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Stereoselectiveseparation of racemic *trans*-paroxol, *N*-methylparoxetine and paroxetine containing two chiral carbon centres by countercurrent chromatography

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ABSTRACT

Racemic *trans*-paroxol, *trans*-*N*-methylparoxetine and *trans*-paroxetine containing two chiral centres were stereoselectively separated using countercurrent chromatography with hydroxypropyl-β-cyclodextrin as the chiral selector. A two-phase solvent system composed of *n*-butyl acetate and 0.1 mol L^{-1} sodium carbonate-sodium bicarbonate buffer at pH 9.2 (1:1, v/v) was selected, and 0.10 mol L^{-1} hydroxypropyl-β-cyclodextrin was added to the aqueous phase as the chiral selector. Racemic *trans*-*N*-methylparoxetine and racemic *trans*-paroxol (20 mg of each) were stereoselectively separated by countercurrent chromatography in an individual run, yielding 7.1–8.3 mg of enantiomers with a purity of 95–98%, where the recovery of each separated isomer reached approximately 70–83%. Racemic *trans*-paroxetine (20 mg) was stereoselectively separated by countercurrent chromatography using a recycling elution mode with a biphasic solvent system composed of *n*-hexane: *n*-butyl acetate: 0.1 mol L^{-1} sodium carbonate-sodium bicarbonate buffer at pH 9.2 (9:1:10, v/v/v), and 0.10 mol L^{-1} hydroxypropyl-β-cyclodextrin was added to the aqueous phase as the chiral selector, yielding 5.0–5.6 mg of enantiomer with a high purity of over 98–99%.

1. Introduction

The stereoselective separation of medicinal components is extremely important in the pharmaceutical industry since many drugs may contain chiral carbon centres. Enantiomers with different optical activities can result in different biological activities due to stereochemical requirements [1]. Paroxetine possesses two chiral carbon centres and has four stereoisomers, two in *cis* and two in *trans* configurations. As shown in Fig. 1, the active stereoisomer is the (-)-*trans* configuration,(-)-*trans*-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine, which is clinically used as a well-known antidepressant drug and for other indications, such as obsessive-compulsive disorder, panic disorder and generalized anxiety disorder [2,3]. Many synthetic routes to prepare (-)-*trans*-paroxetine have been reported, in which racemic *trans*-paroxol, i.e., racemic *trans*-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine, is reported to be a key synthetic intermediate to prepare the antidepressant drug [4–13].

The following two methods are generally applied for the preparation of (-)-*trans*-paroxetine: the first is diastereoisomeric crystallization after synthesis of racemic *trans*-paroxetine and the second is asymmetric synthesis of optically active (-)-*trans*-paroxetine. Although significant progress has been made in asymmetric synthetic methods to obtain optically active (-)-*trans*-paroxetine, the high cost of the stereospecific catalyst and difficult reaction conditions do not allow for most asymmetric reactions to be applied in industrial manufacturing [14–16]. Therefore, enantiomeric separation to obtain (-)-*trans*-paroxetine is still an acceptable method to prepare the optically active enantiomer [17–20]. Meanwhile, it is well known that it would be much more efficient and economical to synthesize enantiomeric drugs if the synthetic route is derived from an enantiomeric starting material with a high optical activity. Therefore, it is important to establish an efficient method for chiral resolution of *trans*-paroxetine and its synthetic intermediates. Fig. 1 also shows a typical synthetic route to prepare racemic *trans*-paroxetine using racemic *trans*-paroxol as the starting material via four steps: esterification, etherification, methyl acylation and hydrolysis [17,21,22].

The stereoselective separation of racemates containing multiple chiral centres using various chromatographic techniques remains a challenging task. Only a limited number of scientific reports are

