# SAR Study, Synthesis, and Biological Activity of Lurasidone Hydrochloride : A New Drug for Treating Schizophrenia

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Lurasidone hydrochloride received approval by the FDA in 2010 for the treatment of schizophrenia. Lurasidone is a full antagonist at dopamine $D_2$ and serotonin 5-$HT_{2A}$ receptors, properties shared by most second-generation antipsychotics. Lurasidone also has high affinity for serotonin 5-$HT_7$ and is a partial agonist at 5-$HT_{1A}$ receptors; it is believed that these properties could be potentially related to effects on cognition and mood[1].

Of particular note is that lurasidone has minimal affinities for receptors that might induce adverse events. The low affinity for alpha-1 noradrenergic receptors predicts a lower risk for orthostatic hypotension. Moreover the minimal affinity for 5-$HT_{2C}$ receptors and histamine $H_1$ receptors predicts lower liability for weight gain as well. The lack of affinity for cholinergic $M_1$ receptors predicts a low propensity for anticholinergic side effects. Our attempts to reduce adverse events had enabled us to obtain lurasidone with better tolerability and efficacy[2]. Here, we report the synthesis, structure and activity relationships and pharmacological profiles of lurasidone.

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## Introduction

Schizophrenia is a chronic psychiatric disorder and its lifetime prevalence is approximately 1%. According to a survey conducted by the Ministry of Health, Labour and Welfare, the number of schizophrenia patients in Japan is estimated to be at least 795,000 as of 2005. Of those schizophrenia patients, the number of inpatients is estimated to be 187,000 and the number of outpatients is estimated to be 66,000 as of 2008.[3] The annual medical cost of schizophrenia amounts to 1 trillion yen. It is therefore urgently necessary to reduce the social and financial losses caused by the disease.

The major symptoms of schizophrenia include positive symptoms, negative symptoms, and cognitive impairment (**Fig. 1**). Positive symptoms include hallucinations, delusions, and disordered thoughts and speech. Negative symptoms include flat effects, apathy, and deletion of sociality. And cognitive impairment includes attention and memory deficits and performance deficits. It is also known that these major symptoms often co-occur with mood disorders.

Schizophrenia treatments involve medications, psychotherapeutic counseling, and social rehabilitation therapy. Medication is the first-choice treatment for the disease. However, some patients do not respond sufficiently to using existing drugs because of their insufficient efficacy or their adverse effects.

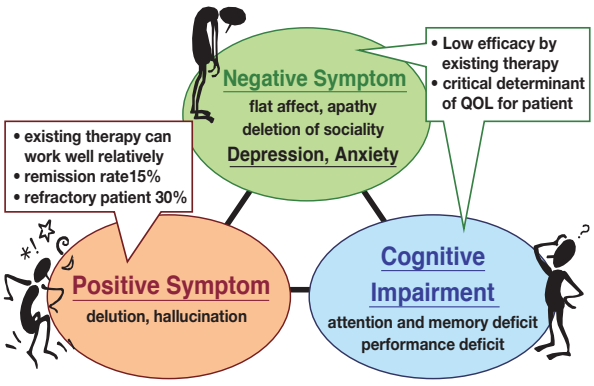


**Fig. 1** Main symptoms of schizophrenia

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## Efficacy of Existing Drugs

### 1. First-Generation (Typical) Antipsychotics

During the 1950s, the fact that chlorpromazine indicated treatment efficacy to the psychiatric symptoms of schizophrenia patients revealed that the dopamine $D_2$ receptor antagonism played an important role in improving positive symptoms. Since then, many treatment drugs having $D_2$ receptor antagonism have been developed as first-generation antipsychotics.

However although these first-generation antipsychotics demonstrate efficacy in treatment of positive symptoms of schizophrenia, they show less efficacy for treatment of negative symptoms. Furthermore, some severe side effects have been clinical issues. Treatment using first-generation antipsychotics frequently are accompanied by extrapyramidal motor dysfunction (e.g. parkinsonism, akathisia, dyskinesia) caused by strong $D_2$ receptor inhibition in the striatum which is one of the motor centers and hyperprolactinemia caused by $D_2$ receptor inhibition in the pituitary gland.

