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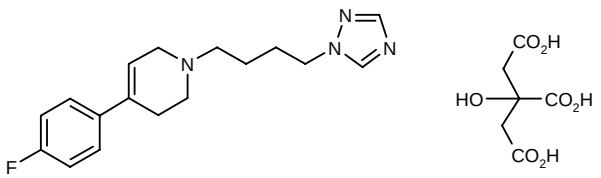
E-5842

Antipsychotic
σ-Receptor Ligand

4-(4-Fluorophenyl)-1-[4-(1,2,4-triazol-1-yl)butyl]-1,2,3,6-tetrahydropyridine citrate



$C_{17}H_{21}FN_4.C_6H_8O_7$ Mol wt: 492.5011

CAS: 177945-45-8 (as hydrochloride)
CAS: 177945-46-9 (as free base)

EN: 256549

Synthesis

E-5842 was prepared by reacting (I) with citric acid monohydrate in ethanol (1). The base (I) can be obtained by two ways: Scheme 1.

1) By condensation of 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (III) or 8-(4-fluorophenyl)-5-azoniaspiro[4.5]dec-7-ene chloride (IV) with 1-(4-chlorobutyl)-1*H*-1,2,4-triazole (V) or 1*H*-1,2,4-triazole, respectively, in dimethylformamide in the presence of potassium hydrogencarbonate.

2) By dehydration of 1-[4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidyl]butyl]-1*H*-1,2,4-triazole (VI) in refluxing hydrochloric acid/ethanol. The piperidinol (VI) can be obtained by two procedures:

a) By condensation of 4-(4-fluorophenyl)-4-hydroxypiperidine (II) with 1-(4-chloro-butyl)-1*H*-1,2,4-triazole (V) in dimethylformamide in the presence of potassium hydrogencarbonate.

b) By condensation of 1,4-dioxa-8-azaspiro[4.5]-decane (VII) with 1-(4-chlorobutyl)-1*H*-1,2,4-triazole (V) and hydrolysis of the acetal to give 1-[4-(4-oxo-1-piperidyl)butyl]-1*H*-1,2,4-triazole (VIII), followed by addition of 4-fluorophenyl lithium or 4-fluorophenyl magnesium bromide in ether or tetrahydrofuran to yield (VI).

Description

Citrate, m.p. 131-2 °C; hydrochloride, m.p. 166-8 °C; free base, m.p. 57-8 °C.

Introduction

Schizophrenia is a poorly understood, complex neuropsychiatric disorder which is generally associated with cognitive and emotional alterations and represents a major social problem (2). Current therapy remains symptomatic rather than disease-based. Despite controversy as to whether schizophrenia should be considered as a single disorder or a combination of various disorders, neurochemical and pharmacological data support the hypothesis that schizophrenia is a heterogeneous group of disorders based on different etiologic and pathogenic mechanisms. The diverse symptoms of the disorder have been classified according to positive and negative symptoms. Positive symptoms include delusions, hallucinations, psychosis, paranoia, disorganized speech and behavior, and negative symptoms include loss of energy, deficiency of speech, lack of initiative, loss of sociability and blunting of emotions.

An abnormal catecholaminergic activity at the CNS, especially that of dopamine, was suggested to underlie psychotic disorders such as schizophrenia when early findings showed that the classic neuroleptics haloperidol and chlorpromazine modified brain dopamine and noradrenaline metabolism (3). Mesocorticolimbic dopamine systems have been shown to be closely involved in the pathophysiology of schizophrenia. It has been suggested that the negative symptoms of schizophrenia could be due to low prefrontal dopamine activity, which would lead to excessive dopaminergic activity in mesolimbic structures producing positive symptoms (4). Blockade of the dopamine D_2 receptor has been considered to be the major therapeutic basis of classic neuroleptics (5, 6). However, the clinical efficacy of dopamine D_2 receptor antagonists has been shown to be limited. Although dopamine D_2 receptor blockade has been proven to be effective for treating positive symptoms, it is generally ineffective for treating negative symptoms and is associated with undesirable effects such as extrapyramidal side effects (EPS) and the development of tardive dyskinesia after chronic administration (7, 8). It was formerly believed that most antipsychotic drugs alleviate the positive symptoms of schizophrenia by acting on the

