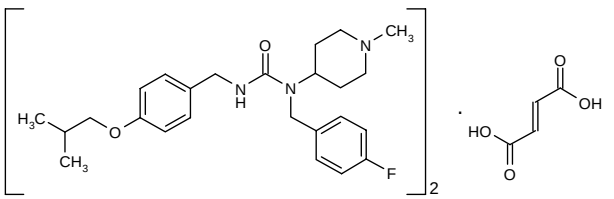
Drugs of the Future 2006, 31(11): 939-943

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.11.1047693

ACP-103

5-HT$_{2A}$ Receptor Inverse Agonist
Treatment of Psychosis
Treatment of Sleep Disorders

N-(4-Fluorobenzyl)-*N'*-(4-isobutoxybenzyl)-*N*-(1-methylpiperidin-4-yl)urea hemifumarate



$C_{54}H_{72}F_2N_6O_8$
Mol wt: 971.1819
CAS: 868855-07-6
CAS: 706779-91-1 (free base)
CAS: 706782-28-7 (D-tartrate [2:1])
EN: 310398

Abstract

The recent discovery that most available antipsychotics possess 5-HT$_{2A}$ receptor inverse agonist activity has spurred interest in developing more effective 5-HT$_{2A}$ inverse agonists for use in the treatment of schizophrenia and other neuropsychiatric disorders. ACP-103 is a potent and selective 5-HT$_{2A}$ inverse agonist shown to possess excellent oral bioavailability and antipsychotic-like effects, as well as to enhance the efficacy and reduce the side effects of antipsychotic agents in animal models. Pharmacokinetic studies indicated that ACP-103 had a long plasma half-life and occupied 5-HT$_{2A}$ receptors in human brain after oral administration. Clinical studies demonstrated that ACP-103 was safe and well tolerated and improved the efficacy of typical antipsychotic drugs such as haloperidol. Phase II studies of ACP-103 in the treatment of insomnia, schizophrenia and treatment-induced dysfunctions in Parkinson's disease have shown promising results, and further clinical studies are under way.

Synthesis

Alkylation of 4-hydroxybenzaldehyde (I) with isobutyl bromide (II) and potassium carbonate yields 4-isobutoxybenzaldehyde (III), which is converted to the corresponding oxime (IV) upon treatment with hydroxylamine in refluxing ethanol. After reduction of oxime (IV) to the benzylic amine (V) by hydrogenation over Pd/C, reaction with phosgene in the presence of triethylamine produces 4-isobutoxybenzyl isocyanate (VI). Reductive amination of 1-methyl-4-piperidone (VII) with 4-fluorobenzylamine (VIII) by means of sodium triacetoxyborohydride furnishes 4-(4-fluorobenzylamino)-1-methylpiperidine (IX). ACP-103 is finally obtained by coupling of isocyanate (VI) with amine (IX), followed by precipitation of the resulting urea adduct with fumaric acid in ethyl acetate (1). Scheme 1.

Background

Antipsychotic drug development over the past 40 years has been based on the "hyperdopaminergic hypothesis" of schizophrenia, whereby excessive production of dopamine and/or increased D2 receptor density or postsynaptic dopamine overactivity is implicated in the pathogenesis of the disorder. Of the marketed antipsychotic drugs used for the treatment of schizophrenia, all act at least in part by decreasing dopaminergic neurotransmission (2-4). The atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, sertindole, etc.), which act as both dopamine D2 and 5-HT$_{2A}$ receptor antagonists, were developed in an attempt to reduce the side effects (motor, endocrine and cognitive) associated with D2 receptor antagonism and enhance the antipsychotic efficacy (5, 6).

It was recently found that most antipsychotics act as 5-HT$_{2A}$ receptor inverse agonists, stimulating efforts to discover new and more effective 5-HT$_{2A}$ receptor inverse agonists (7). Acadia researchers identified AC-90179 as a prototype, but it was associated with poor oral bioavailability thought to be due to rapid metabolism (8). Modification of this molecule led to ACP-103, which proved to be a potent and orally active 5-HT$_{2A}$ receptor inverse agonist with potential in the treatment of psychotic and other neuropsychiatric disorders, including schizophrenia and psychosis in Parkinson's disease (9). Phase

