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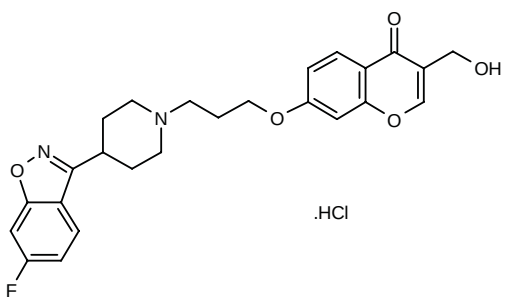
Abaperidone Hydrochloride

Prop INNM

Antipsychotic
Dopamine D_2 Antagonist
5-HT_{2A} Antagonist

FI-8602.HCl

7-[3-[4-(6-Fluorobenzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-(hydroxymethyl)-4*H*-1-benzopyran-4-one hydrochloride
7-[3-[4-(6-Fluorobenzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-(hydroxymethyl)-4*H*-chromen-4-one hydrochloride



$C_{25}H_{25}FN_2O_5$.HCl Mol wt: 488.9404

CAS: 183849-45-8
CAS: 183849-43-6 (as free base)

EN: 271569

Synthesis

Abaperidone hydrochloride was prepared by alkylation of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (I) with 7-(3-chloropropoxy)-3-(hydroxymethyl)-4H-chromen-4-one (II) in the presence of potassium carbonate and potassium iodide in refluxing acetonitrile, followed by conversion to the hydrochloride salt upon treatment with hydrochloric acid in methanol (1, 2). Scheme 1.

The precursor (chloropropoxy)chromenone (II) was obtained by several different procedures. In the original procedure, 2',4'-dihydroxyacetophenone (III) was selectively alkylated at the 4-hydroxyl group with 1-bromo-3-chloropropane (IV) in the presence of potassium carbonate to yield the 4-(3-cloropropyl)ether (V). Subsequent condensation with the Vilsmeier reagent, followed by aqueous work-up, provided the 3-formylchromenone (VI), which was reduced to the (hydroxymethyl)chromenone (II) by means of sodium borohydride in chloroform/ethanol (3). Scheme 2.

Intermediate (II) was synthesized by an alternative method, which requires no chromatographic purification steps. Methyl 2,4-dihydroxybenzoate (VII) was selectively protected as the 4-benzyl ether (VIII) with benzyl bromide in the presence of potassium carbonate. Condensation with sodium (methylsulfinyl)methyde provided the corresponding methylsulfinyl ketone (IX). This was condensed with two equivalents of formaldehyde to yield (X). Subsequent pyrolysis of the sulfoxide group furnished chromenone (XI). Deprotection of the benzyl ether was achieved by treatment with boron trichloride, and the resulting 7-hydroxychromenone (XII) was then alkylated with 1-bromo-3-chloropropane (IV) (4). Scheme 3.

Since this synthetic method did not allow the scale-up preparation, mainly due to safety concerns regarding the use of sodium (methylsulfinyl)methyde, an improved and scalable procedure was further developed. Claisen condensation of acetophenone (V) with ethyl formate in the presence of sodium methoxide produced the 2-hydroxychromanone (XIII). This was condensed with formaldehyde, employing sodium acetate as the catalyst, and the intermediate 3-(hydroxymethyl)-2-hydroxychromanone (XIV) was subsequently dehydrated by treatment with HCl to give (II) (5). Scheme 4.

Description

White crystals, m.p. 242-4 °C; free base, m.p. 200-2 °C.

Introduction

Schizophrenia, a severe and disabling psychotic disorder occurring in about 1% of the population, still causes considerable social concern, which can be in part attributed to incomplete efficacy or to concomitant side effects of current therapies. Although conventional neuroleptics (chlorpromazine, fluphenazine, haloperidol) are effective in the management of positive symptoms of schizophrenia, namely hallucinations, delusions,