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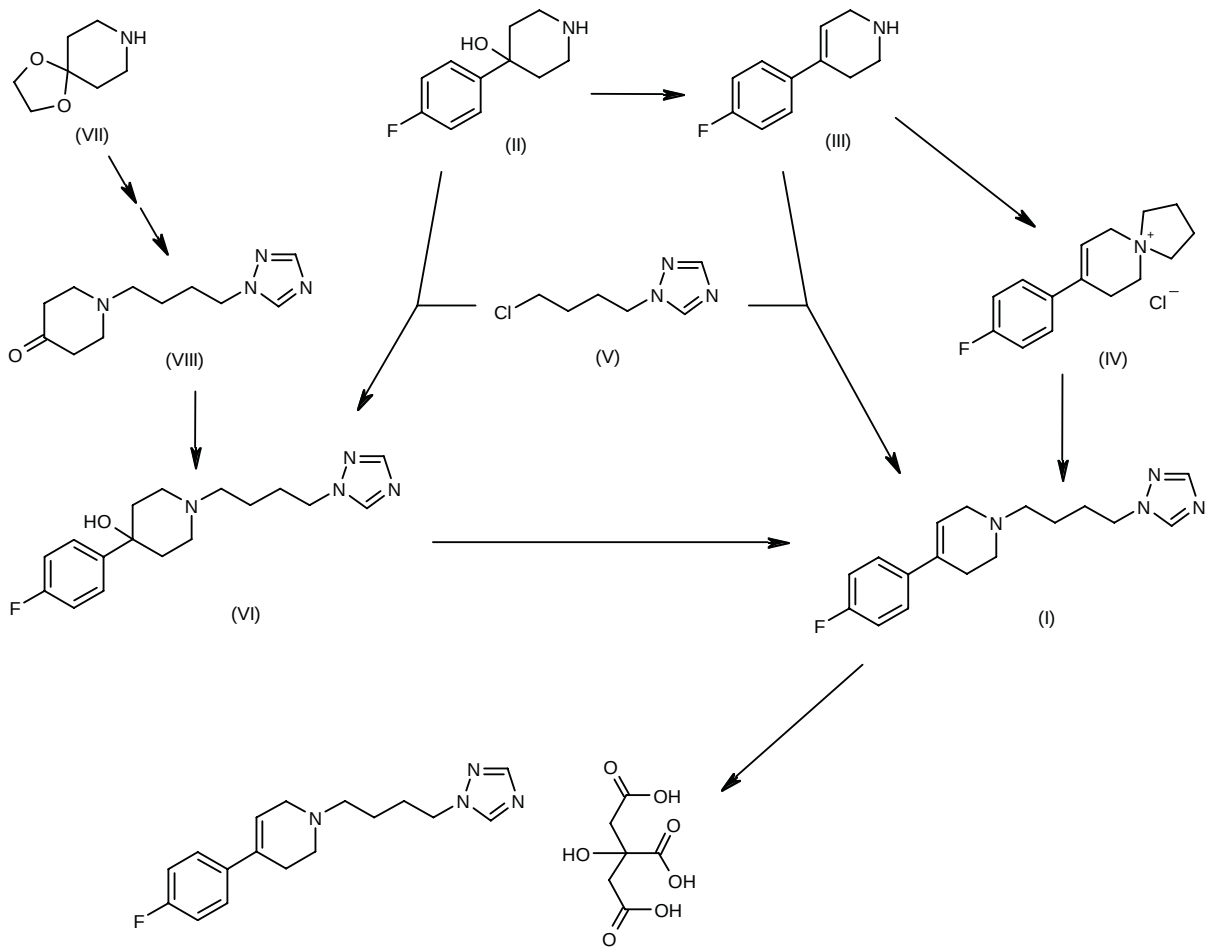
Scheme 1: Synthesis of E-5842



mesolimbic dopaminergic system in areas such as nucleus accumbens as opposed to striatal regions of the brain, while blockade of striatal dopamine D_2 receptors would lead to the development of undesirable side effects such as EPS (9-12). However, the traditional view of schizophrenia as a simple consequence of dopamine alteration is no longer adequate, since other neurotransmitter systems such as glutamatergic (13) and serotonergic (14) have been shown to be involved in the pathophysiology of schizophrenia.