### 2. Second-Generation (Atypical) Antipsychotics

Inhibition at the serotonin-2A (5-$HT_{2A}$) receptor is reported to enable (1) improvement of negative symptoms of schizophrenia and (2) decrease in extrapyramidal adverse effects caused by the first-generation antipsychotics.[4), 5)] This information served as a trigger to develop the second-generation antipsychotics with strong 5-$HT_{2A}$ and $D_2$ receptor antagonism. The second-generation antipsychotics have become the first choice for medications due to efficacy in positive symptoms and fewer side effects such as extrapyramidalsymptoms and hyperprolactinemia. However, medication efficacies toward negative symptoms and cognitive impairment remain as problems in many cases. Furthermore, additional observed adverse effects such as weight gain and increased risk of diabetes have been noted treatment using some second-generation antipsychotics. Some agents also demonstrate strong antagonism at histamine $H_1$, adrenergic alpha-1 receptors and the muscarinic acetylcholine $M_1$ receptor. The side effects related to those receptors are also of concern.

Here we explain how we overcame various challenges and discovered the novel antipsychotic agent lurasidone through structure-activity relationship-based drug design.

## Drug Design Initiative for Monotherapy – Originating with the Anxiolytic Agent Tandospirone –

### 1. Synthesizing Strategy

We accumulated abundant data on structure-activity relationships and a wealth of pharmacological expertise on central serotonin system through research into and development of the serotonin-1A (5-$HT_{1A}$) agonist, or anxiolytic agent tandospirone (1) (**Fig. 2**)[6), 7)]

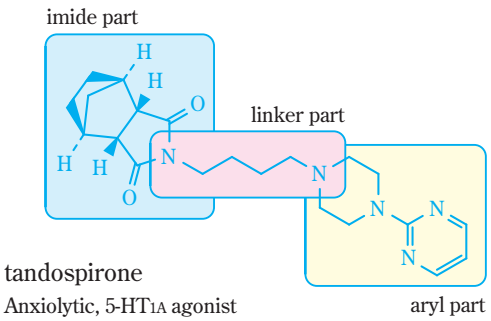



**Fig. 2** Structure of tandospirone

Focusing on the selective 5-$HT_{1A}$ agonism of tandospirone, we planned to develop a schizophrenia treatment drug which had anxiolytic efficacy. Throughout the transformation from the tandspirone backbone, we set a first goal of adding the $D_2$ and 5-$HT_{2A}$ receptor antagonism that enables compounds to take second-generation antipsychotic performance.

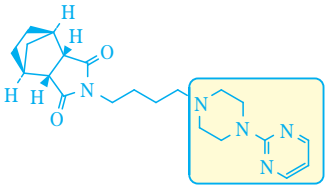
It has been estimated that the interaction between our molecule and relative receptors are realized by the comprehensive structural characteristics of the molecular length (linker moiety) and both ends of the molecule (aryl moiety, imide moiety) (**Fig. 2**). Accordingly, we optimized each of the three parts of tandospirone (imide moiety; linker moiety and aryl moiety) to maximize the psychiatric efficacy and to minimize adverse effects.

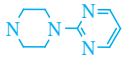
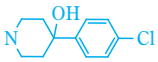
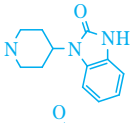
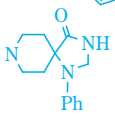
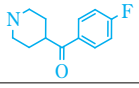
### 2. Transformation of Aryl Moiety

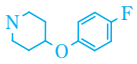
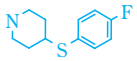
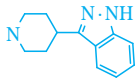
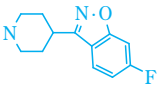
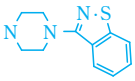
We started optimization from the transformation of the aryl moiety. The major part of the results is shown in **Table 1**. The activity values shown in the table indicate the compounds' inhibition rates against labeled ligand-binding to each receptor at a drug level of 10 nM. A larger figure means a stronger binding affinity toward the receptor.

