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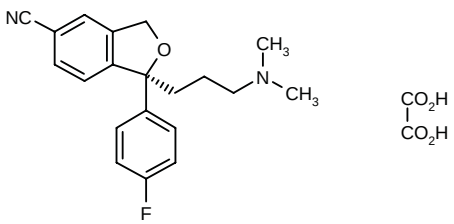
Escitalopram Oxalate

Prop INNM; USAN

Antidepressant
5-HT Reuptake Inhibitor

(+)-(*S*)-Citalopram Oxalate
Lu-26-054-0
Cipralex™

(+)-1(*S*)-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate



$C_{20}H_{21}FN_2O.C_2H_2O_4$ Mol wt: 414.4307

CAS: 219861-08-2
CAS: 128196-01-0 (as free base)

EN: 157449

Synthesis

Escitalopram can be prepared by two different ways:

1) The Grignard condensation of 5-cyanophthalide (I) with 4-fluorophenylmagnesium bromide (II) in THF gives 1-(4-fluorophenyl)-1-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile bromomagnesium salt (III), which slowly rearranges to the benzophenone (IV). A new Grignard condensation of (IV) with 3-(dimethylamino)propylmagnesium chloride (V) in THF affords the expected bis(magnesium) salt (VI), which is hydrolyzed with acetic acid to provide the diol (VII) as a racemic mixture (1). Selective esterification of the primary alcohol of (VII) with (+)-3,3,3-trifluoro-2-methoxy-2-phenylacetyl chloride (VIII) gives the monoester (IX) as a mixture of diastereomers. This mixture is separated by HPLC and the desired diastereomer (X) is treated with potassium *tert*-butoxide in toluene (2). Scheme 1.

Alternatively, the optical resolution of the racemic diol (VII) can also be performed by crystallization with (+)-di-*p*-toluoyltartaric acid. The resulting (*S*)-diol (XI) is first cyclized by reaction with methanesulfonyl chloride and then, without isolation, the resulting mesylate intermediate is treated with TEA in toluene (2). Scheme 1.

2) The chlorination of 1-oxo-1,3-dihydroisobenzofuran-5-carboxylic acid (XII) with refluxing $SOCl_2$ gives the acyl chloride (XIII), which is condensed with 2-amino-2-methyl-1-propanol (XIV) in THF to yield the corresponding amide (XV). The cyclization of (XV) by means of $SOCl_2$ affords the oxazoline (XVI), which is treated with 4-fluorophenylmagnesium bromide (XVII) in THF to give the benzophenone (XVIII). This compound (XVIII), without isolation, is treated with 3-(dimethylamino)propylmagnesium chloride (XIX) in the same solvent to provide the carbinol (XX), which is submitted to optical resolution with (+)- or (–)-tartaric acid, or (+)- or (–)-camphor-10-sulfonic acid (CSA) to give the desired (*S*)-enantiomer (XXI). Cyclization of (XXI) by means of methanesulfonyl chloride and TEA in dichloromethane yields the chiral isobenzofuran (XXII), which is finally treated with $POCl_3$ in refluxing pyridine (3). Scheme 2.

Description

Oxalate: m.p. 147-8 °C, $[\alpha]_D$ +12.31° (c 1, MeOH); free base: oil, $[\alpha]_D$ 12.33° (c 1, MeOH) (2).

Introduction

Depression – or feelings of unhappiness or disappointment – is an extremely common state affecting up to one-third of all people at some time. However, when these feelings become exaggerated, pervasive and interfere with the normal functioning of everyday life, they are considered pathological depression (4). Depressive disorders encompass a variety of conditions including two major forms of unipolar depression (*i.e.*, major depression and dysthymia), adjustment disorder, subsyndromal depression (or minor depression), seasonal affective disorder (SAD), premenstrual dysphoric disorder (PMDD), postpartum depression, atypical depression and bipolar disorder. These disorders affect more than 19 million adults in the U.S. each year and the World Health

