chiral and achiral binding sites on the CSP must be considered [28–31]. This modifier–CSP interaction appears to be dependent on the polarity and the steric bulk of the alcoholic modifier, which can affect the geometry and/or steric environment of the chiral cavities, and thus the stereoselectivity [32].

On the Chiralpak AD column, the 8-NO_2 analogue also showed some deviations from the trend as it was slightly better resolved than the 8-triflate mianserin, although the latter has the higher log *P* value. Here, the bulkiness of the triflate group can be considered a restraint to fully profit from the charge-transfer interactions between the π-basic chiral selector and the π-acidic analyte.

3.2. 6-Azamianserin and its derivatives

Since the chemical structures of mianserin and 6-azamianserin only differ in the nature of one of the

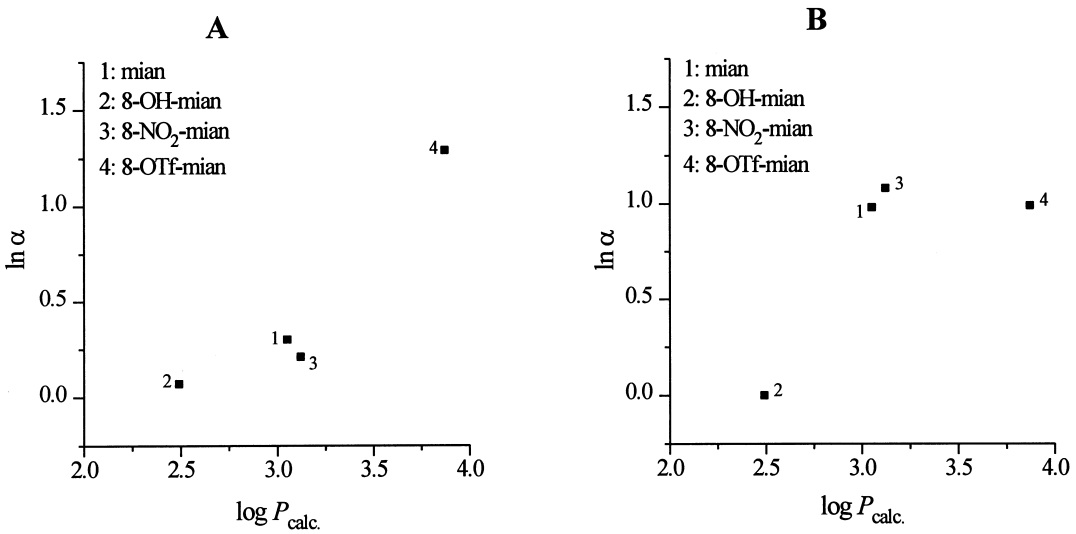

Fig. 4. Relationship between the lipophilicity parameters and the enantioselectivities of mianserin and its derivatives on Chiralcel OD (A) and Chiralpak AD (B), respectively. HPLC conditions: 5% ethanol in *n*-hexane, 0.1% TEA, 1.0 ml/min, 250 nm.

aromatic rings, one would expect that these two substances, and their respective derivatives, show a similar selectivity on both types of stationary phases. With regard to the Chiralcel OD column, this assumption was confirmed by the results obtained (Table 3).

The resolution of the enantiomers of 6-azamianserin on the Chiralcel OD column was even higher with both eluent mixtures, as compared to mianserin. The change in polarity, caused by the introduction of a nitrogen into the aromatic ring system may be responsible for this behaviour. The electron density distribution of the pyridine ring is quite different from that in the benzene ring. In the latter the electrons are, in the unsubstituted state, equally distributed over the ring. In the case of a pyridyl ring, the highest electron density is located on the nitrogen atom, whereas it is the lowest at positions 2,

Table 3
Chromatographic data of 6-azamianserin and its derivatives obtained on the analytical Chiralcel OD (CC-OD) and Chiralpak AD (CP-AD) columns