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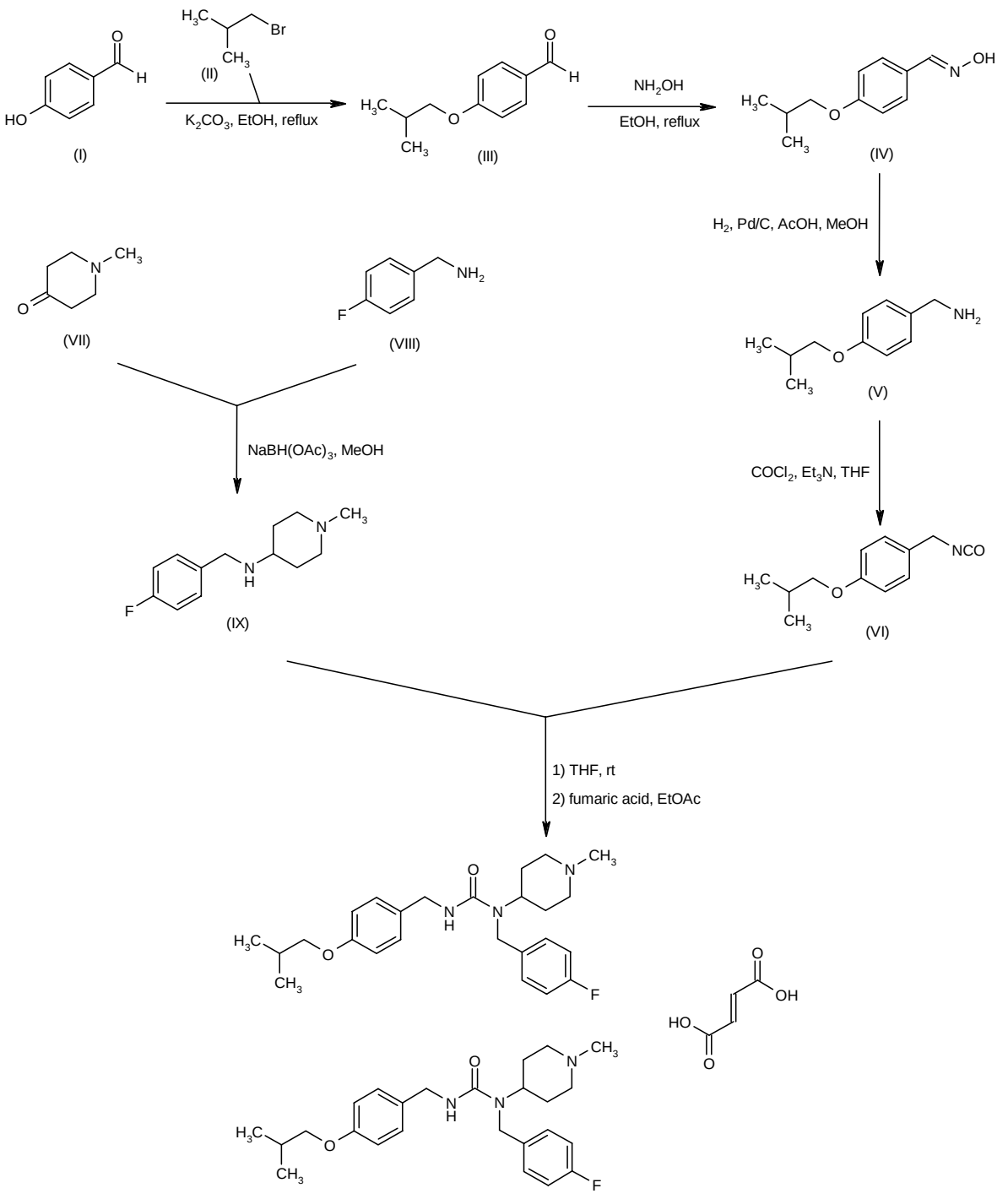
Scheme 1: Synthesis of ACP-103



II clinical development is under way at Acadia for its use as an adjunct to other antipsychotics in the treatment of schizophrenia, for treatment-induced psychosis in Parkinson's disease, as well as for use in sleep maintenance insomnia.

Preclinical Pharmacology

In vitro and *in vivo* pharmacological studies of ACP-103 showed that the drug competitively antagonized [^{3}H]-ketanserin binding to 5-HT$_{2A}$ receptors with a mean pK$_i$ of

9.3 and 9.7 in membranes and whole cells, respectively. ACP-103 also displayed selective and potent inverse agonist activity in functional assays, with a mean pIC_{50} of 8.7. It exhibited lower affinity for 5-HT_{2C} receptors (pK_i = 8.8 and 8.0, respectively; pIC_{50} = 7.1) and no affinity for or activity at 5-HT_{2B}, D2 or other monoaminergic receptors at up to 10 μM. Behavioral analysis indicated that ACP-103 was able to attenuate 5-HT_{2A} agonist-induced head twitch responses (3 mg/kg p.o.) and prepulse inhibition deficits (1-10 mg/kg s.c.) in rats and to reduce dizocilpine-induced hyperactivity in mice (0.1 and 0.3 mg/kg s.c.; 3 mg/kg p.o.), confirming a 5-HT_{2A} receptor mechanism of action *in vivo* and antipsychotic-like efficacy. ACP-103 also demonstrated an oral bioavailability of > 40% in rats (9, 10).

Combination of ACP-103 with the antipsychotic drugs haloperidol and risperidone was evaluated in mice and rats. The results indicated that ACP-103 enhanced the antipsychotic efficacy and significantly reduced the side effects of antipsychotic drugs. It enhanced haloperidol- and risperidone-induced reductions in amphetamine- and dizocilpine-induced hyperactivity, while also reducing or eliminating the hyperprolactinemia and catalepsy associated with these antipsychotic agents (10, 11).