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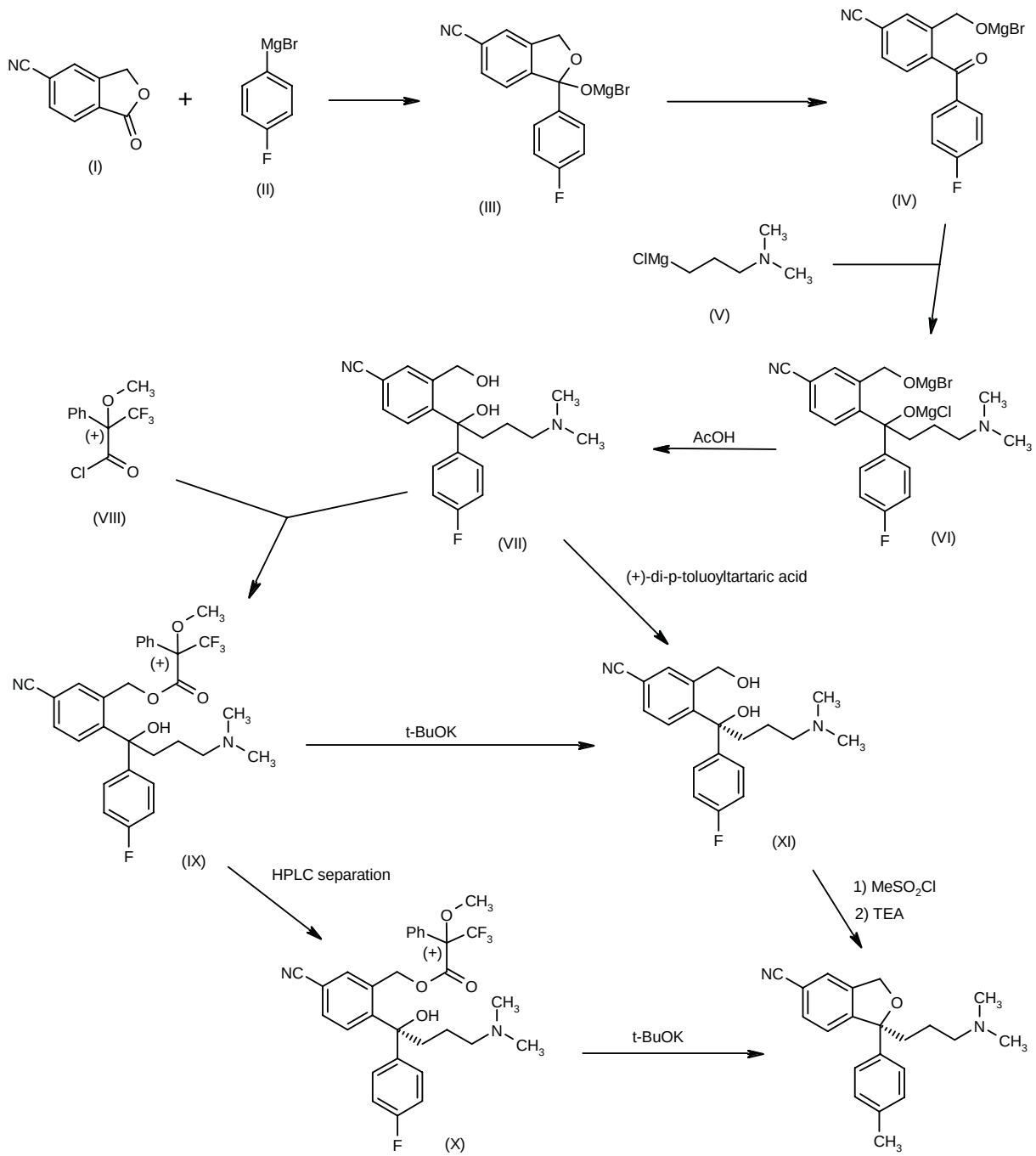