Much research has been directed towards the search for an "ideal" antipsychotic that would be effective against both positive and negative symptoms but without the undesirable side effects of the classic neuroleptics. Research efforts led to the discovery of a new generation of antipsychotic drugs, the atypical antipsychotics (*e.g.*, clozapine, seroquel, risperidone, sertindole, olanzapine). Atypical antipsychotics have been shown to be effective in the treatment of a wide range of psychotic disorders, including neuroleptic-resistant schizophrenia, and are as effective as the classic neuroleptics against positive symptoms, more effective against negative symptoms and have less EPS liability (15-17).

σ Receptors are involved in a number of CNS and peripheral disorders, although their precise biological role remains unclear (18). Recently, growing interest has focused on σ receptors as potential pharmacological targets for developing compounds with antipsychotic properties. The existence of multiple σ receptor sites was early suspected (18) and at least two subtypes of σ receptor have been identified and pharmacologically characterized: σ_1 and σ_2 (19-22). The σ_1 receptor was recently cloned (23, 24), while the σ_2 receptor remains to be purified due to the lack of selective and high affinity ligands. Interestingly, the existence of more than two subtypes has been suggested (25, 26).

The hypothesis implicating σ receptors in the pathophysiology of schizophrenia came from early studies showing that many neuroleptics, such as haloperidol,

Table I: Receptor binding profile of E-5842.

Receptor	Tissue	Radioligand	Ki (nM)
σ_1	[^{3}H](+)-Pentazozine	Guinea pig brain	4
σ_2	[^{3}H] Ifenprodil	Rat brain	220
α_{1A}	[^{3}H] Prazosin	Rat submaxillary gland	119
α_{1B}	[^{3}H] Prazosin	Rat liver	116
α_{2A}	[^{3}H] RX821002	Rabbit spleen	800
α_{2B}	[^{3}H] Yohimbine	Rat kidney	89
H_1	[^{3}H] Pirilamine	Guinea pig cortex	389
D_2	[^{3}H] Raclopride	Rat striatum	>1000
D_2	[^{3}H] YM-09151-2	Rat striatum	510
D_3	[^{3}H] (+)-7-OH-DPAT	Rat cloned	418
D_4	[^{3}H] Spiperone	Human cloned	>1000
5-HT_{1A}	[^{3}H] 8-OH-DPAT	Rat hippocampus	460
5-HT_2	[^{3}H] Ketanserin	Rat cortex	817
5-HT_3	[^{3}H] GR 65.630	Rat cortex	>1000
$GABA_A$	[^{3}H] Muscimol	Rat cortex	>10,000
M_1	[^{3}H]NMS	Human cloned	>10,000
M_2	[^{3}H]NMS	Human cloned	>10,000
M_3	[^{3}H]NMS	Human cloned	>10,000

exhibit high affinity for binding to σ sites in the brain (19). This observation, together with the observation that σ ligands induced psychotomimetic symptoms (27), suggest that σ ligands may provide a therapeutic basis for a new class of antipsychotics without the side effects associated with neuroleptics. Further data supporting σ receptor involvement in schizophrenia were provided by studies detecting σ receptors in areas of the human brain closely associated with schizophrenia (*i.e.*, cortical and limbic structures) (28) and studies demonstrating selective loss of σ sites in schizophrenia (29, 30). However, the precise mechanism by which σ receptors are involved in this disorder remains to be established, although several hypotheses have been proposed considering that σ receptors were shown to modulate neuronal responses of the glutamatergic and dopaminergic pathways known to be involved in schizophrenia (31-33).

Since antipsychotic properties of σ receptor ligands have been demonstrated in both animal studies (34-36) as well as clinical trials (37-41) with negligible incidence of EPS, the implication of σ receptors in the pathophysiology of schizophrenia is further strengthened. Thus, compounds such as remoxipride, umespirone, rimcazole, panamesine, NE-100, SR-31742A, DuP-734 and BMY-14802, all with high affinities for σ receptors over dopamine receptors, have been or are currently under investigation as potential antipsychotic drugs.

