The Imperial Invention Prize

Invention of a novel antipsychotic drug aripiprazole (PAT. No.2893175)

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Schizophrenia is a severe chronic mental disorder with a global lifetime prevalence of about 1%, regardless of race or gender. The onset of symptoms usually occur in young adulthood and include positive symptoms such as hallucinations, paranoia and delusions and negative symptoms such as blunted affect and emotional withdrawal.

The pathogenesis of schizophrenia has not been established, however, it is believed that hyperactivity of dopaminergic neurotransmission might play a major role in causing the symptoms (i.e. the dopamine hyperactive theory).

In the 1950s-1960s, a number of drugs that improved the symptoms of schizophrenia were discovered and it was found that they also inhibit dopamine neurotransmission by blocking the postsynaptic DA D2 receptors. However, DA antagonism also causes serious side effects such as extrapyramidal symptoms (EPS), tardive dyskinesia (TD), and hyperprolactinemia. Nowadays these drugs are referred to as first generation antipsychotics (FGAs) or 'typical' antipsychotics. These FGAs are effective against positive symptoms but less effective against negative symptoms.

In the 1990s, serotonin-dopamine antagonists were developed for the treatment of schizophrenia. These second generation antipsychotics (SGAs) or 'atypical' antipsychotics, inhibit both DA and serotonin neurons. They can reduce some of the safety issues of FGAs such as EPS and TD, however they bring new problems such as weight gain, lipid metabolism abnormalities, and QTc interval extension. Therefore patients with schizophrenia were still suffering from undesirable side effects. A new and safer treatment option was required.

All of the commercially available antipsychotics, including FGAs and SGAs, blocked the D2 receptor and acted as antagonists. Therefore it was difficult to prevent side effects such as EPS and hyperprolactinemia. In order to try to limit these types of side effects, molecules which reduce dopaminergic neurotransmission by the stimulation of DA autoreceptors were considered. However, a DA autoreceptor has not yet been successfully developed as an antipsychotic.

In order to find a more effective agent for treating both the negative and positive symptoms of schizophrenia with fewer side effects, we started to search for compounds which worked as both an agonist at the DA autoreceptors and an antagonist at the postsynaptic DA receptors. We thought that if we could discover this type of compound, it would be an effective agent for the treatment of both the positive and negative symptoms of schizophrenia, with minimal adverse effects.

We therefore synthesized a series of new chemical compounds and examined the postsynaptic DA receptor antagonist activity by evaluating their ability to antagonize the DA agonist apomorphine (APO) in the stereotypy test.

Selected compounds, which showed potent postsynaptic DA receptor antagonist activity, were evaluated for their DA autoreceptor agonist activity by testing their reversing effects on the γ-butyrolactone (GBL) - induced increase in L-dihydroxyphenylalanine (DOPA) synthesis in the mouse brain.

The current 'invention' compound, aripiprazole has a new structure which has a 2,3-dichloro phenyl piperazinyl moiety combined by the butoxy linker at the 7th position of a 3,4-dihydrocarbostyril as shown in Fig. 1.

In contrast with all conventional antipsychotics that block the D2 receptor, aripiprazole is the first and only partial agonist at the D2 receptor. Both *in vivo* and *in vitro* studies have demonstrated that aripiprazole acts as an antagonist in the hyper dopaminergic situation and as an agonist in the hypo dopaminergic situation as shown in Fig.2.

In a clinical setting, aripiprazole improves both the positive and negative symptoms of schizophrenia with less side effects; less EPS and TD, as well as weight gain, lipid abnormality and hyperprolactinemia. Due to the combination of its robust efficacy and superior side effect profile, patients are able to take aripiprazole without discontinuation and it can therefore contribute to the prevention of future relapses and help patients be part of the society again.

In addition to an indication for schizophrenia, aripiprazole has also been approved as a treatment option for bipolar mania in Japan. In the US, aripiprazole is also approved for mental diseases in children and adolescents: schizophrenia, bipolar mania and autism as well as adjunct treatment for major depressive disorders.

Since its approval for the treatment of schizophrenia in 2002, aripiprazole, now classified unique third generation antipsychotic drug, has been approved in at least 70 countries worldwide. We expect that this drug will continue to contribute to the improvement of the lives of patients and families who suffer from mental diseases.

Fig.1

aripiprazole

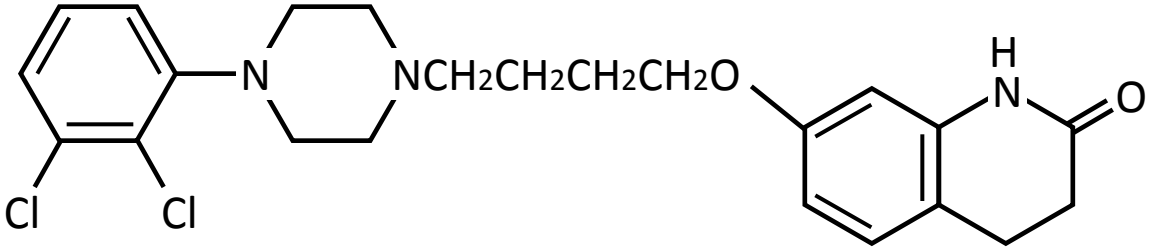

Fig.2