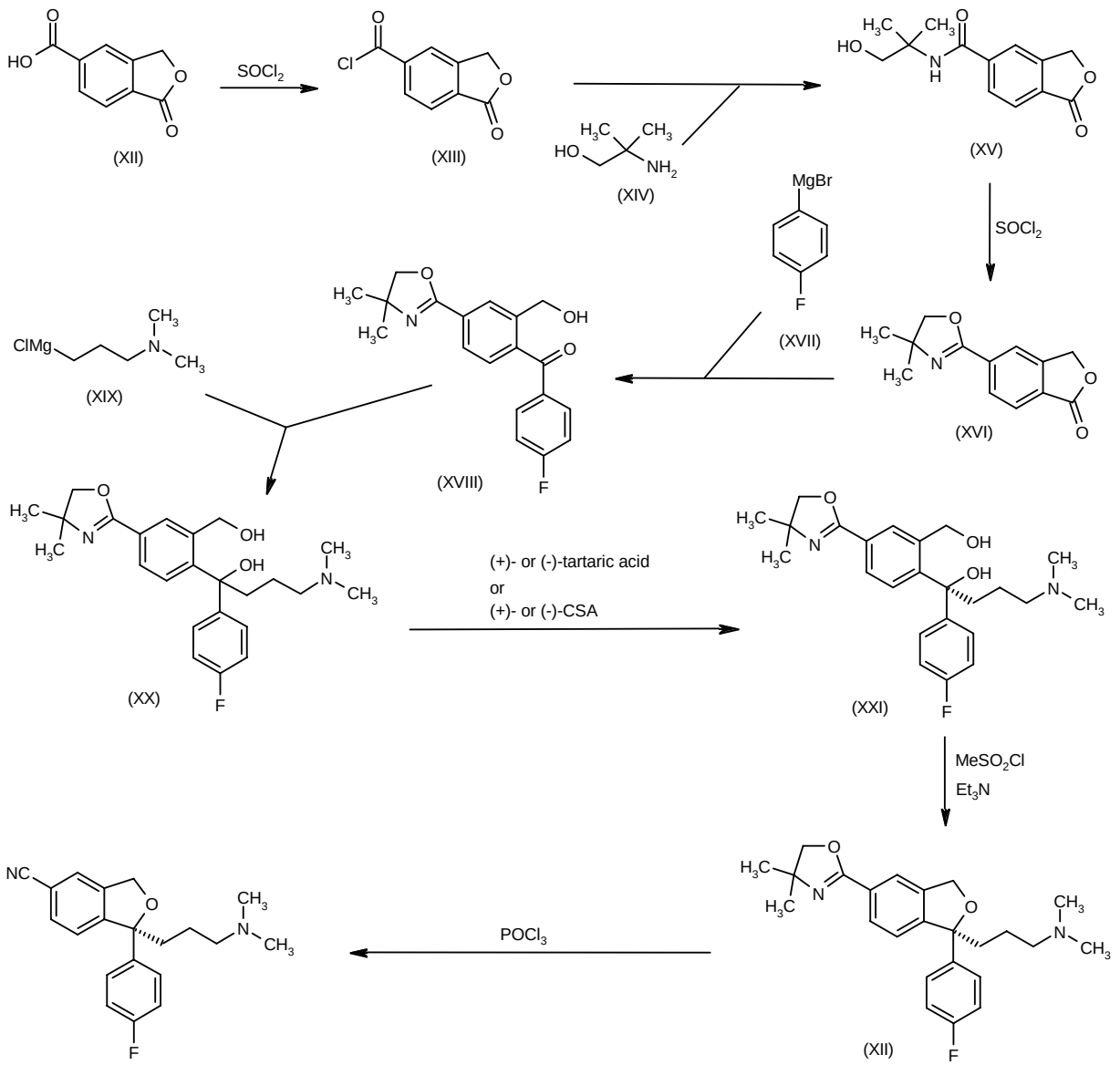
Scheme 1: Synthesis of Escitalopram