As seen in **Table 1**, the binding affinities have changed significantly along with the transformation of

**Table 1** Effect of aryl groups



| No. | structure | binding inhibition (%) | |
|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ |
| tandospirone 1 |  | 0 | 0 |
| 2 |  | 10 | 14 |
| 3 |  | 14 | 6 |
| 4 |  | 19 | 11 |
| 5 |  | 68 | 85 |
| 6 |  | 78 | 85 |

| No. | structure | binding inhibition (%) | |
|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ |
| 7 |  | 58 | 81 |
| 8 |  | 70 | 84 |
| 9 |  | 89 | 75 |
| 10 |  | 92 | 86 |
| 11 |  | 97 | 90 |
| 12 |  | 95 | 85 |

the aryl moiety of tandospirone (1) which binds to neither the $D_2$ nor 5-$HT_{2A}$ receptors. In particular, the compounds demonstrated higher binding affinities toward the $D_2$ and 5-$HT_{2A}$ receptors when the benzisothiazolyl group and its relative bicyclic aryl fragments (10, 11) were introduced. These results indicate that the bulky bicyclic aryl structure is essential for the interaction between the compounds and the receptors.[2), 8)]

In order to address this issue, after the development of lurasidone, we examined binding models between compounds and the $D_2$ receptor. With regard to compound 12 and the $D_2$ receptor, the characteristic interaction is the salt bridge between the positively charged nitrogen atom on the piperazine moiety of compound 12 and Asp114 on the pocket inner surface. Moreover we could identify another specific interaction, the hydrogen bonding between the succinic imide oxygen atom of compound 12 and Thr412 (**Fig. 3**).

Comparing the binding model of the starting structure tandospirone with that of compound 12, it was revealed that the aryl moiety of compound 12 had much higher complementarity with the pocket shape than tandospirone. These data fit with the tendency seen in the transformation of the aryl moiety; that the bulky bicycle

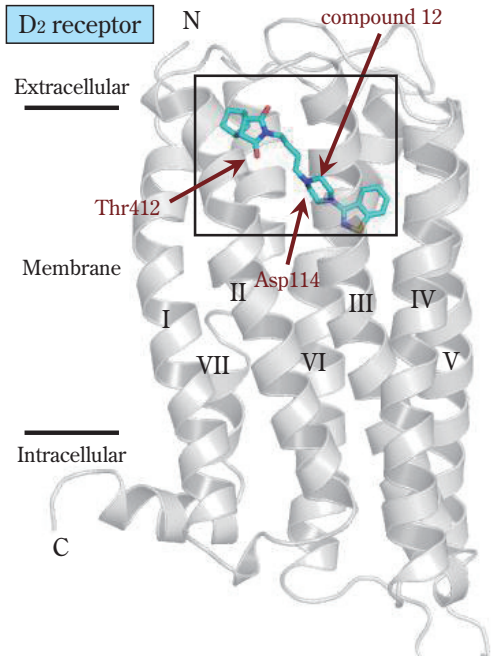



**Fig. 3** Binding model of compound 12 to the $D_2$ receptor

aryl structure is essential to bind to the $D_2$ receptor (**Fig. 4**).

We obtained several compounds that indicate high binding affinities toward both $D_2$ and 5-$HT_{2A}$ receptors.

