

(e.g., **18.36**) with CuCN. One of the cyano-substituted compounds was **18.39**, later known as citalopram. The compound was synthesized in August 1972. The cyano group could be metabolically labile, but it was subsequently shown not to be the case for citalopram neither in animals nor in humans. Citalopram displayed the best overall preclinical profile within this series and was consequently selected for development. The 5-cyano substituent in citalopram also proved to be chemically stable in a surprising manner; for example, it does not react with Grignard reagents which has led to a new and patentable process for its production.

Citalopram was launched for the treatment of MDD in 1989 in Denmark as Cipramil® and subsequently marketed worldwide, including the United States in 1998 under the trade name Celexa®. Overall, citalopram was on par with the other SSRIs with respect to efficacy, but had more favorable drug metabolism and pharmacokinetic (DMPK) properties (see Chapter 5), which are the likely reasons why citalopram became such a commercial success, attaining blockbuster status, even though it was the fifth SSRI introduced onto the US market.

18.3.5 DISCOVERY OF ESCITALOPRAM

Citalopram is a racemate, having an asymmetric carbon at the 1-position. When the first attempts to separate the enantiomers of citalopram were made in 1980, classical resolution via diastereomeric salt formation was the only option for separation of enantiomers. However, it is generally difficult to make salts of citalopram, and eventually direct resolution was given up. Chiral high-pressure liquid chromatography (HPLC) was in its infancy, and the available analytical columns were tried with negative results. Various attempts to asymmetric syntheses, avoiding acid ring closure of resolved intermediates due to the risk of racemization, failed.

Finally, attempts to resolve the so-called diol formed in the second last step was made. The diastereomeric esters with the enantiomers of α -methoxy- α -trifluoromethyl acetic acid (Mosher's acid) were prepared and separated on preparative (non-chiral) HPLC by repeated peak shaving. Small samples of the pure diastereomeric esters were obtained. Importantly, a seemingly spontaneous slow ring closure to citalopram of the mixture of diastereomeric esters (in the presence of triethylamine) was noticed. Encouraged by this observation, a stronger base was tried (potassium *tert*-butoxide) which surprisingly resulted in a stereoselective ring closure of the pure diastereomers to afford a small sample of the pure citalopram enantiomers. Later, it was realized that the diol could be resolved by diastereomeric salt formation with di-*p*-toluoyltartaric acid and, in this way, it became possible to produce larger quantities of the (*S*)- and (*R*)-enantiomers of citalopram.

The 5-HT reuptake inhibition of citalopram proved to reside in the (*S*)-enantiomer (escitalopram), whereas the (*R*)-enantiomer was about 100 times less potent. Escitalopram was launched as a single-enantiomer drug in 2002 and proved to be an effective antidepressant (trade names Cipralex® and Lexapro®) with several advantages as compared to citalopram and other SSRIs. In preclinical studies, escitalopram showed greater efficacy and faster onset of action than comparable doses of citalopram. This is attributed to the fact that the (*R*)-enantiomer of citalopram counteracts the activity of the (*S*)-enantiomer, possibly through the interaction at a second allosteric site on SERT (see further reading for a discussion of the allosteric site on SERT and its potential role in the effectiveness of escitalopram as an antidepressant drug). Further, in randomized, controlled clinical studies, escitalopram showed better efficacy than citalopram, with higher response and remission rates and faster onset of action. Indeed, a study from 2009 showed that escitalopram had the most favorable profile among all the antidepressants that were in clinical use at that time when taking efficacy and tolerability into consideration.

18.3.6 OTHER SELECTIVE SEROTONIN REUPTAKE INHIBITORS

In Figure 18.5, the seven SSRIs that have reached the market, with the priority dates of the first patent application indicated, are shown. However, the two first compounds on the market were both withdrawn due to serious, although rare, side effects. Zimelidine (**18.43**) was found to