Organization predicts that depression will be the second leading cause of disability worldwide by the year 2020 (4, 5).

Depression can affect emotion, cognition, physical functioning and behavior. Both men and women of all ages suffer from depression and the incidence increases with age. Some individuals may experience a single depressive episode while others suffer from a chronic condition. The causes of depression are usually multifactorial. Heredity and childhood environment may predispose an individual to depression or a traumatic event may trigger a depressive episode. However, it is generally accepted that neurochemical abnormalities are ultimately responsible for the emergence of depressive symptoms (4).

Scheme 2: Synthesis of Escitalopram



Although depression can represent an extreme disability, with appropriate treatment up to 80% of all individuals affected can improve and return to their normal daily life activities. In addition to nonpharmacological treatment (*e.g.*, cognitive, behavioral and psychodynamic therapies), there are currently three major classes of drugs available for the treatment of depression. Tricyclic antidepressants (TCAs), which act by altering the balance of norepinephrine and serotonin in the brain, were first introduced in the late 1950s and have been the standard treatment for depression for many years despite their slow onset of action and unpleasant and often serious (*e.g.*, cardiac toxicity in overdose) side effects. A second class of compounds are the monoamine oxidase (MAO) inhibitors, which slow the breakdown of norepinephrine and serotonin (5-HT) in the brain allowing prolonged activity of these neurotransmitters. Since the late 1980s, selective serotonin reuptake inhibitors (SSRIs) have overtaken TCAs in the market due to their excellent safety profiles. SSRIs enhance the activity of 5-HT via inhibition of its reuptake without affecting other neurotransmitter systems. The result is considerably fewer side effects as compared to TCAs and MAO inhibitors. Other antidepressants include lithium salts, which are usually indicated for bipolar disorder and inhibit inositol phosphatase resulting in suppression of norepinephrine release and

enhancement of norepinephrine uptake, and additional new-generation antidepressants such as bupropion, mirtazapine, nefazodone and venlafaxine, which possess novel mechanisms of action and good safety profiles (4).

Since the launch of the first SSRI in 1985, SSRIs have become widely used due to their reactive safety if taken in an overdose situation and their overall superior safety profiles. SSRIs do not produce anticholinergic, hypotensive, cognitive or sedative side effects seen with TCAs and their most common associated side effects (*e.g.*, vomiting, nausea, insomnia, headache and sexual dysfunction) tend to be mild and resolve with continued treatment (4, 6). SSRIs, therefore, remain an attractive treatment for depression and investigation to find newer, more effective SSRIs continues.

Citalopram, an SSRI launched in 1989 for the treatment of depression, is a racemic mixture of (*S*)-(+)- and (*R*)-(–)-citalopram of which the (*S*)-enantiomer, escitalopram, possesses the SSRI activity. Escitalopram has a high selectivity for inhibition of 5-HT reuptake with a relatively low propensity to inhibit reuptake of epinephrine and dopamine and has been selected for further development.

Pharmacological Studies

Escitalopram was twice as effective as the racemate and over 100-fold more potent than the (*R*)-(–)-enantiomer in inhibiting 5-HT reuptake *in vitro* in rat brain synaptosomes (IC_{50} = 2.1 *vs.* 3.9 and 275 nM, respectively). Moreover, escitalopram was highly selective as a 5-HT reuptake inhibitor. The agent was found to be devoid of activity in more than 140 receptor binding, reuptake and enzyme assays. These systems included monoamine receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_6; norepinephrine $\alpha_{1,2}\beta$; dopamine $D_{1\text{-}5}$), acetylcholine, GABA, glutamate, histamine and opiate receptors, peptidergic receptors (neurokinins, neuropeptide Y, neurotensin), ion channels (Ca^{2+}, K^+, Na^+), MAO and nitric oxide synthase (NOS) (7-9). Further *in vitro* studies assessing the activity of escitalopram against cloned human 5-HT (hSERT), norepinephrine (hNET) and dopamine (hDAT) transporters showed that the enantiomer more potently and selectively bound hSERT (K_i = 1.13 ± 0.10 nM) over hNET (K_i = 7841 ± 998 nM) and hDAT (K_i = 27410 ± 3107 nM) (10).

Results from an *in vitro* study using monolayers of bovine brain microvessel endothelial cells to investigate the transport mechanisms of citalopram across the blood-brain barrier revealed that transport was nonstereoselective, bidirectional and via a symmetrical carrier-mediated mechanism. No active efflux systems or MAOs were involved (11).