Pharmacokinetics and Metabolism

The relationship between oral dose, plasma levels and uptake of ACP-103 in living human brain was studied in 4 healthy volunteers using positron emission tomography (PET) with the radioligand *N*-methylspiperone ([^{11}C]-NMSP). Two of the 4 volunteers received doses of 1, 5 and 20 mg of ACP-103, and the other 2 received doses of 2, 10 and 100 mg; doses were separated by 2 weeks. ACP-103 was seen to displace radioligand binding at doses as low as 1 mg, which reached a maximum after doses of 10-20 mg (12).

A phase I clinical trial examined the pharmacokinetics and safety of single and multiple oral doses of ACP-103 in healthy volunteers. Pharmacokinetics were linear to dose and t_{max} and $t_{1/2}$ values of 6 and 55 h, respectively, were reported, indicating the feasibility of once-daily dosing (13).

The pharmacokinetics of ACP-103 (25 and 100 mg once daily for 14 days) were also evaluated in a randomized, double-blind, placebo-controlled, dose-escalation study in 12 Parkinson's disease patients administered multiple oral doses. The study indicated that the pharmacokinetics in Parkinson's disease patients were comparable to those previously reported in healthy volunteers (14).

Safety

Results from the phase I study in healthy volunteers (13) demonstrated good tolerance after single doses of up to 300 mg. The maximum tolerated dose (MTD) following repeated dosing was 100 mg once daily for 14 days.

Excellent safety was also observed in Parkinson's disease patients treated for 14 days, with no serious drug-related adverse events and no worsening of motor deficits (14).

Clinical Studies

A randomized, double-blind, placebo-controlled trial was conducted in 18 healthy volunteers in Sweden to examine the effects of ACP-103 in combination with an antipsychotic agent. All volunteers were administered a single 7.5-mg dose of haloperidol and 13 developed measurable akathisia, as well as an increase of approximately 3-fold in prolactin secretion. A single dose of ACP-103 (100 mg) reduced haloperidol-induced akathisia compared to placebo and also significantly reduced haloperidol-induced increases in prolactin secretion. There were no serious adverse events (15).

The efficacy and tolerability of ACP-103 were also evaluated in 60 Parkinson's disease patients suffering from treatment-induced psychosis in a multicenter, double-blind, placebo-controlled, dose-escalation phase II study. The antipsychotic efficacy of ACP-103 was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) Part I, the Scale for the Assessment of Positive Symptoms (SAPS) and the Clinical Global Impression - Severity of Mental Illness Scale (CGI-S). ACP-103 treatment was started at 20 mg once daily and doses could be increased up to 60 mg. Compared to placebo, ACP-103 significantly reduced the severity of psychosis measured on the UPDRS and significantly improved the positive symptom score. No significant differences in the CGI-S score were seen in the ACP-103 and placebo groups, although more patients showed improvement on ACP-103 than on placebo. Motor symptoms did not worsen on ACP-103 and a trend for improvement in clinical fluctuations, dyskinesia and other complications associated with Parkinson's disease therapy was seen (16).

Acadia Pharmaceuticals conducted a double-blind, randomized, placebo-controlled phase II study of ACP-103 in 34 patients with schizophrenia. Thirty of the 34 patients completed the study, 14 of whom received 60 mg of ACP-103 orally and 16 placebo once daily over a 5-day period. The patients maintained their prestudy dose of haloperidol during the course of the study and were evaluated on days 1, 3 and 5 using the Barnes Akathisia Scale (BAS), which comprises objective akathisia (item 1), subjective awareness of restlessness (item 2), subjective distress related to restlessness (item 3), and global clinical assessment of akathisia (item 4). Overall, ACP-103 reduced akathisia relative to placebo. There were no significant differences between ACP-103- and placebo-treated patients for BAS item 4 on day 5, the primary outcome measure, which was attributed to a large placebo effect. However, ACP-103 significantly reduced BAS item 1 on day 5 and there were statistically significant improvements or statistical trends on day 3 for item 1, item 2, item 3 and the BAS total score. No significant effects were

observed on extrapyramidal side effects other than akathisia, or on plasma prolactin levels. As expected due to the short treatment period, no significant effects on positive or negative symptoms of schizophrenia were reported (17).

Acadia also conducted a double-blind, placebo-controlled, proof-of-concept study to assess the effect of ACP-103 on slow-wave sleep in 45 healthy older (40-64 years old) volunteers. The volunteers were randomized to either placebo or one of four doses (1, 2.5, 5 and 20 mg) of ACP-103 once daily in the morning for 14 consecutive days. Polysomnography findings indicated that once-daily administration of 5 and 20 mg of ACP-103 significantly increased slow-wave sleep as defined by the time spent in stage 3 and stage 4 sleep, both after the first dose and on day 13. The two lower doses (1 and 2.5 mg) were less effective than the two higher doses, indicating a dose-related effect. The study also demonstrated that treatment with ACP-103 was associated with trends for improvement on measures of sleep maintenance, including decreases in the number of awakenings and in time awake after sleep onset, whereas ACP-103 did not alter latency to sleep onset and did not impair daytime functioning (18).

ACP-103 is currently undergoing a phase II trial in combination with haloperidol and risperidone in patients with schizophrenia (19).

Source

Acadia Pharmaceuticals, Inc. (US).

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