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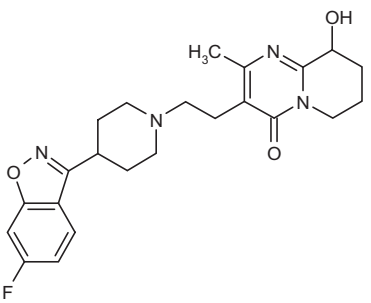
Paliperidone

Prop INN; USAN

Antipsychotic Agent
Treatment of Bipolar Disorder
Dual Dopamine D2/5-HT$_{2A}$ Receptor Antagonist

R-76477
9-Hydroxyrisperidone

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one



$C_{23}H_{27}FN_4O_3$
Mol wt: 426.4840

CAS: 144598-75-4

EN: 162578

Abstract

Paliperidone is an active metabolite of risperidone (Risperdal™), a widely prescribed antipsychotic agent used for the treatment of schizophrenia and bipolar disorder. Paliperidone acts as a dual antagonist of dopamine D2 receptors in the mesolimbic pathway and 5-HT$_{2A}$ receptors in the prefrontal cortex. Its ability to bind to these receptors corresponds with its antipsychotic effect and stabilization of some of the antisocial behaviors in patients with schizophrenia. Paliperidone has a favorable pharmacokinetic profile and is being developed using the OROS™ extended-release formulation technology with the aim of providing smooth 24-h exposure to the drug, leading to an improved safety and tolerability profile. A long-acting i.m. formulation of the palmitate salt is also being developed for use in schizophrenia.

Synthesis

Paliperidone can be synthesized in the following way.

Reaction of 2-amino-3-benzyloxypyridine (I) with 2-acetyl-γ-butyrolactone (II) in the presence of phosphoryl chloride in hot toluene gives 9-benzyloxy-3-(2-chloroethyl)-2-methylpyrido[1,2-*a*]pyrimidin-4-one (III), which is hydrogenated over Pd/C to produce the debenzylated tetrahydropyridopyrimidinone (IV) (1). Paliperidone is then obtained by condensation of the chloroethyl derivative (IV) with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (V) in the presence of a basic amine in hot MeOH (1, 2). Scheme 1.

Racemic paliperidone (VI) can be resolved as follows:

Acylation of paliperidone (VI) with (+)-3,4-dihydro-2*H*-1-benzopyran-2-carbonyl chloride (VII) and DMAP produces a mixture of the diastereomeric esters (VIII) and (IX), which are separated by means of column chromatography. Each isomer is then separately hydrolyzed with diisopropylamine in aqueous methanol to furnish the respective enantiomers (1). Scheme 2.

Background

Schizophrenia is a common (approximately 1% of the population) and disabling psychotic disorder characterized by extreme disturbances of cognition and thought, affecting language, perception and sense of self. It is a chronic disorder typified by a life-long pattern of acute psychotic episodes superimposed upon chronically poor psychosocial adjustment. Schizophrenia is characterized by positive 'psychotic' symptoms (auditory hallucinations, disorganized or bizarre thoughts, delusions and irrational fears) and negative symptoms of social withdrawal, poor motivation, poverty of speech, apathy and lack of energy. All schizophrenics experience positive symptoms and negative symptoms are present in most patients. Many patients also experience cognitive dysfunction ranging from impaired attention to abnormal executive function, as well as memory impairment, depression and/or anxiety. Despite the availability of a number of agents for the treatment of schizophrenia, it remains a significant burden on healthcare systems. The first antipsychotic drug,