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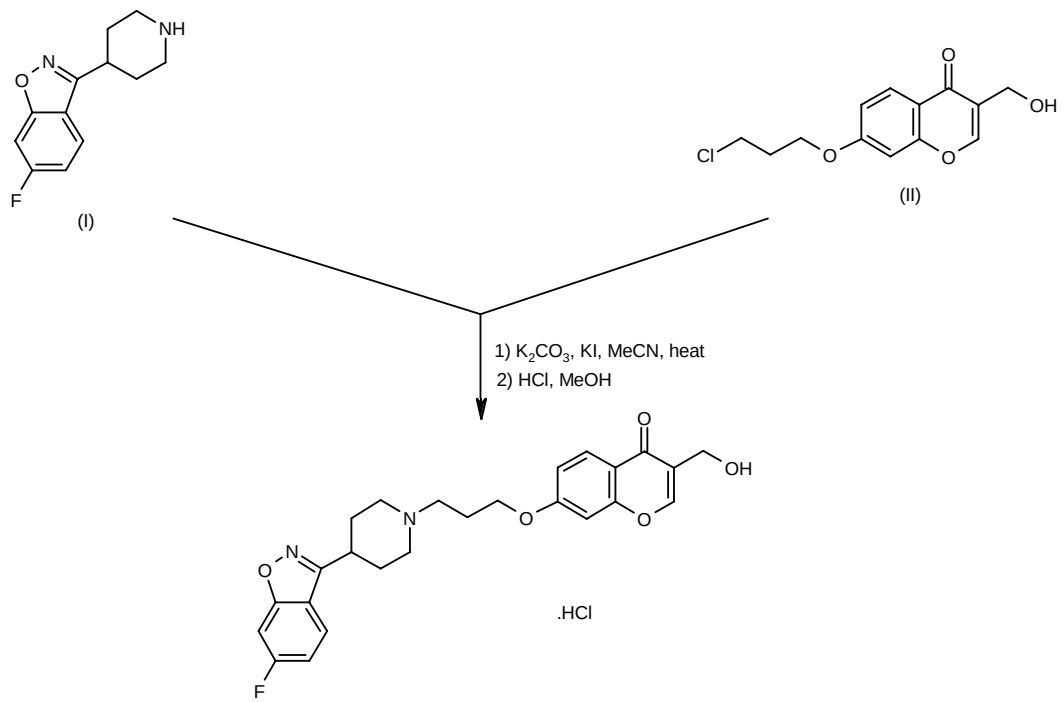
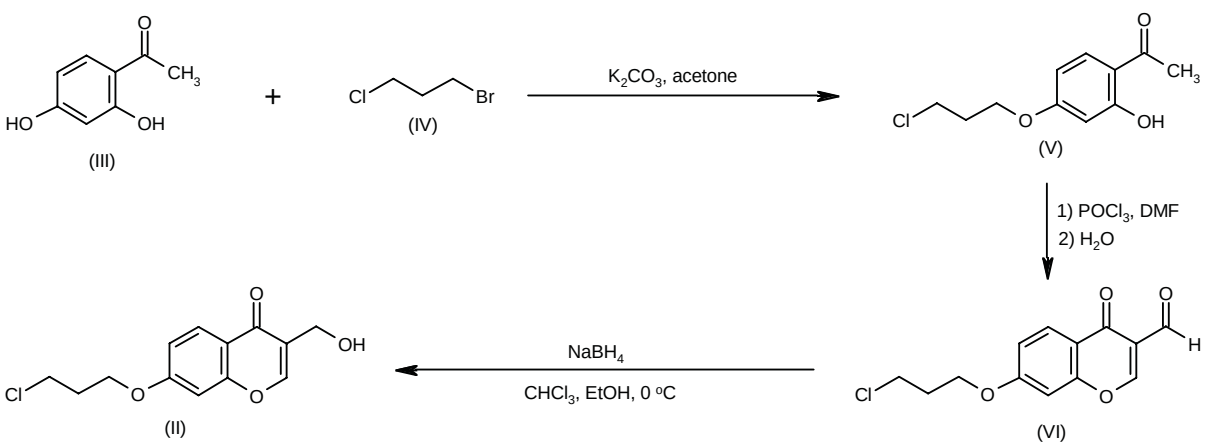
Scheme 1: Synthesis of Abaperidone Hydrochloride