Escitalopram was also evaluated in mice, with results showing that the agent is a potent 5-HT reuptake inhibitor in vivo. The agent dose-dependently potentiated the L-5-hydroxytryptophan (100 mg/kg s.c. 30 min after test compound)-induced 5-HT syndrome (symptoms include head weavings, tremor and hind limb abduction) with an ED_{50} value of 1.7 μmol/kg s.c.; (*R*)-(–)-citalopram had no activity in this model (7-9).

The antidepressant effects of citalopram and its enantiomers were also evaluated in the forced swim test in adult mice. Both escitalopram (12, 24 and 49 μmol/kg) and the racemic mixture (24 and 49 mcmol/kg) administered s.c. 30 min before the test significantly decreased the duration of immobility; the (*R*)-enantiomer had no effect. The activities of the (*S*)-enantiomer and the racemate were similar (8).

Metabolism

The racemate citalopram is predominantly metabolized by *N*-demethylation forming desmethylcitalopram (DM-CIT) and didesmethylcitalopram (DDM-CIT). Other metabolites detected in plasma and urine are the *N*-oxide of citalopram and various propionic acid metabolites (12, 13).

In order to determine the enantiomers of citalopram in human plasma, various quantification methods have been described. Several HPLC methods have been developed to measure escitalopram and (*R*)-(–)-citalopram and their demethylated and propionic acid metabolites in plasma from both healthy and depressed individuals (14-17). Recently, a stereoselective HPLC assay was described and validated that allows rapid and sensitive determination of escitalopram and its active metabolites. The lower detection limit for this method was 2 ng/ml. The procedure was used to measure trough levels of citalopram, DM-CIT and DDM-CIT and their respective enantiomers in 16 elderly patients treated daily with citalopram (20-40 mg). The mean plasma levels of the (*S*)- and (*R*)-enantiomer, respectively, for citalopram and DM-CIT following the 20 mg dose were: 27.4 ± 13.1 and 36.2 ± 15 ng/ml; 7.7 ± 3.8 and 7.2 ± 3.1 ng/ml, whereas DDM-CIT was only detectable as (*R*)-enantiomer in 8 cases (13.2 ± 12.1 ng/ml) (18).

The metabolism of citalopram was further examined in several *in vitro* studies using human liver microsomes and cDNA-expressed cytochrome P450 (CYP) enzymes. Results revealed that CYP3A4, CYP2C19 and CYP2D6 were involved in the first demethylation step with all three enzymes favoring the conversion of the (*S*)-enantiomer versus the (*R*)-enantiomer (19-22).

Pharmacokinetics and Clinical Studies

The pharmacokinetics, neuroendocrine responses and tolerability of citalopram (20 mg i.v. infusion over 30 min) were examined in a randomized, placebo-controlled, single-blind, crossover study in 8 healthy male volunteers. Plasma levels of the parent compound were found to decay in a double exponential manner. Although DM-CIT and DDM-CIT were not detected, low plasma levels of the propionic acid metabolites of citalopram were

identified (1-5.2 ng/ml). Escitalopram and (*R*)-(–)-citalopram displayed a ratio of 0.9-1.2. Citalopram was well tolerated with only 1 subject experiencing marked adverse effects which included nausea (without vomiting), sweating, flush, tremor and peripheral paresthesia; no mental status changes were noted. Administration of the agent was accompanied by increases in plasma prolactin and cortisol and the agent was found to inhibit a surge in growth hormone seen following saline infusion in all subjects except the 1 patient who developed pronounced side effects. Rectal temperature and heart rate were not altered by citalopram administration (23).

The steady-state pharmacokinetics of multiple-dose citalopram (40 mg/day for 21 days) were determined in 10 healthy male and female subjects who were extensive metabolizers of sparteine (CYP2D6 substrate) and mephenytoin (CYP2C19 substrate). The pharmacokinetics for escitalopram and (*R*)-(–)-citalopram were similar. A significant stereoselective disposition of citalopram and DM-CIT and DDM-CIT was seen. The serum concentrations of the *S*-(+)-enantiomers of citalopram, DM-CIT and DDM-CIT were 37 ± 6, 42 ± 3 and 32 ± 3% of their total racemic serum concentrations, respectively. Faster elimination was noted for the (*S*)-enantiomers as compared to their antipodes. Serum $t_{1/2}$ and AUC values at steady-state for the (*S*)- and (*R*)-enantiomers of citalopram were 35 ± 4 h and 47 ± 11 h, respectively, and 2562 ± 1190 and 4193 ± 1118 h·nmol/l, respectively (24).