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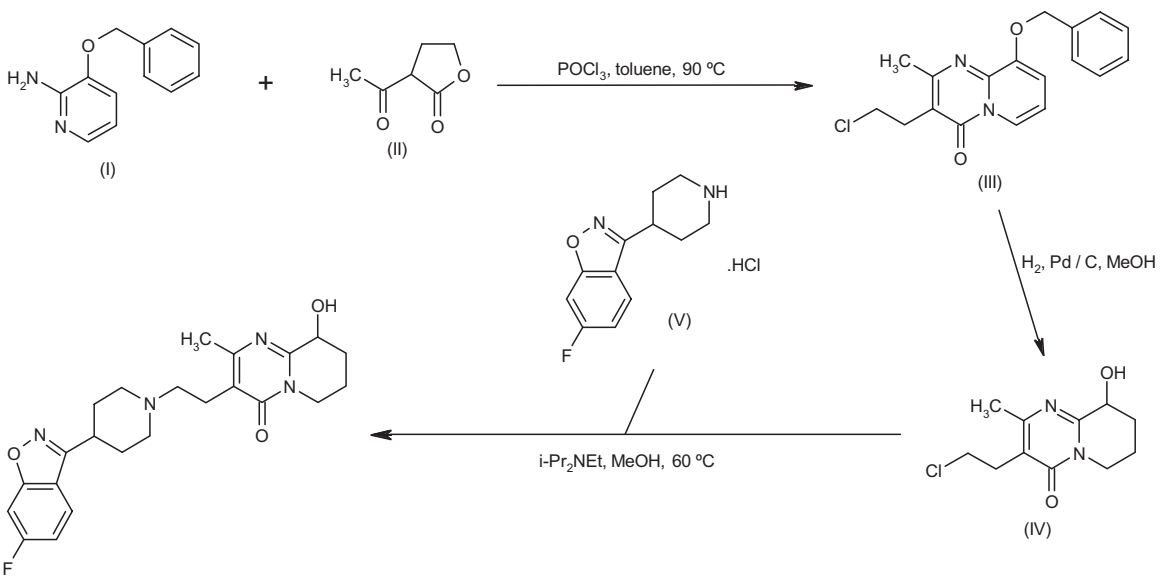
Scheme 1: Synthesis of Paliperidone



chlorpromazine, was discovered in the early 1950s. Chlorpromazine and other first-generation antipsychotics (or typical antipsychotics) antagonize the dopamine D2-like class of receptors. Although effective against psychosis, they do not improve and may even exacerbate the negative symptoms of schizophrenia and are associated with dose-limiting extrapyramidal symptoms (EPS). The second-generation dual-action dopamine D2/5-HT_{2A} receptor blockers (or atypical antipsychotics) retain the antipsychotic effect of the typical antipsychotics, but show a much reduced propensity to cause EPS, and also may improve negative symptoms of schizophrenia. Clozapine, the first of this class, was approved for the treatment of schizophrenia in the 1970s and throughout the 1990s many other atypical antipsychotics were approved, including olanzapine (Zyprexa™), risperidone (Risperdal™), quetiapine (Seroquel™) and ziprasidone (Geodon™). However, despite the advantages of the atypical antipsychotics, they too are not without problems and typical side effects include weight gain, hyperglycemia and hypertriglyceridemia (3-8).