E-5842 is a new compound which was selected for further development due to its high affinity for the σ_1 receptor, its very low affinity for other receptors (*i.e.*, dopamine receptors) and its potential as an atypical antipsychotic in animal studies (42). The *in vitro* and *in vivo* preclinical profiles of this compound correspond to an atypical antipsychotic and E-5842 appears to have a low liability for EPS and potential efficacy in the treatment of negative symptoms of schizophrenia.

Pharmacological Actions

The binding profile of E-5842 is shown in Table I (43). E-5842 had a high degree of selectivity for the σ_1 receptor (K_i = 4 nM) with less affinity for the σ_2 receptor (K_i = 220 nM). E-5842 displayed moderate affinity for α_{2B}-, α_{1A}-and α_{1B}-adrenergic receptors, which was 20- to 30-fold less than its affinity for the σ_1 receptor, and negligible affinity for dopamine D_2 and D_4, serotonin 5-HT_2 and 5-HT_3, $GABA_A$ and muscarinic receptors.

The behavioral profile of E-5842 has been evaluated in a range of animal models in which both typical and atypical antipsychotics have proven to be effective, with results demonstrating not only the antipsychotic properties but also the low EPS liability of the compound. E-5842 was shown to antagonize apomorphine-induced climbing (ED_{50} = 7.7 mg/kg i.p.) (44) and to be orally active against mescaline-induced scratching (ED_{50} = 7 mg/kg p.o.) in mice (45). E-5842 also blocked apomorphine-induced disruption of prepulse inhibition (42) and dose-dependently reduced the conditioned avoidance response and *d*-amphetamine-induced hyperactivity in rats (Table II). Despite the fact that the agent was as effective as other sigma ligands such as BMY-14802 in the mescaline-induced scratching test, E-5842 was less active than haloperidol, risperidone and clozapine (45). However, E-5842 was as effective as clozapine both in reducing conditioned avoidance response and by reversing *d*-amphetamine-induced hyperactivity, although haloperidol was again the most active compound tested in these models (Table II).

Table II: Inhibition of the conditioned avoidance response (CAR), lack of cataleptogenic activity (CAT) and d-amphetamine-induced hyperactivity (AMH) in rats.

Compound	CAR	CAT	AMH
E-5842	13.3	>80	3.8
Haloperidol	0.4	0.15	0.2
Clozapine	10.4	>80	4.1

Compounds were administered p.o., s.c. and i.p. for the CAR, CAT and AMH tests, respectively. Values are expressed as ED_{50} (mg/kg).

The induction of catalepsy is commonly used to assess potential induction of EPS by antipsychotics. E-5842 did not induce catalepsy in rats even at doses of 80 mg/kg s.c., which were higher than haloperidol and similar to clozapine (Table II), suggesting that E-5842 has a low EPS liability similar to that of clozapine and much lower than that of haloperidol. Although it has been postulated that blockade of the 5-HT_2 receptor can account for the reduction of cataleptogenic activity of several antipsychotics, the moderate activity of E-5842 in the mescaline-induced scratching test and data from binding studies suggest that this is not the case for E-5842. The lack of cataleptogenic activity of this compound is probably due to its poor interaction with dopamine receptors. It is assumed that low doses of amphetamine increase locomotor activity by activating the mesolimbic pathway in the ventral tegmental area to the nucleus accumbens, while the action of antipsychotics on the nigrostriatal dopamine system is responsible for EPS. Thus, calculation of EPS separation, *i.e.*, the ratio between the potency of a functional antipsychotic agent to block *d*-amphetamine-induced hyperactivity and to produce catalepsy, indicates the EPS liability of the compound. The EPS separation calculated from the data in Table II for E-5842 was >20, similar to that of clozapine but very different from haloperidol (0.75). Therefore, the EPS separation value for E-5842 is large enough to suggest a clear difference in potency between catalepsy induction and hyperactivity inhibition, indicating a low of EPS liability.