Column	Eluent	Chrom. data	6-Azamian	8-OH-6-azamian	8-NO_2-6-azamian	8-OTf-6-azamian
CC–OD	A	α	1.37	1.17	1.33	3.29
		k'_2	1.36	4.29	2.76	2.09
		R_S	3.69	1.30	2.99	11.41
	B	α	1.62	1.05	1.29	3.84
		k'_2	1.71	3.69	2.77	3.12
		R_S	4.68	0.45	2.42	11.27
CP–AD	A	α	1.23	1.24	1.31	1.24
		k'_2	2.07	5.99	6.61	1.14
		R_S	2.54	2.24	3.62	1.98
	B	α	1.10	1.14	1.46	1.36
		k'_2	1.36	2.52	4.73	0.99
		R_S	0.95	0.84	5.54	2.61

[a]95% *n*-hexane, 5% ethanol, 0.1% TEA.
[b]90% *n*-hexane, 10% 2-propanol, 0.1% TEA.

6 and 4 [33]. This is caused by the higher electronegativity of the nitrogen atom, as compared to the carbon atom. Another feature that expresses the polarity of the pyridine molecule is the dipole moment. Since it is supposed that chiral recognition on polysaccharide-based stationary phases is also a matter of dipole–dipole interactions, a change of the dipole moment in certain regions of a molecule can have an impact on the separation behaviour of this particular analyte.

The introduction of a hydroxy group in the 8-position of the 6-azamianserin molecule causes a similar retention behaviour as seen with the 8-OH-mianserin, at least for the Chiralcel OD column. With both eluent mixtures only small separations were obtained.

This is not the case with regard to the Chiralpak AD column. When using eluent A, a baseline separation of 8-OH-6-azamianserin could be observed, whereas there was no separation at all for the 8-OH derivative of mianserin. When using eluent B, the racemic mixture of 8-OH-mianserin was better resolved, as compared to the 8-OH derivative of 6-azamianserin. In all cases, the high k_2' values indicate a strong achiral interaction of the analytes with the CSPs.

The optical isomers of the 8-nitro analogue of 6-azamianserin can be resolved on the Chiralcel OD in a comparable way to the respective enantiomers of the 8-nitro derivative of mianserin. However, the parent compound, 6-azamianserin, was slightly better separated than the 8-nitro derivative with both eluent mixtures. When looking at the chromatographic behaviour of the enantiomers of 8-NO_2-6-azamianserin on the Chiralpak AD column, as compared to the Chiralcel OD column, we do not see such a dramatic increase in selectivity and resolution, as observed for the respective mianserin analogue. As with the latter analyte, the selectivity of the amylose-based stationary phase for 8-nitro-6-azamianserin was better with eluent mixture B, as compared to eluent mixture A.

In contrast to the 8-OTf derivative of mianserin where, on both polysaccharide stationary phases, the retention behaviour depended on the organic modifier chosen, the separation of the enantiomers of 8-OTf-6-azamianserin was virtually independent on the eluent mixture on either CSP. The differences in the chromatographic data of eluent A and B on the particular columns are only small. However, the Chiralcel OD column showed a much better selectivity for this compound than the Chiralpak AD column.