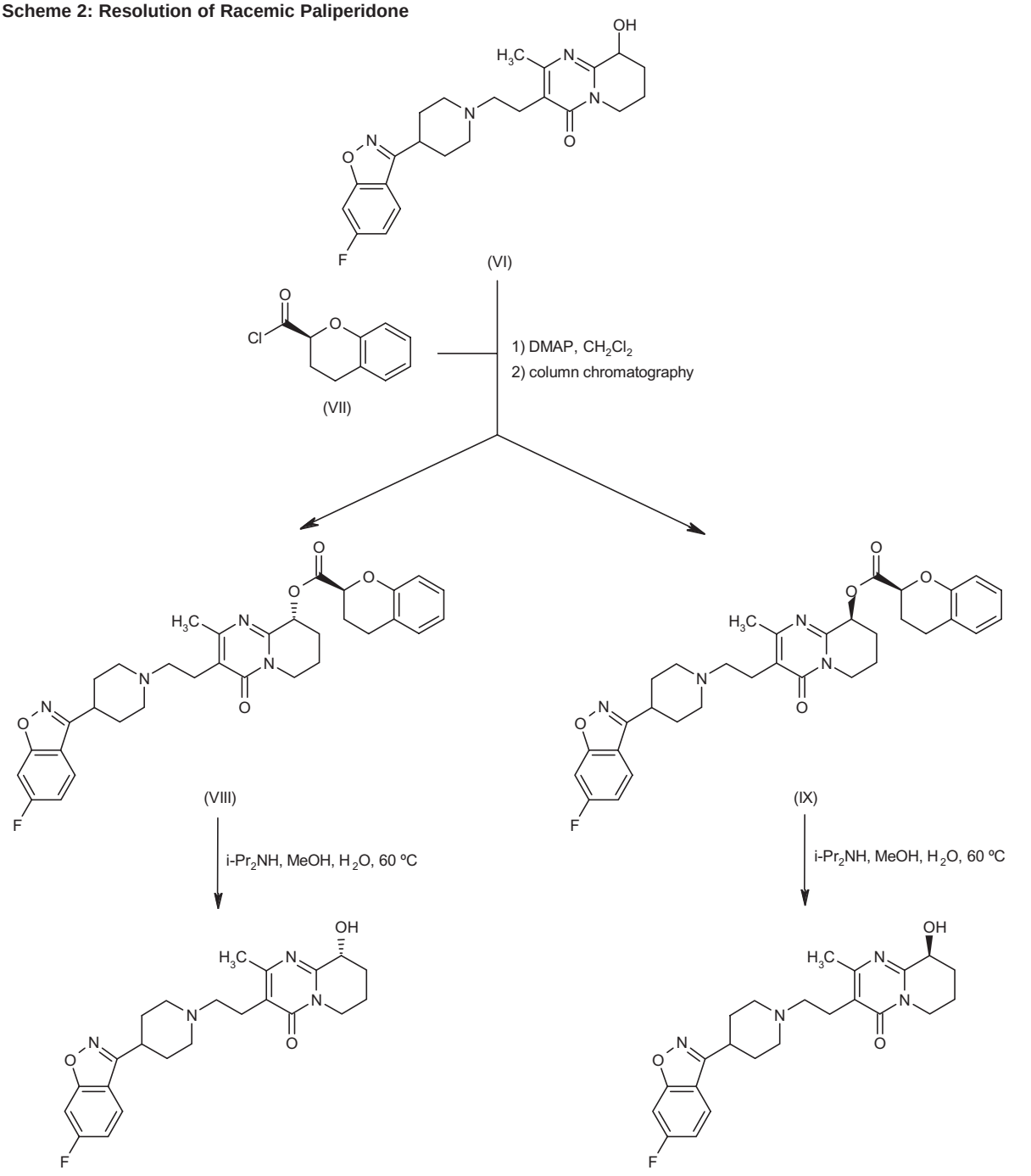
Paliperidone, an atypical antipsychotic, is an active metabolite of risperidone formed by cytochrome P-450 CYP2D6-catalyzed C-9 hydroxylation of the parent drug. Paliperidone has an extended half-life, reduced clearance and a reduced potential for drug interactions, and is being developed by Johnson & Johnson using the OROS™ slow-release drug delivery system to provide 24-h controlled release. Smoothing out the peaks and troughs of the drug levels in the blood is expected to provide efficacy with fewer side effects. Paliperidone palmitate is also being tested in phase III trials as a long-acting injectable formulation using Elan's NanoCrystal® technology for the treatment of schizophrenia.

Pharmacokinetics and Metabolism

Five healthy subjects (2 poor metabolizers and 3 with elevated levels of CYP2D6 activity) were given a single oral dose of immediate-release [^{14}C]-paliperidone (1 mg). The drug was well absorbed, and over the first week a mean of 80% of the administered dose was excreted in the urine, about 60% of which was in the form of unchanged drug; a mean of 11.4% was excreted in the feces as metabolites. The C_{max} of paliperidone was 8.85 ng/ml, t_{max} was 1.5 h, $t_{1/2}$ was 24.8 h and total body clearance averaged 91 ml/min. Four urinary metabolites were found: R-084852, with an opened benzisoxazole moiety, represented 4.1% of the dose, the ketone metabolite R-125239 represented 2.7%, monohydroxy-paliperidone (detected in extensive metabolizers only) represented 3.8%, and a metabolite produced by oxidative *N*-dealkylation (R-093725) represented 4.6% of the dose. Overall, there was little variation between extensive and poor metabolizers, indicating that paliperidone is not extensively metabolized and that interactions with drugs that induce metabolism should be limited (9, 10).