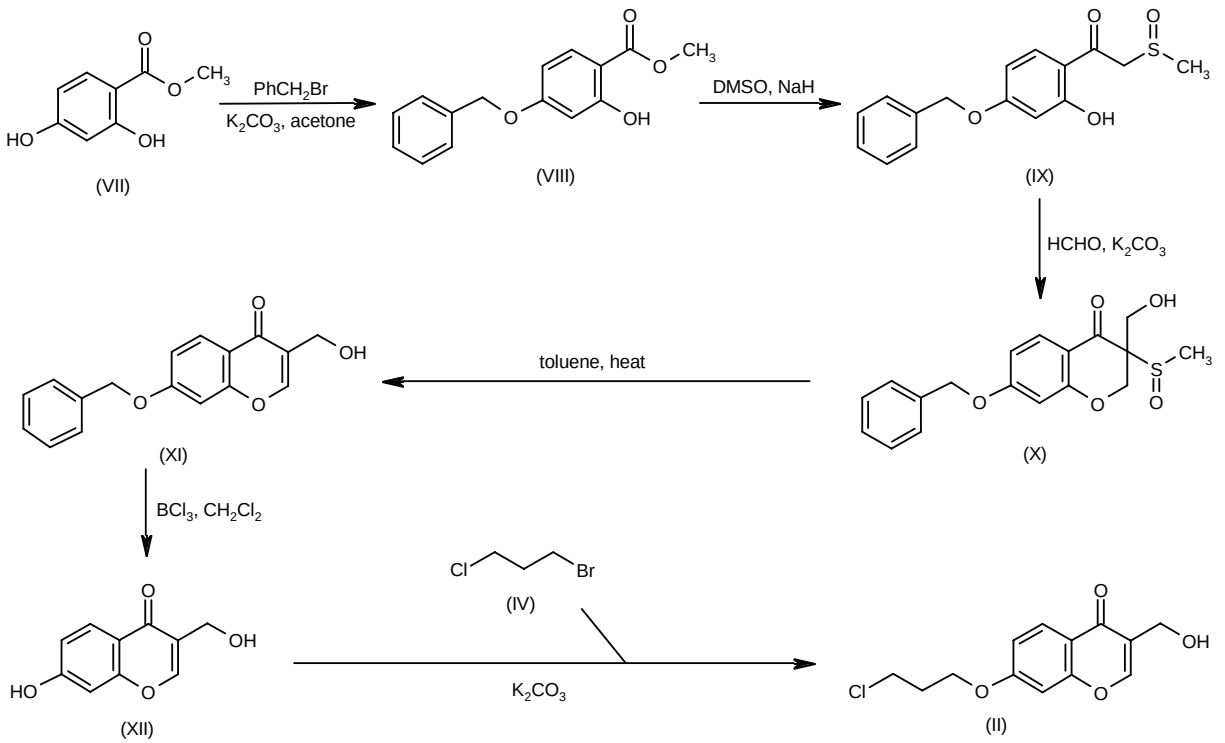


Scheme 2: Synthesis of Intermediate (II)