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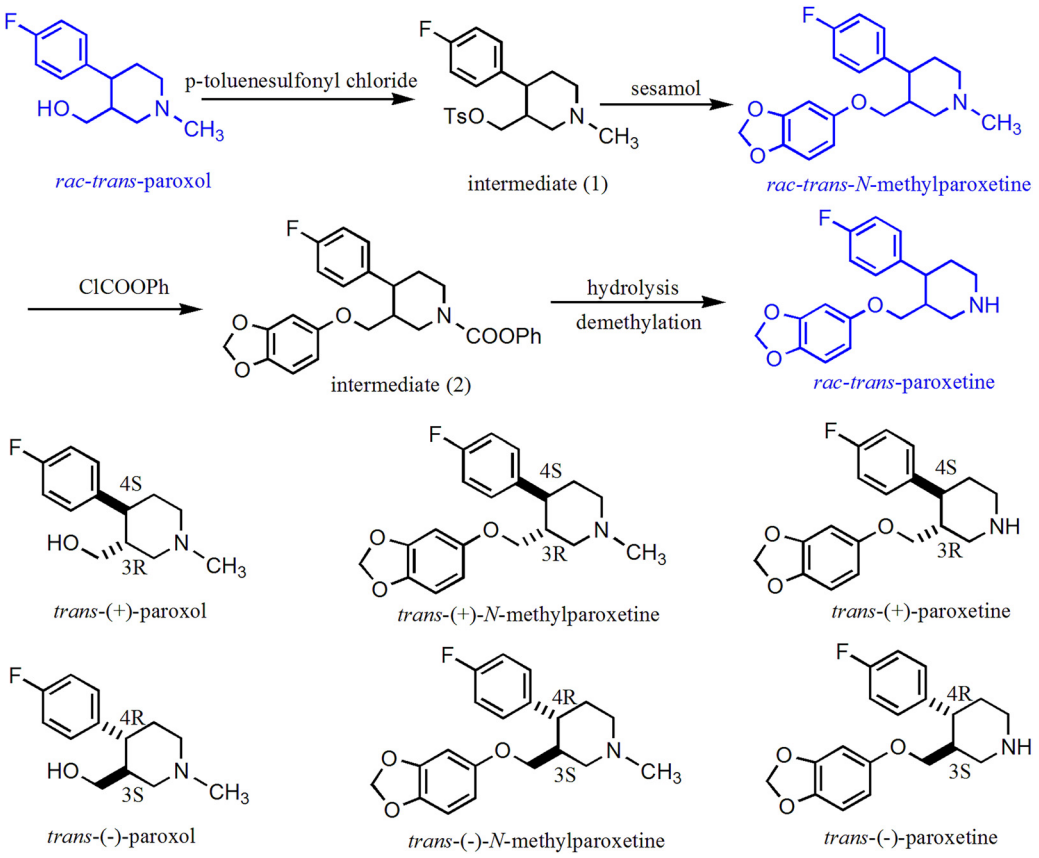

Fig. 1. Synthesis of racemic *trans*-paroxetine from racemic *trans*-paroxol through four steps and their stereochemical structures.

available that focus on the stereoselective separation of racemates with more than one chiral centre by chromatography and capillary electrophoresis [23–29]. Though many literature reports about the stereoselective analysis of racemic *trans*-paroxetine and its two precursors, *trans*-*N*-methylparoxetine and *trans*-paroxol, by liquid chromatography are available, all reported chromatographic methods have mainly been developed for analytical purposes [30–36]. Countercurrent chromatography is a liquid-liquid partition chromatography technique that can easily be scaled up with a low cost of operation and maintenance. This technique has been widely used for the preparative separation of chemical components from natural products [37]. However, only a small number of literature reports examining enantioseparations and stereoselective separations by countercurrent chromatography are available compared with traditional chromatographic methods due to the low number of theoretical plates of separation columns. Furthermore, it is difficult to find a chiral selector showing higher enantiorecognition than in traditional chromatography [38]. Almost all applications of countercurrent chromatography in stereoselective separations involve enantioseparation of racemates with one chiral centre [39,40]. In our previous work [41], two β-adrenergic blocking agents containing two chiral centres were stereoselectively separated by countercurrent chromatography using di-*n*-hexyl L-tartrate and boric acid as the chiral selectors. This study demonstrates the first successful stereoselective separation of optical isomeric compounds containing two chiral centres by countercurrent chromatography. In the present work, the successful stereoselective separation of racemic *trans*-paroxetine and its two precursors containing two chiral centres by countercurrent chromatography with substituted β-cyclodextrin as the chiral selector is reported.

2. Experimental section

2.1. Apparatus

TBE-200 V and TBE-300 A preparative multilayer coil planet centrifuges (Shanghai Tauto Biotechnique, Shanghai, China) were used in the present work, each equipped with a set of three multilayer coil separation columns connected in series. The preparative column consisted of 1.6 mm ID PTFE tubing with a total capacity of 190 ml (TBE-200 V) and 270 ml (TBE-300 A). The β values of the preparative columns ranged from 0.45 to 0.81 for 200 V and 0.46 to 0.73 for 300 A (β=r/R, R = 5.5 cm for 200 V and R = 6.5 cm for 300 A, where r is the distance from the coil to the column holder shaft, and R is the revolution radius or the distance between the column holder shaft and the central axis of the centrifuge). The revolution speed of the coiled columns can be regulated with a speed controller in the range of 0 to 1000 rpm for the preparative centrifuge, where the optimum speed of 800 rpm was used. The separation columns were installed in a vessel that maintains column temperature by a model SDC-6 constant-temperature controller (Ningbo Scientz Biotechnology Co. Ltd., Ningbo, China). The solvents were pumped into the column with a model TBP 5002 constant-flow pump (Shanghai Tauto Biotechnique, Shanghai, China). Continuous monitoring of the effluent was achieved with a model UVD-200 detector (Shanghai Jinda Biotechnology Co., Ltd., Shanghai, China), and a SEPU3000 workstation (Hangzhou Puhui Technology, Hangzhou, China) was employed to record the chromatogram.

The high-performance liquid chromatography (HPLC) used was a CLASS-VP Ver.6.1 system (Shimadzu, Japan) comprised a Shimadzu SPD20Avp UV detector, a Shimadzu LC-20ATvp Mul-

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