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Note

Direct resolution of the optical isomers of fenoldopam and one of its derivatives

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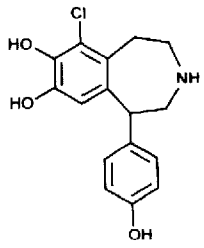
Fenoldopam (**1**) (6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol) is a new drug currently at an advanced stage of development by Smith Kline and French. Oral administration of this drug leads to an increase in renal blood flow and a corresponding reduction in arterial pressure[1]. The biological activity of fenoldopam is attributed[2] to stimulation of renal dopamine D_1-receptors.



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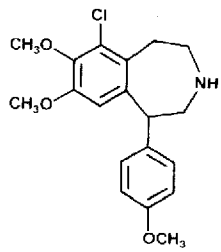

2

Following oral administration, fenoldopam is extensively metabolised[3] to give methoxy, sulphate and glucorinide derivatives. Both fenoldopam and its metabolites have been successfully analysed[4,5] under reversed-phase conditions. All these studies were carried out using racemic fenoldopam.

In this Note we describe an analytical method that is suitable to differentiate between the optical isomers of fenoldopam. This method was also used to resolve the optical isomers of **2**, where the three hydroxy groups in fenoldopam have been replaced by methoxy substituents. These studies are expected to be relevant for pharmacokinetics and pharmacodynamic studies on fenoldopam. The enantiomers of fenoldopam have been chemically resolved[6] previously after formation of a single diastereoisomeric salt with enantiomerically pure dibenzoyl tartaric acid.

EXPERIMENTAL

Chemicals

n-Hexane (Rathburn, Walkerburn, U.K.) and propan-2-ol (BDH, Poole, U.K.) were filtered through a Millipore 0.45-μm membrane filter and degassed with helium

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before use. The racemic **1** and **2** used were greater than 98% purity. **2** is an intermediate in the penultimate step in the preparation[7] of **1**.

High-performance liquid chromatography

A Perkin-Elmer Series 3B liquid chromatograph was used. Enantiomers were monitored with a Perkin-Elmer LC90 UV spectrophotometric detector set at 220 nm. The chromatographic column used for the chiral separation was a Chiralcel OJ (250 × 4.6 mm I.D., 10 μm) column (Daicel, Tokyo, Japan), operated at room temperature. The best resolution of the enantiomers of **1** and **2** was obtained using hexane–ethanol (80:20) and flowing at 1 ml min^{-1}.

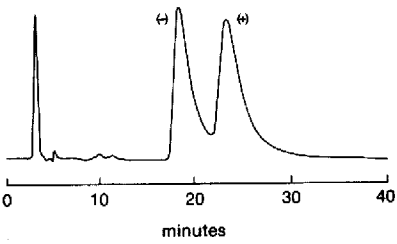
Specific rotation $[\alpha]_D^T$

Repeat injections of racemic **1** gave adequate quantities of the respective optical isomers for the measurement of their specific rotations. These were determined by dissolving the samples in methanol and measuring optical rotation in a cell of 100 mm pathlength, thermostatted at 25°C and using a Perkin-Elmer 241 polarimeter set at the sodium D-line (589 nm).

RESULTS AND DISCUSSION

Fig. 1 and 2 show the chiral resolution of the optical isomers of fenoldopam **1** and its methoxy derivative **2**. The α values were measured as 1.32 and 1.33, respectively. In the case of **1** the (−)-enantiomer elutes before the (+)-isomer with retention times of 18.4 and 23.5 min. The retention times of the enantiomers derived from **2** are shorter than those of **1** and were measured as 13.3 and 16.4 min. Unfortunately, the enantiomers from **2** could not be characterised by their optical rotation as the racemic material was not available in a sufficient quantity.

From an examination of the chemical structure of fenoldopam **1** and its methoxy derivative **2** it is expected that the former is more hydrophilic than the latter compound. This agrees with the order of elution of these molecules using the reversed-phase conditions in this study. Thus the more hydrophilic compound **1** is



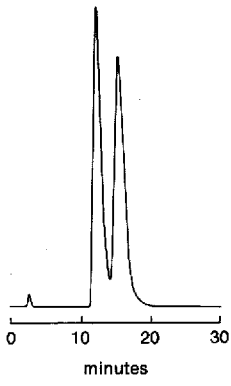


Fig. 1. Separation of the enantiomers of fenoldopam **1**. For conditions, see Experimental.

Fig. 2. Resolution of the optical isomers of **2**. For conditions see Experimental.

retained by the polar stationary phase to a greater extent than **2**. This difference in retention time is augmented if the ratio of hexane to ethanol is increased and could be convenient for the study of any stereoselective metabolism involving methoxylation or dehydroxylation of any of the three hydroxy groups in fenoldopam. At least four of the metabolites formed from fenodopam have in fact been found to result from such processes[5], although no stereoselective studies have been carried out. These types of metabolites are expected to have retention times lying in between those of **1** and **2**.

Polarimetric analysis of enriched fractions from repeat injections was carried out in order to characterise the optical isomers of fenoldopam by their ability to rotate the plane of polarisation of plane-polarised light. Reanalysis of the first and second fractions collected showed that each contained the respective optical isomers in a purity greater than 99%. The specific rotations, $[\alpha]_D^{25}$ for the first and second eluted isomers (corresponding to the first and second fractions) were measured in methanol at a concentration of 2 mg ml^{-1} and were found to be $-11.3°$ and $+11.8°$ respectively. These values are of the same order of magnitude as the values of $-10.5°$ and $+9.2°$ reported[6] for the *S*- and *R*-isomer, respectively. Combining our $[\alpha]_D^{25}$ values with the latter information it also appears that the *S*-isomer elutes before the *R*-isomer using a Chiralcel OJ column operated under the chromatographic conditions reported in this Note.

REFERENCES

1 R. M. Stote, J. W. Dubb, R. G. Familiar, B. B. Erb and F. Alexander, *Clin. Pharmacol. Ther.*, 34 (1983) 309.
2 H. O. Ventura, F. H. Messerli, E. D. Frohlich, I. Kobrin, W. Oigman, F. G. Dunn and R. M. Carey, *Circulation*, 69 (1984) 1142.
3 J. A. Ziemiak, N. Allison, V. K. Boppana, J. Dubb and R. Stote, *Clin. Pharmacol. Ther.*, 41 (1987) 275.
4 V. K. Boppana, F. C. Heineman, R. K. Lynn, W. C. Randolph and J. A. Ziemniak, *J. Chromatogr.*, 487 (1984) 385.
5 V. K. Boppana, K. M. Dolce, M. J. Cyronak and J. A. Ziemniak, *J. Chromatogr.*, 487 (1989) 385.
6 C. Kaiser, P. A. Dandridge, J. Weinstock, D. A. Ackerman, H. M. Saru, P. E. Setler, R. L. Webb, J. W. Horodniak and E. D. Matz, *Acta Pharm. Suec.*, 2 (1983) 132.
7 J. Weinstock, J. W. Wilson, D. L. Ladd, C. K. Brush, F. R. Pfeiffer, G. Y. Kuo, K. G. Holden, N. C. F. Yim, R. A. Hahn, J. R. Wardell, A. J. Tobia, P. E. Setler, H. M. Sarau and P. T. Ridley, *J. Med. Chem.*, 23 (1980) 973.