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[C001]

An improved process for the preparation of S-Citalopram

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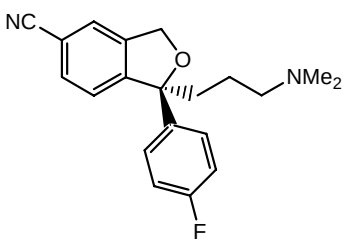
The three major classes of drugs available for the treatment of depression are the tricyclic antidepressants (TCAs), monoamine oxidase (MAO) inhibitors and the selective serotonin reuptake inhibitors (SSRIs). Citalopram, an SSRI introduced in 1989 for the treatment of depression, is a racemic mixture and the entire inhibition activity resides in the S-(+)-enantiomer, also known as escitalopram 1.

The resolution of the intermediate 4-(4-dimethylamino)-1-(4′-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl) benzonitrile, II, into its enantiomers and finally the stereoselective conversion of the desired enantiomer to the corresponding S-citalopram has also been reported.



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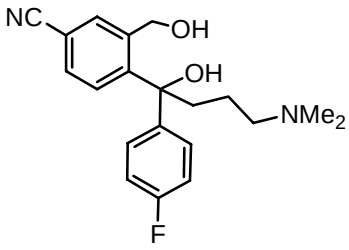

II

We herein, report a convenient and efficient resolution process for the intermediate, the racemic diol, wherein the S-diol is obtained in pure form, which is basified and then cyclized to give S-citalopram of >99% enantiomeric purity. The method provides an easy way to improve the enantiomeric purity of S-citalopram that is obtained by diastereomeric salt crystallization method as compared to the other processes. The novelty of this process is that the enriched diastereomeric salt is crystallized two times using a medium polar solvent, before it is released as a free base. This does away with the cumbersome two stage purification process of the other reported processes.

All chemicals were obtained from Aldrich Chemical Company (USA) and racemic diol hydrobromide from Ind-swift Laboratories (INDIA). Proton magnetic resonance (NMR) spectra were recorded on a Bruker 300MHz spectrometer in $CDCl_3$. The chemical shifts are reported in δ (ppm) relative to internal standard tetramethylsilane (TMS). Mass spectroscopy was conducted using Shimadzu QP5000 mass spectrometer. Specific rotations were taken on Autopol IV automatic polarimeter.

Chromatographic separation: - Chiral HPLC was done using Chiral AGP column (150x4.0 mm) and a mobile phase of 10 mM hexanoic acid and 3.0 mM SB-12 [dodecyldimethyl (3-sulfopropyl) ammonium hydroxide, inner salt, lauryl sulfobetaine] in phosphate buffer pH 6.5. The other conditions used for the chiral column are the flow rate being 0.5 ml /min, column temperature 30^0C, injection volume 15µl and UV detector wavelength 254 nm.

REFERENCES

1. L. A. Sorbera, L. Revel, L. Martin and J. Castaner, *Drugs of the Future*, **26,** 115 (2001).
2. K. P. Boegeso, EP 0347066 (1989); *Chem. Abstr.*, **113**, 78150 (1990).
3. K. P. Boegeso, (H. Lundbeck A/S), US 4650884 (1987).
4. K. P. Boegeso, J. Perregard, (H. Lundbeck A/S), JP 036177 (1990), JP 292867 (1999), US 4943590 (1990).
5. L. Dall'asta, U. Cassazza, H. Petersen, (H. Lundbeck A/S), WO 0023431 (2000).
6. K. P. Boegeso, J. Perregard, (H. Lundbeck A/S), US 4,943,590 (1990)
7. US 4,650,884 (1987) and WO 03/006449
8. L. F. Solares, R. Brieva, M. Quiros, I. Llorente, M. Bayod and V. Gotor, *Tetrahedron: Asymmetry*, **15**, 341 (2004).
9. C. Brian, H. R. Eva, P. Hans, D. Robert, (H. Lundbeck A/S), WO 04/056754.