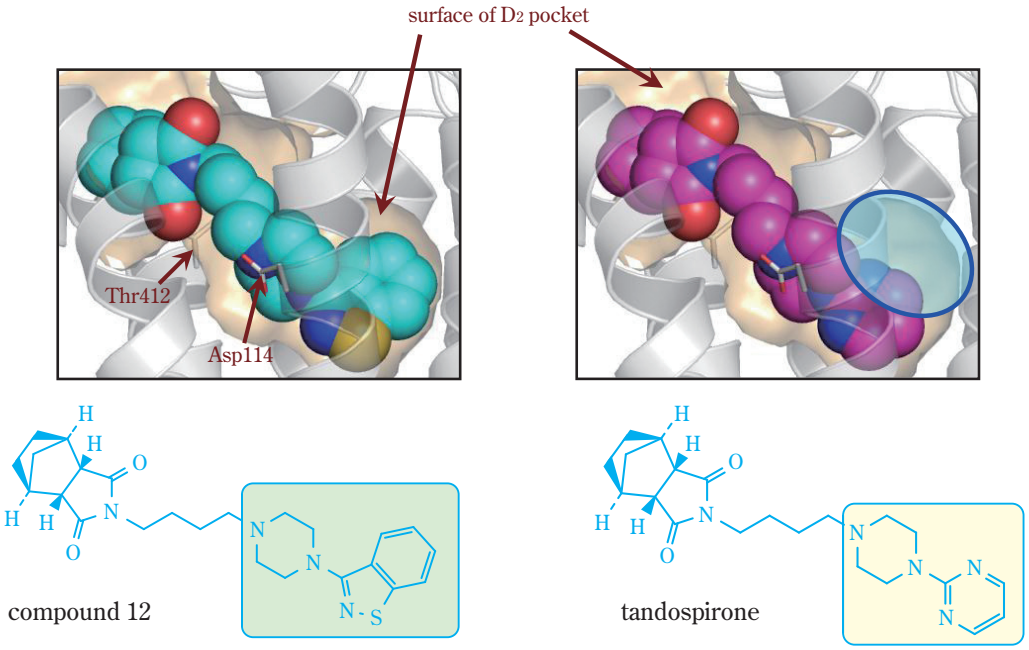


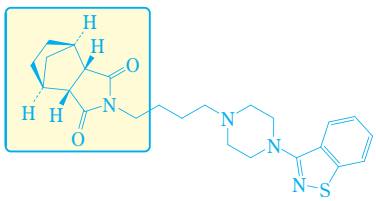

**Fig. 4** Binding model of compound 12 and Tandospirone to the $D_2$ receptors

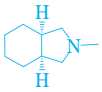
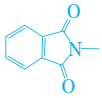
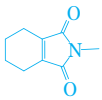
Examining all factors regarding pharmacological activity, physical properties and safety, we pressed ahead with the study of imides and linker moieties optimization as benzisothiazolyl derivatives.

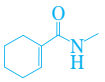
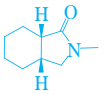
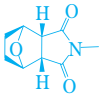
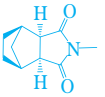
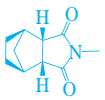
### 3. Transformation of Imide Moiety

Although we revealed that it is essential to introduce a bulky bicyclic structure into the aryl moiety for high binding affinities toward $D_2$ and 5-$HT_{2A}$ receptors, when we consider pharmacokinetics such as brain-permeability, it is also necessary to reduce the molecular size by transformation of linker and/or imide moiety. We therefore examined the contribution of imide moiety to investigate whether the succinic imide structure derived from tandospirone is essential to give a binding affinity toward $D_2$ and 5-$HT_{2A}$ receptors (**Table 2**).

**Table 2** Effect of imide groups



| No. | structure | binding inhibition (%) | |
|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ |
| 13 |  | 15 | 64 |
| 14 |  | 54 | 55 |
| 15 |  | 25 | 64 |
| 16 |  | 36 | 61 |
| 17 |  | 39 | 59 |

| No. | structure | binding inhibition (%) | |
|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ |
| 18 |  | 73 | 87 |
| 19 |  | 81 | 80 |
| 20 |  | 57 | 81 |
| 21 |  | 55 | 64 |
| 12 |  | 95 | 85 |

As a result of transformations on imide moiety, it was revealed that regardless of the saturability, whether aryl or alkyl, various structures can maintain a binding affinity toward $D_2$ and $5HT_{2A}$ receptors.