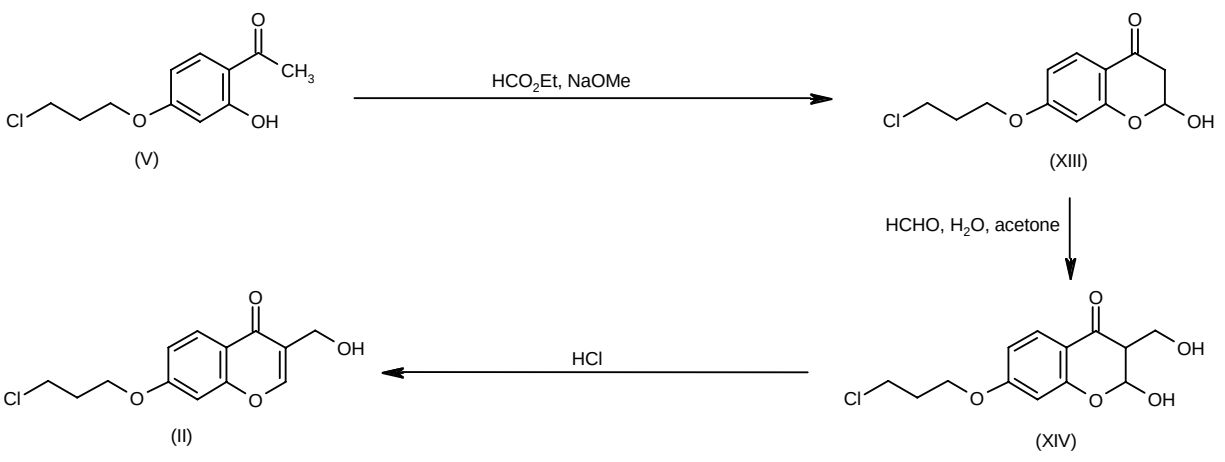


unorganized behavior and thought disorders, these compounds show poor or no efficacy against the negative symptoms (blunted affect, apathy, social withdrawal) (6, 7). Furthermore, their clinical use is limited by the frequent appearance of serious side effects, such as extrapyramidal syndrome (8), tardive dyskinesia (9) and hyperprolactinemia (10). These side effects of classic neuroleptics were originally thought to be inherent to the same mechanism of action of the drugs. Thus, according to the dopamine hypothesis of schizophrenia (11), all

Scheme 3: Synthesis of Intermediate (II)



Scheme 4: Synthesis of Intermediate (II)



antipsychotic drugs share a common profile of D_2 receptor antagonism at the mesolimbic system of the brain (12), whereas dopamine antagonism at other brain structures is considered to be responsible for some unwanted side effects (13). In particular, extrapyramidal effects and hyperprolactinemia are attributed to dopamine blockade at the nigrostriatal system and pituitary dopamine receptors, respectively. However, further efforts to discover more effective antipsychotic medications introduced a new class of compounds challenging this initial concept, which were classified as atypical antipsychotics (14).

Clozapine is considered to be the prototype of these new drugs. This compound proved to be effective in the management of both positive and negative symptoms,

Table I: Receptor binding affinities of abaperidone at several neurotransmitter receptors.[a]

Receptor	Tissue	[^{3}H]Radioligand	Nonspecific	IC_{50} (nM)
D_1	Rat striatum	SCH-23390	Apomorphine	514
D_1	Human recombinant Sf9 cells	SCH-23390	(+)-Butaclamol	98
D_2	Rat striatum	Methylspiperone	Haloperidol	17
D_{2S}	Human recombinant Sf9 cells	Spiperone	Haloperidol	21
D_3	Human recombinant CCL 1.3 cells	Spiperone	(–)-Eticlopride	7.6
$D_{4.2}$	Human recombinant CHO cells	Spiperone	Haloperidol	338
5-HT_{1A}	Rat cortex	8-OH-DPAT	Buspirone	125
5-HT_{1A}	Human recombinant Sf9 cells	8-OH-DPAT	Metergoline	82
5-HT_{2A}	Rat cortex	Ketanserin	Mianserin	3.6
5-HT_{2C}	Rat cortex	Mesulergine	Mianserin	4.2
5-HT_3	Rat cortex	BRL-43694	MDL-7222	>2500
5-HT_4	Guinea pig hippocampus	GR-113808	Serotonin	2220
5-HT_6	HEK 293 cells	LSD	Serotonin	309
5-HT_7	Guinea pig cortex	5-CT	Serotonin	768
α_1-Adrenergic	Rat cortex	Prazosin	WB-4101	6.6
α_2-Adrenergic	Rat cortex	Clonidine	Sodium bitartrate	324
β-Adrenergic	Rat cortex	DHA	Isoprenaline	6500
Muscarinic	Rat cortex	QNB	Atropine	4940
H_1	Guinea pig cerebellum	Pyrilamine	Triprolidine	3.2
σ	Guinea pig brain	3-PPP	3-PPP	617

[a]The SEM for all values was < 10%.