Clinical pharmacological management of schizophrenia generally implies long-term drug treatment with neuroleptic agents which can be accompanied by many undesirable side effects. It is known that prolonged antipsychotic drug treatment may produce dopamine D_2-like receptor upregulation in striatal areas (46). Since the degree of D_2 receptor blockade in the basal ganglia has been related to the incidence of EPS following chronic antipsychotic treatment (11), dopamine receptor upregulation resulting from chronic drug treatment limits the clinical usefulness of neuroleptics and even some atypical antipsychotics. Such an effect is not expected for E-5842 because of its low affinity for dopamine receptors. However, the dopaminergic antagonistic properties of E-5842 observed *in vivo*, such as suppression of apomorphine- and *d*-amphetamine-induced responses, indicates that an indirect regulation of the D_2 receptor after long-term administration cannot be ruled out.

Chronic neuroleptic treatment-induced dopamine receptor hypersensitivity in animals can be measured by the enhanced response (stereotypy) to apomorphine after withdrawal of the drug (47). In this regard, E-5842 was given to rats for 21 days at different doses (up to 30 mg/kg/day i.p.) followed by apomorphine administration. E-5842, even at the higher dose tested, showed only a small nonsignificant tendency to increase the stereotypy score. Using a similar experimental paradigm, binding studies in rats examined alterations in striatal receptor density. Results showed that chronic administration of E-5842 did not induce any change in the striatal dopamine D_2 receptor, neither in affinity (K_D = 0.185 ± 0.040 and 0.212 ± 0.053 nM for control and treated rats, respectively) nor in receptor density (B_{max} = 455 ± 65 and 418 ± 34 fm/mg protein, for control and treated rats, respectively). These data indicate that E-5842 does not induce behavioral supersensitivity or dopamine D_2 receptor upregulation, probably due to its lack of affinity for dopamine receptors.

The putative ability of E-5842 to act on negative symptoms of schizophrenia was evaluated using the social interaction test in rats. This test is a preclinical correlate to the negative symptoms of schizophrenia such as withdrawal and reduced social interaction and a range of atypical antipsychotics including clozapine have been shown to increase social interaction in rodents using this technique (48). As shown in Table III, E-5842 at doses of 0.01-0.5 mg/kg i.p. increased social interaction without decreasing locomotor activity (43), similar to results observed with atypical antipsychotic compounds. The exact mechanism of action for this effect remains unclear, although only atypical antipsychotics are known to be active in this test.

In addition to its potential action on the negative symptoms of schizophrenia, E-5842 may also exhibit anxiolytic activity similar to other atypical antipsychotics such as clozapine, olanzapine (49) and ORG-5222 (50) in animal models. For example, E-5842 displayed clear

Table III: Effect of E-5842 on the social interaction test and locomotor activity in rats.

	Social interaction	Locomotor activity
Vehicle	40 ± 2	121 ± 1
E-5842 (0.01 mg/kg i.p.)	59 ± 3*	117 ± 8
E-5842 (0.02 mg/kg i.p.)	71 ± 3*	119 ± 5
E-5842 (0.05 mg/kg i.p.)	76 ± 4*	124 ± 3
E-5842 (0.10 mg/kg i.p.)	100 ± 4*	121 ± 5
E-5842 (0.50 mg/kg i.p.)	105 ± 11*	120 ± 5
E-5842 (2.20 mg/kg i.p.)	78 ± 8*	91 ± 11#

Values represent seconds for the social interaction test and line crossings for the locomotor activity test. *Significant statistical difference from vehicle (p <0.05). #Significant statistical difference from vehicle (p <0.05).

anxiolytic activity in the black and white box test; E-5842 treatment was highly potent and effective, with maximum activity observed at doses of 0.05, 0.5 and 4.5 mg/kg i.p.