Paliperidone is a mixture of two equipotent enantiomers with an *in vivo* interconversion rate of 7.9 l/h, irrespective of the direction of conversion. The pharmacokinetics of the enantiomers were investigated in a randomized, crossover trial in 20 subjects who received a 30-min i.v. infusion of 1 mg paliperidone, an immediate-release (IR) oral formulation containing 1 mg paliperidone, a 1-mg solution of the (+)- or (–)-enantiomer and an extended-release (ER) formulation delivering 3 mg paliperidone. The disposition of the two enantiomers was quite distinct, with the (–)-enantiomer having a higher volume of distribution in the periphery (192 l) compared to

Scheme 2: Resolution of Racemic Paliperidone



the (+)-enantiomer (70.6 l), and a higher clearance rate (intercompartmental clearance = 282 l/h and elimination clearance = 8.15 l/h *vs.* 78.8 l/h and 1.41 l/h, respectively, for the [+]-enantiomer). The bioavailability of the IR and ER formulations was 121% and 28%, respectively (11).

The pharmacokinetics and dopamine D2 and 5-HT_{2A} receptor occupancy were evaluated for both an immediate-release formulation of paliperidone (paliperidone IR) and an extended-release formulation (paliperidone ER). In two separate studies, healthy subjects were administered single doses of paliperidone IR (1 mg; n=3) or paliperidone ER (6 mg; n=4). Median C_{max} and t_{max} for the IR formulation were 6 ng/ml and 4.2 h, respectively, *versus* respective values for paliperidone ER of 11.3 ng/ml and 24 h. Receptor occupancy was measured by PET using [^{11}C]-raclopride for D2 receptors and [^{11}C]-M-100907 for 5-HT_{2A} receptors. At around the time of

C_{max}, D2 receptor occupancy was 48% for paliperidone IR and 64% for paliperidone ER, and 5-HT_{2A} occupancy was 65% for paliperidone IR (ER not measured). Previous studies had shown that optimal antipsychotic activity is achieved at 65-80% D2 receptor occupancy, with higher occupancy leading to EPS. It was calculated that plasma concentrations of 15-25 ng/ml of paliperidone IR and 10-17 ng/ml of paliperidone ER would be required to achieve 70-80% occupancy. Based on pooled data, it was suggested that paliperidone ER doses above 3 mg/day should be effective for the treatment of psychosis (12-14).

Safety

In an *in vitro* experiment, paliperidone did not interact with the muscarinic receptor when tested at doses higher than expected therapeutic doses, suggesting it would not produce anticholinergic activity (which adversely affects memory and causes confusion and delirium) (15).

The safety and tolerability were explored in a double-blind study using flexible doses of paliperidone ER in 114 elderly schizophrenic patients. Patients were randomized to daily oral doses of paliperidone ER (3-12 mg with the option of 3-mg increments from day 7) or placebo for a total of 6 weeks. Paliperidone was well tolerated, with a similar rate of discontinuation due to adverse events as for placebo (7% and 8%, respectively). The overall frequency of adverse events was comparable for both the treatment and control groups (67% *vs.* 71%), with hypertonia (3%) and tremor (3%) occurring only in the treatment group (16).

Clinical Studies

Efficacy was also evaluated in the above study, with a decrease of 14.6 ± 14.6 in the PANSS (Positive and Negative Syndrome Scale) scores on paliperidone compared to an increase of 9.9 ± 15.0 on placebo (16).