Our examination revealed that hydrogen bonding by carbonyl groups is essential to give antagonism at both receptors. It suggested that a succinic imide structure is not essential (18, 19). However, it has been estimated that a certain level of bulkiness is essential in order to enhance the activity (14→12, 13→18), thus indicating the fact that the norbornane structure derived from tandospirone (bicyclo[2.2.1]heptane) contributes to giving a high binding affinity toward the $D_2$ and $5HT_{2A}$ receptors. These findings correspond to the fact that the imide moiety of compound 12 fills the pocket (**Fig. 4**).

## Maximizing the Therapeutic Efficacy by Conformation Design

### 1. Modification Effect on Linker Moiety

Subsequent to the investigation of the essential structure for $D_2$ and 5-$HT_{2A}$ receptor binding affinities, we subsequently examined the modification of the linker moiety that greatly contributes to molecular length and flexibility. **Table 3** shows a part of the results of the transformation of linker moiety.

At first we introduced a carbon chain and a simple substituent into the linker moiety. As a result, the butylene chain (12) showed the highest binding affinity. Additionally, an obvious difference was observed in the activity between the cis form (24) and the trans form (25). Moreover, introducing a methyl group to the butylene linker revealed that the activity can differ greatly at every substituted position (26, 27, 28 and 29).

It is interesting that, in the extremely flexible side chain structure, the activity can be changed by a simple modification or stereo control. This suggests the possibility that the bioactive conformation contributing to the binding affinity toward $D_2$ and 5-$HT_{2A}$ receptors may exist close to those conformations around the examined compounds.

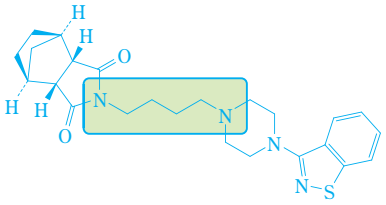
### 2. Separation of Alpha 1 Receptor Binding Affinity

Many existing antipsychotics have side effects such as oversedation and orthostatic hypotension. It has been estimated that these are caused by the antagonistic action at the alpha 1 receptors. In fact, many existing antipsychotics have a binding affinity toward alpha 1 receptors, and compound 12 also has high binding affinity toward alpha 1 receptors (**Table 4**).

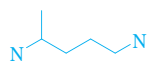
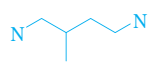
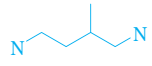
**Table 4** Major existing drugs and compound 12 affinities (Ki; nM)

| | risperidone | haloperidol | aripiprazole | compound 12 |
|---|---|---|---|---|
| $D_2$ | 4.9 | 2.0 | 0.9 | 0.2 |
| 5-$HT_{2A}$ | 0.2 | 53 | 8.7 | 0.3 |
| $\alpha_1$ | 5.0 | 12 | 25 | 1.6 |

**Table 3** Effect of linker groups (1)



| No. | structure | binding inhibition (%) | |
|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ |
| 22 |  | 11 | 61 |
| 12 |  | 95 | 85 |
| 23 |  | 48 | 77 |
| 24 |  | 21 | 27 |
| 25 |  | 80 | 75 |

| No. | structure | binding inhibition (%) | |
|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ |
| 26 |  | 90 | 85 |
| 27 |  | 93 | 81 |
| 28 |  | 67 | 70 |
| 29 |  | 47 | 49 |

In many cases, compounds having a binding affinity toward the $D_2$ and 5-$HT_{2A}$ receptors also have strong binding affinity toward alpha 1 receptors, suggesting that those compounds have similar binding properties.

### 3. Introduction of Cyclic Structure into Linker Center

Consequently, even though the separation of the binding affinity toward alpha 1 receptors has been desired for the purpose of reducing side effects, it has been assumed that reducing the alpha 1 binding affinity while simultaneously maintaining the binding affinity for the $D_2$ and 5-$HT_{2A}$ receptors is not readily achievable in terms of binding properties.