A pilot study involving 10 elderly (77.2 ± 8.2 years) patients with dementia and significant behavioral disturbances examined the efficacy and plasma levels of citalopram (10 mg/day for 3 days followed by 20 mg/day for 2 weeks) and its enantiomers and metabolites. Steady-state plasma levels for the *S*-(+)- and *R*-(–)-enantiomers of citalopram and DM-CIT were 11.2-92.2 ng/ml and 12.8-95.7 ng/ml, respectively, and 11-22 ng/ml and 9.2-22 ng/ml, respectively. Stereoselective metabolism in these patients was found to be different from that described for younger patients, with elderly patients displaying a 3.5 times higher citalopram level and dose ratio and slightly higher (*S/R*)-enantiomer ratios for both citalopram (0.65 ± 0.18 *vs.* 0.56 in younger subjects) and DM-CIT (1.08 ± 0.29 *vs.* 0.72 in younger subjects). This observation may indicate that CYP2C19 activities vary with age. At the completion of 17 days of treatment, 6 patients exhibited a marked clinical response according to 6 target items (disinhibition, agitation, hostility, suspicion, hallucinations and delusions) on the Neurobehavioral Rating Scale (25).

Results from a pilot study conducted in 7 female patients suffering from a major depressive episode (ICD-10) without psychotic symptoms, recurrent depressive disorder, severe current episode without psychotic symptoms or a moderate depressive episode with or without somatic syndrome (Montgomery and Asberg Depression Rating Scale [MADRS] equal to or more than 12) showed that coadministration of fluvoxamine (50 mg/day on days 0-7 and 100 mg/day on days 14-21) increased plasma citalopram levels. This interaction could lead to a potentiation of the serotonergic effects of citalopram and synergism between the two agents. Patients were nonresponders to previous treatment with citalopram (40 mg/day for 3 weeks [days -21 to 0]) who were continued on citalopram (40 mg/day days 0-21) for another 3 weeks in combination with fluvoxamine for this study; all subjects were extensive metabolizers of mephenytoin and dextromethorphan (CYP2D6 substrate) except for 1 patient who had a genetic deficiency of CYP2D6. A significant increase in plasma levels of escitalopram (27 ± 14 to 83 ± 38 μg/l) and (*R*)-(–)-citalopram (55 ± 23 to 98 ± 44 μg/l) were observed from days 0-21. Coadministration also increased the mean ratio of (*S/R*)-citalopram from 0.48 to 0.84. Analysis of clinical responses according to MADRS scores from 5 patients revealed that 4 patients had a decrease in scores of at least 50% so that responders had a final MADRS score of 13 or less; the only patient who did not respond had a severe personality disorder. All patients showed marked improvements in the Covi Anxiety rating Scale (from 7.86 ± 2.6 to 2.86 ± 0.37 on day 21) and the Behavioral Dyscontrol Scale (from 21 ± 8.9 to 10.4 ± 10.2 on day 21). Coadministration was relatively well tolerated with no patients developing 5-HT syndrome. Four patients had nausea from days 0-14 although symptoms were resolved in 3 by day 21. The most common adverse effects possibly related to combination treatment were tremor and nausea. No changes in vital signs or ECG parameters were seen throughout the study (26).

Phase III trials conducted in more than 2000 patients have shown that escitalopram has a clinically relevant and significant effect in depressed individuals (major depression, DSM-IV). Lundbeck is expected to launch escitalopram as Cipralex™ by the end of 2001 and Forest will submit an NDA this year seeking approval for the agent from the FDA for the treatment of depression (27).

Manufacturer

Developed by H. Lundbeck A/S (DK); licensed to Forest Laboratories, Inc. (US) and Almirall Prodesfarma, S.A. (ES).

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