Neuroleptic drugs may attenuate and sometimes suppress instrumental responding in rats (51). Under experimental conditions, a clear intersession decrease in food-reinforced responses is often observed with neuroleptics that cannot be attributed to pharmacokinetic factors. However, intersession decreases in response are not produced by all atypical antipsychotic drugs (52). E-5842 produced a dose-related decrease in overall response rates in a fixed-ratio schedule of 10 (where 10 was the number of responses needed to obtain food reinforcement) without affecting the rate of within-session responses (53), similar to the pattern of response seen with atypical antipsychotics.

The effect of E-5842 on cerebral dopamine levels was examined since most known antipsychotics affect these levels especially in the nucleus accumbens, dorsolateral striatum and prefrontal cortex. Atypical antipsychotics such as clozapine increased dopamine release in the medial prefrontal cortex, while haloperidol had no effect (54), suggesting that classical and atypical antipsychotics differentially affect the dopamine activity of medial prefrontal cortex. Acute administration of E-5842 (20 mg/kg i.p.) in rats modified extracellular dopamine levels in projection areas of both the mesolimbic/mesocortical and nigrostriatal dopaminergic pathways as measured by *in vivo* microdialysis technique (55). Acutely administered E-5842 induced a clear increase of dopamine release in the striatum lasting for at least 3 h after drug administration, reaching a maximum of approximately 200% over the basal levels of the neurotransmitter. E-5842 had a significant effect in the medial prefrontal cortex, where it induced an up to 3.5-fold increase in extracellular dopamine levels. Conversely, the compound induced only a modest and transient decrease of dopamine levels in the nucleus accumbens (> 40%). Again, E-5842 behaved in a manner similar to atypical antipsychotics such as clozapine (54) and the putative atypical antipsychotic MDL-100907 (56). This effect could be relevant in terms of efficacy, since it has been suggested that the negative symptoms of schizophrenia may be associated with decreased cortical dopaminergic activity (4, 57).

The effect of antipsychotic drugs and other psychotropic drugs on the expression of Fos, the protein product of the c-fos gene, has been widely discussed (58, 59). Fos expression was increased by several physiological and pharmacological stimuli in different brain regions (60), and it appears that there is a region-specific pattern of induction by classical versus atypical antipsychotic drugs; antipsychotic drugs with relatively high EPS liability induce Fos expression in the dorsolateral section of the striatum while atypical antipsychotics enhance Fos preferentially in the medial prefrontal cortex (12, 58, 61). From these observations, it has been suggested that an increase in the medial prefrontal cortex may predict efficacy against the negative symptoms of schizophrenia while dorsolateral striatal Fos induction reflects EPS liability for different antipsychotics. The effects of E-5842 on Fos expression in brain structures were evaluated in an *ex vivo* study in rats which were acutely administrated the drug (20 mg/kg s.c.), followed by removal of the medial prefrontal cortex, accumbens and striatum 2 h later. Results showed that E-5842 potently and significantly increased the induction of Fos protein in the medial prefrontal cortex (up to 186%) and the nucleus accumbens (up to 139%), while Fos levels in the dorsolateral striatum were unaltered (62). Clozapine produced similar effects in which induction of Fos expression was restricted to limbic structures. Again, the ability of these compounds to increase cellular activity in the prefrontal cortex, measured as an increase of Fos immunoreactivity, with no effects observed in the striatum, suggests that E-5842 is capable of ameliorating the negative symptoms of schizophrenia with a low EPS liability after both acute and prolonged treatment.

Pharmacokinetics

Preliminary pharmacokinetic studies (Esteve S.A., data on file) showed that substantial plasma levels of E-5842 were achieved after oral administration of different doses. Higher levels of the drug were detected in brain than in plasma 1-3 h after administration. However, the exact concentrations of unaltered compound in the whole brain or in specific regions of rat brain have not yet been determined.

Conclusions

E-5842 appears to be a preferentially selective σ_1 ligand, although interactions with other receptors cannot be ruled out. Data from behavioral and neurochemical studies indicate that E-5842 behaves in a manner similar to atypical antipsychotics such as clozapine. Thus, preclinical evaluation indicates that E-5842 exhibits an atypical antipsychotic profile with activity against both positive and negative symptoms of schizophrenia with low EPS liability.

Phase II trials are expected to begin in September.

Manufacturer

Laboratorios Dr. Esteve S.A. (ES)

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