without essentially any tendency to produce extrapyramidal side effects (15). Unfortunately, clozapine is not devoid of other severe undesirable effects, mainly agranulocytosis and seizures in a significant number of cases, which has impaired its clinical utility (16, 17). New substitutes for clozapine are thus required as a safe treatment for schizophrenia. Nevertheless, attempts to rationalize the particular mechanism of action of clozapine are hampered by the binding of this drug to a variety of central nervous system receptors (18). At present, although several models have been proposed, there is not a single theory that satisfactorily explains the atypical antipsychotic profile. Currently, several potential atypical antipsychotics displaying different mechanisms of action are being developed. Some proposed explanations for the mesolimbic selectivity of the atypical antipsychotics include preferential binding to dopamine receptors other than D_2, mainly D_3 (19) and D_4 (20, 21) dopaminergic receptors, and modulation of the D_2 side effects through a counterbalanced effect on other nondopaminergic neurotransmitter systems such as serotoninergic (22) and alpha-adrenergic receptors (23, 24). Abaperidone hydrochloride is a novel chemical entity with pharmacological and biochemical properties suggestive of highly potent antipsychotic action together with a reduced side effect profile in comparison with the conventional antipsychotic medications. This compound is currently undergoing clinical evaluation as a promising new treatment for schizophrenia and psychoses.

Pharmacological Actions

In vitro *studies*

Abaperidone exhibits a mixed binding profile on a variety of CNS receptors, which is consistent with the expected profile for an atypical antipsychotic drug. The affinities of abaperidone for a number of neurotransmitter receptors are shown in Table I. Antagonism at D_2 receptors can be correlated with the potency of the drug (25). Moreover, a greater affinity for 5-HT_2 receptors than D_2 receptors has been related to a reduced incidence of extrapyramidal effects (22). Antagonism at alpha1-adrenoceptors could be associated with some cardiovascular side effects; however, this has also been proposed as one of the determinants of an atypical profile (23, 24). Abaperidone binds with high affinity to D_3 receptors. Since the D_3 subtype of dopaminergic receptors has been found to be more abundant in some areas of the limbic system and scarce or even absent in the pituitary gland and striatum, antagonism at these receptors has been proposed as a target for newer atypical antipsychotics (19, 26).

In vivo *studies*

Animal behavioral models predict that abaperidone should display clinical antipsychotic efficacy with reduced extrapyramidal side effects. Thus, abaperidone hydrochloride proved to be very potent in animal models of

Table II: Pharmacological data[a] of abaperidone and several reference antipsychotics in behavioral models of antipsychotic efficacy and side effects liability.

	Abaperidone	Haloperidol	Clozapine	Risperidone
Inhibition of apomorphine-induced climbing in mice	0.24 (0.22-0.26)	0.31 (0.14-0.69)	15.40 (10.13-23.26)	0.29 (0.24-0.36)
Inhibition of PCA-induced hyperactivity in mice	0.16 (0.11-0.22)	0.30 (0.15-0.58)	6.41 (4.82-8.51)	0.20 (0.11-0.38)
Inhibition of apomorphine-induced loss of startle response in rats	71.4 (59.3-83.4)[b]	NT	52.7 (39.0-66.5)[b]	64.0 (50.6-77.4)[b]
Inhibition of DOI-induced head twitches in mice	0.08 (0.06-0.11)	0.56 (0.35-0.89)	0.85 (0.35-2.05)	0.03 (0.02-0.04)
Induction of catalepsy in rats	8.48 (7.05-10.18)	2.0 (1.30-2.61)	>100	5.0 (4.10-6.25)
Inhibition of apomorphine-induced stereotypy in rats	18.60 (13.24-25.26)	1.75 (0.90-2.85)	>100	9.70 (8.30-11.40)

[a]Results are expressed as ED_{50} values in mg/kg p.o.; 95% confidence limits are shown in parentheses. [b]Results expressed in % prepulse inhibition. NT = not tested.