The antipsychotic efficacy of paliperidone ER was evaluated in three similar double-blind, parallel-group, dose-finding studies in young adults. Patients (n=243; mean age = 22.5 years) with a baseline mean PANSS score of 95 were randomized to oral paliperidone ER at doses of 3, 6, 9, 12 or 15 mg once daily, olanzapine 10 mg once daily or placebo for 6 weeks. Treatment was effective at all doses, with PANSS showing a dose-dependent response of –16 (3 mg) to –23 (15 mg), compared to –4 for placebo. On a second measure of response, the Personal and Social Performance (PSP) scale, improvements were also noted and ranged from +7.2 on 3 mg to +15.8 on 15 mg compared to –1.2 on placebo. The frequency of adverse events for the treatment groups (64-76%) was similar to the placebo group (70%). Olanzapine showed a mean improvement in PANSS of –20.4, a mean improvement in PSP of +11 and a 78% incidence of adverse events (17).

Three large double-blind, parallel-group, placebo- and active-controlled dose-response trials were then conducted in patients with acute schizophrenia. In all, 1,665 patients with a mean baseline PANSS score of 93-94 were randomized to daily oral doses of 3, 6, 9, 12 or 15 mg paliperidone ER, placebo or olanzapine (10 mg) for 6 weeks. Improvements in the paliperidone treatment groups were noted from day 4 for the 12- and 15-mg groups, and from day 8 for the other doses when compared to placebo. Mean improvements in PANSS were in the range of –15 to – 23.3 compared to –18 to –19.9 on olanzapine and –2.8 to –8.0 on placebo. Response rates (improvement of at least 30% in PANSS total score) were also significantly higher for the paliperidone treatment groups compared to placebo: 50-56% at 6 mg, 51% at 9 mg and 51-61% at 12 mg, compared to 30-34% for placebo and 46-52% for olanzapine. PSP scores likewise improved by 8.3 on 3 mg, 8.8-9.1 on 6 mg, 7.6-8.1 on 9 mg, 6.6-11.5 on 12 mg and 12.2 at 15 mg, compared to –1.5-2.9 for placebo. Overall, paliperidone ER was well tolerated and the discontinuation rate was low and comparable for all groups including placebo (4-6%). Adverse events attributable to paliperidone treatment were headache and dry mouth, and at 9 mg or above symptoms of EPS, tachycardia, hyperkinesia and dizziness began to emerge. Serious adverse events across all treatment groups were no different from placebo (3-8% for paliperidone, 2-10% for olanzapine and 2-11% for placebo groups). Over the 6-week study period, mean weight gains ranged from 0.2 to 2 kg on paliperidone and from 1.3 to 2.7 kg on olanzapine (18-23).

Post hoc analysis of these studies examined the effect of paliperidone ER on the 'negative' component of the PANSS score. After correcting for the indirect effects (change in positive symptoms [51%], depressive symptoms [18%] and movement disorders [–2.1%]), it was calculated that 33% of the improvement in negative symptoms was attributed to a direct effect of paliperidone ER (24).

A series of worldwide phase II and phase III studies evaluating the efficacy and safety of paliperidone ER for the treatment of schizophrenia are under way (25-32), and approval is being sought for paliperidone ER in the treatment of schizophrenia in the U.S. and Europe. Paliperidone ER is also being evaluated in phase III trials for the treatment of bipolar I disorder (33-35). Paliperidone palmitate is being developed for intramuscular injection in a long-acting formulation and several phase III trials are in progress to determine its efficacy and safety in schizophrenic patients (36-41).

Drug Interactions

A single oral dose of extended-release paliperidone (6 mg) was administered to 30 healthy subjects in the presence or absence of trimethoprim (200 mg b.i.d. for 5 days). In accordance with the known action of trimethoprim (an inhibitor of tubular secretion of organic cations), creatinine clearance decreased by 14%. However, trimethoprim had no significant effect on the pharmacokinetics of paliperidone (42).

Source

Johnson & Johnson Pharmaceutical Research and Development (BE, US).

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