Given the results of transformation of the linker moiety as shown in **Table 3**, we had an idea about further modification of linker moiety. If we can obtain an active conformation that maximizes the binding affinity for the $D_2$ and 5-$HT_{2A}$ receptors by the linker moiety modification, it will in turn maximize the selectivity of alpha 1 receptors over the $D_2$ and 5-$HT_{2A}$ receptors to give the maximum drug efficacy.

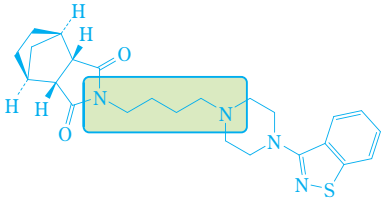
Accordingly, to control a flexible linker moiety, we undertook the strategy of fixing conformation by introducing a cyclic structure into the center of the butylene linker. We introduced various types of cyclic structures, including 1,2-cyclohexanediyl, cyclopentanediyl, cyclobutanediyl and cyclopropanediyl, in both its cis and trans forms, and we examined the effect on separation of the alpha 1 receptor affinity over the $D_2$ and 5-$HT_{2A}$ receptors (**Table 5**). The activity values (Ki) in the table indicate the inhibition constants toward the receptor labeling ligands. A smaller Ki value indicates stronger activity.

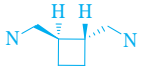
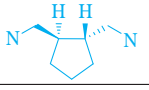
As shown in **Table 5**, introducing the ring structure to the linker center demonstrated that the larger cyclic substituent indicates a greater effect in reducing the affinity for alpha 1 receptors (compounds 30 to 33). In every case, the binding affinities toward the $D_2$ and 5-$HT_{2A}$ receptors were maintained at high levels, thus suggesting that the selectivity for desired receptors was improved.

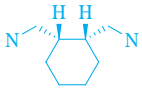
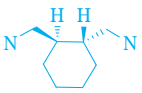
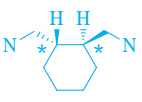
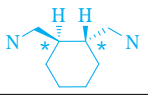
Moreover, although it is not shown in the table, those compounds derived from the original form of tandospirone maintained their high affinity for the 5-$HT_{1A}$ receptors through the transformation.

Regarding the stereoisomerisms of the introduced cyclic structures, the $D_2$ and 5-$HT_{2A}$ receptor binding affinities of the trans form tended to be twice as high as those of the cis form. Furthermore, a larger cyclic structure indicated a lower binding affinity for alpha 1 receptors. The effect of separation of the $D_2$ receptor affinity reached its maximum when cyclohexanediyl was introduced (35). Subsequently, the optically active substances of the racemic body (35) were synthesized and their properties were investigated. Comparing the results between the (*R, R*) isomer (37) and the (*S, S*) isomer (36), the (*R, R*) isomer showed approximately twenty times higher $D_2$ receptor binding affinity and fifty times higher 5-$HT_{2A}$ receptor binding affinity than that

**Table 5** Effect of linker groups (2)



| No. | structure | binding affinity Ki (nM) | | |
|---|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ | $\alpha_1$ |
| 12 |  | 0.23 | 0.32 | 1.60 |
| 30 |  | 5.28 | 1.39 | 12.9 |
| 31 |  | 1.79 | 0.36 | 12.9 |
| 32 |  | 0.80 | 1.52 | 5.69 |
| 33 |  | 0.68 | 0.48 | 13.3 |

| No. | structure | binding affinity Ki (nM) | | |
|---|---|---|---|---|
| | | $D_2$ | 5-$HT_{2A}$ | $\alpha_1$ |
| 34 |  | 0.87 | 2.16 | 36.2 |
| 35 racemic |  | 0.51 | 1.02 | 41.4 |
| 36 (*S, S*) |  | 7.99 | 23.1 | 34.3 |
| 37 (*R, R*) lurasidone |  | 0.32 | 0.47 | 47.9 |