psychosis, with ED_{50} values of 0.24 mg/kg p.o. and 0.037 mg/kg i.v. for inhibition of apomorphine-induced climbing behavior in mice and an ED_{50} of 0.16 mg/kg p.o. for inhibition of *p*-chloroamphetamine-induced hyperactivity in mice. On the other hand, lower potency was observed in the induction of catalepsy in rats (ED_{50} = 8.48 mg/kg p.o. and 11.68 mg/kg i.p.) and in the inhibition of apomorphine-induced stereotypy in rats (18.6 mg/kg p.o.), effects which indicated a reduced risk of dopamine D_2 receptor-associated side effects in humans (27). The potential antipsychotic effects of abaperidone hydrochloride were also evaluated against apomorphine-induced loss of startle response in rats, with a 71.4% increase in prepulse inhibition at 1 mg/kg p.o. (28). Furthermore, abaperidone was highly potent in inhibiting DOI-induced head twitches in mice (ED_{50} = 0.08 mg/kg p.o.), a characteristic test of activity on central 5-HT_2 receptors. The pharmacological behavioral data for abaperidone and some reference antipsychotics in several animal models of antipsychotic efficacy and extrapyramidal side effects liability are shown in Table II.

In a comparative study of serum prolactin levels after oral administration at the toxicological dose of 5 mg/kg in rats, abaperidone produced significantly smaller increases than the standard antipsychotics haloperidol and risperidone (2).

The hemodynamic side effects of abaperidone were evaluated in anesthetized rats (0.01-0.6 mg/kg i.v.) (29) and in conscious rats (1 and 3 mg/kg p.o.) (30), where only slight and transient hypotension and a slight increase in heart rate were found at the highest doses. In long-term treatment with abaperidone (2.5 mg/kg p.o. for 10 days) in conscious rats telemetrically implanted, no significant changes in hemodynamic and motor activity parameters were shown (29). These effects were milder than those observed with risperidone and clozapine at comparable doses. Abaperidone did not interfere with CNS functions and not produce gastrointestinal side effects (29).

Pharmacokinetics

The pharmacokinetics of abaperidone hydrochloride were studied in rats (31) and dogs (32). After i.v. administration, abaperidone was rapidly excreted, with a $t_{1/2\beta}$ of 24-44 min in rats and 3-6 h in dogs. Plasma levels were found to decrease rapidly, with a rapid tissue distribution. Distribution volume after i.v. administration was 1.5 l/kg in rats and 4 l/kg in dogs. After oral administration, the compound was rapidly absorbed and peak plasma concentrations were reached within 15 min in rats (C_{max} = 0.9 μg/ml at 6 mg/kg) and 30 min in dogs (C_{max} = ~ 0.1 μg/ml at 3 mg/kg). Rapid distribution to cerebral tissues was observed after oral administration at the toxicological dose of 6 mg/kg in rats, with a mean concentration of 0.6 μg/g at 30 min and 0.08 μg/g at 2 h. The absolute oral bioavailability (6 mg/kg administered as suspension in agar) was 19% in rats and 10% in dogs. The greater distribution volumes after oral administration (5.8-10 l/kg in rats and 32-72 l/kg in dogs) as compared to i.v. administration indicated first-pass metabolism.

Toxicology

Acute toxicological studies after oral administration to mice and rats showed a very low toxicity, with no lethality observed at oral doses up to 500 mg/kg. Toxic effects included catalepsy and weight loss, both of which were reversible after a few days. No mortality was observed at the maximum administered i.v. dose of 10 mg/kg.

In subacute studies (28 days), orally administered abaperidone was well tolerated in rats at doses of 0.5-6.25 mg/kg/day and in dogs at doses of 0.5-4.5 mg/kg/day. The only observed effects were catalepsy in rats, sedation and trembling in dogs (at the highest doses), slight alterations in hepatic and renal function in rats and splenic congestion in dogs (species-specific effect) (33).

Safety was also demonstrated in genotoxicity studies using the Ames test in Salmonella typhimurium (34), a chromosome aberration test in human lymphocytes and the micronucleus test (35), with results showing that the compound did not induce any promutagenic, mutagenic or clastogenic effects.

Thus, abaperidone hydrochloride demonstrates a good safety margin and no adverse effects are expected in clinical use.

Conclusions

Preclinical studies demonstrate that abaperidone hydrochloride has potential as a new atypical antipsychotic drug. Based on its biochemical and pharmacological properties, abaperidone is expected to have therapeutic advantages and reduced extrapyramidal side effects in comparison with conventional antipsychotic compounds. The safety and efficacy of abaperidone are currently being evaluated in clinical trials.

Manufacturer

Interquim, S.A. (Grupo Ferrer) (ES).

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