Generally, the separation of the enantiomers of

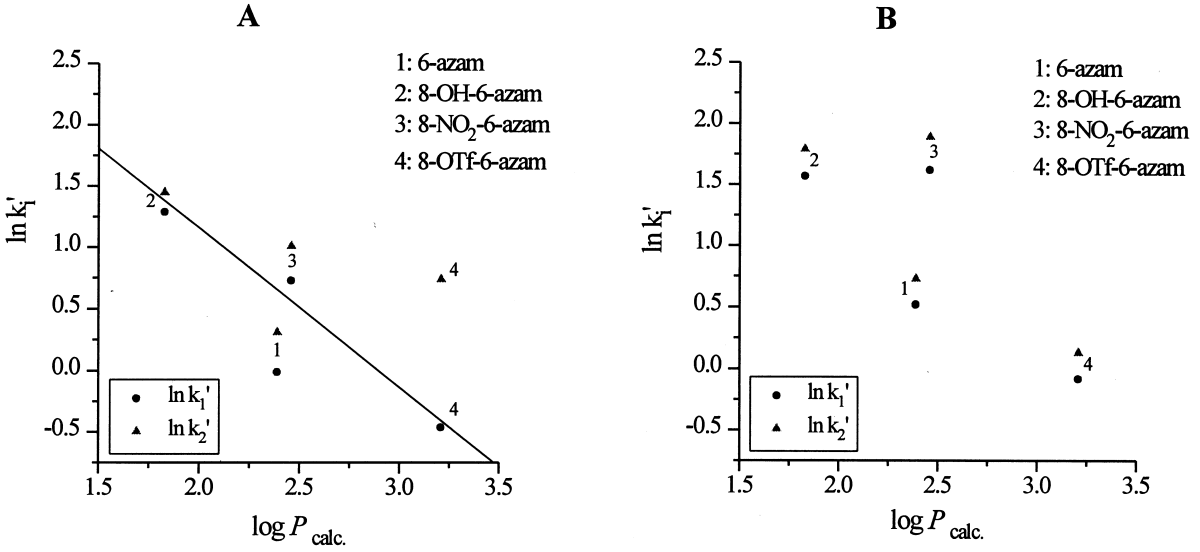

Fig. 5. Plots of $\ln k_i'$ vs. $\log P_{calc.}$ for 6-azamianserin and derivatives on the basis of retention parameters obtained on Chiralcel OD (A) and Chiralpak AD (B), respectively. HPLC conditions: 5% ethanol in *n*-hexane, 0.1% TEA, 1.0 ml/min, 250 nm.

Table 4
Log P values of 6-azamianserin and its derivatives as calculated by means of the PALLAS program [25]

	6-Azamianserin	8-OH-6-azamian	8-NO_2-6-azamian	8-OTf-6-azamian
Log $P_{calc.}$	2.39	1.83	2.46	3.21

6-azamianserin and its 8-nitro and 8-triflate derivatives on the Chiralpak AD column is much smaller, as compared to their respective mianserin analogues.

As with mianserin and its derivatives, we investigated for the 6-azamianserin series the relation between the calculated log P values and ln k_i' values, which is shown in Fig. 5 and Table 4.

The log $P_{calc.}$ values of 6-azamianserin and its derivatives are lower than the respective ones for the mianserin series, because the pyridyl ring in the 6-azamianserin derivatives has a higher polarity than the benzene ring in the corresponding mianserin derivatives.

From Fig. 5A and Fig. 5B it can be seen that on the Chiralcel OD column the relation between ln k_1' and log $P_{calc.}$ for the 6-azamianserin derivatives remained ($r=-0.988$, $n=3$), whereas on the Chiralpak AD column the nitro derivative deviates significantly from the earlier observed trend and, yet, the non-substituted mother compound is closer to it. Furthermore, the shapes of the imaginary curves for ln k_2' of the 6-azamianserin derivatives, relative to the x-axis, remained the same as observed for the mianserin derivatives.

The enantiomers of 8-triflate 6-azamianserin could be resolved by either eluent mixture on the Chiralcel OD column with excellent chromatographic results. Since the triflate derivative has the highest log P value, this result is in agreement with our earlier finding, that the higher the lipophilicity, expressed by the log P value, the higher the selectivity factors. Contrary to the mianserin series, we observed on the Chiralcel OD column, with either eluent mixture, a slightly better separation of the parent compound, 6-azamianserin, as compared to the 8-nitro derivative, although the lipophilicity parameters of both compounds are in the same order. For the Chiralpak AD column this relationship was reversed. Generally, on the Chiralpak AD column, the selectivity factors remained rather low and, above all, the same for the various compounds, despite increasing log P values.

4. Conclusions

The general trend found in the present investigations is: the higher the lipophilicity of the racemic compound, the better the enantiomeric separation. In the case of mianserin and 8-nitro mianserin, the Chiralpak AD column showed better chromatographic results than the Chiralcel OD column, whereas for the 8-triflate derivative the selectivity of the cellulose-based CSP was higher. For 6-azamianserin and its 8-triflate derivative the situation is reversed. Here the cellulose-based stationary phase is more selective. The 8-nitro derivative of 6-azamianserin can best be resolved on the Chiralpak AD column. The chiral resolution is dependent on the eluent composition. In general, using 2-propanol as organic modifier revealed higher selectivities than ethanol, without substantial increases in capacity factors. The optical isomers of the 8-OH derivatives of both compounds could neither be adequately resolved on the Chiralcel OD nor on the Chiralpak AD column. This is likely due to the strong interaction of the hydroxy substituent with the non-chiral support material, silica gel.

Acknowledgements

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