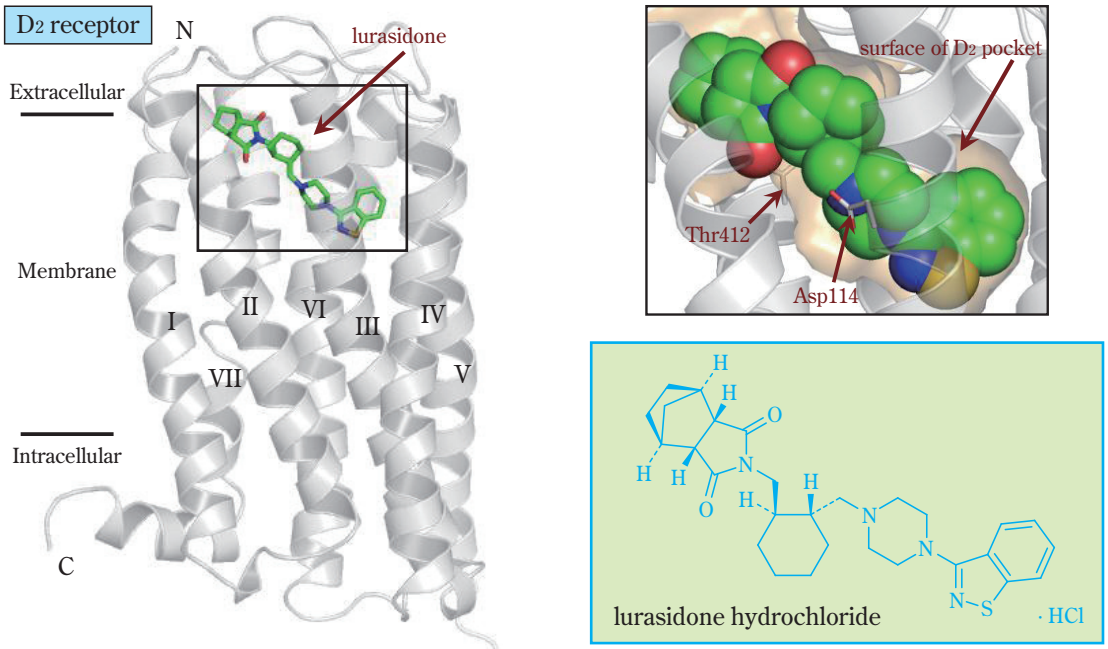



**Fig. 5** Binding model of lurasidone to $D_2$ receptor

of the (*S, S*) body. As shown, we achieved separation of the alpha 1 receptor affinity with over 100 times lower affinity, by exquisite conformation control via the introduction of the cyclic structure into the linker moiety and optimization of stereo isomers. This is how we discovered lurasidone.

Subsequent to the development of lurasidone, we compared the binding models of lurasidone with compound 12 in order to examine the effect of cyclic substituent on the linker moiety (**Fig. 5**).[9] It can be observed that complex pocket space is even more firmly filled by the cyclohexanediyl structure of the linker moiety, as well as the filling effect of the bulky structure of the imide and aryl moieties. Fortunately, as compared to the existing agents, this compound showed much smaller extrapyramidal side effects and central inhibition side effects, both of which are considered to be class effects of antipsychotics.[2] Furthermore, the subsequent inspection revealed that these linker modifications (i.e. ring introduction) also contributed to a significant effect on the separation between the desired activities (through $D_2$ and 5-$HT_{2A}$ receptors) and the adverse activities through $H_1$ and $M_1$ receptors.

### 4. Synthetic Scheme

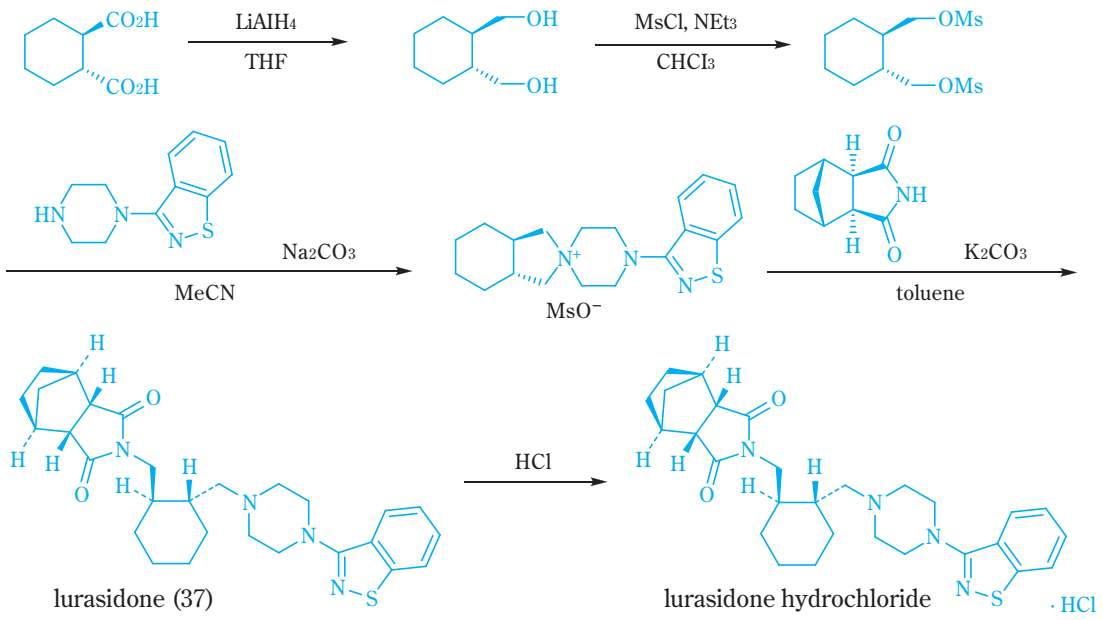
One example of the synthetic schemes of lurasidone is shown in **Scheme 1**.

The scheme shows the following procedures: First, the optical active (*R, R*)-cyclohexane-1, 2-dicarboxylate was reduced to the corresponding diol. It was then converted to dimesylate and affected with 4-benzisothiazole piperazine to give intermediate quaternary salts. Subsequently, lurasidone (37) was obtained by causing succinimide to act on the intermediate under basic conditions. Finally, lurasidone hydrochloride was obtained through hydrochlorination. Despite the composition of three fragments and the fact that it contains several chiralities, we have successfully established a highly effective industrial synthetic route by optimization of the synthetic scheme and reaction conditions.

## Pharmacological Properties of Lurasidone

### 1. Receptor Binding Profile

As described above, lurasidone hydrochloride (hereinafter referred to as lurasidone) possesses a similar level of high binding affinity for the $D_2$ and 5-$HT_{2A}$ receptors. The binding affinity for the alpha 1 receptors of lurasidone has been reduced but its affinity for the 5-$HT_{1A}$ receptors has been maintained. As a result of a battery of binding assays toward various receptors, lurasidone showed high binding affinity for the 5-$HT_7$ and adrenaline $\alpha_{2C}$ receptors but showed low affinity for the 5-$HT_{2C}$ receptors and almost no affinity for the histamine $H_1$ and muscarinic $M_1$ receptors (**Table 6**). Furthermore, the *in vitro* functional evaluation has revealed that lurasidone is a 5-$HT_{1A}$ receptor partial agonist (Emax = 33%) and a 5-$HT_7$ receptor antagonist.[1]




**Scheme 1** Synthetic scheme of lurasidone (example)

**Table 6** Receptor binding profile of lurasidone

| Receptor | Preparation | $K_i$ value (nM) |
|---|---|---|
| Dopamine $D_2$ | Rat Striatum | 1.68 ± 0.09 |
| 5-$HT_{1A}$ | Rat Hippocampus | 6.75 ± 0.97 |
| 5-$HT_{2A}$ | Rat Cortex | 2.03 ± 0.46 |
| 5-$HT_{2C}$ | Pig Choroid Plexus | 415 ± 81 |
| 5-$HT_7$ | Human Recombinant | 0.495 ± 0.09 |
| $\alpha_1$ | Rat Cortex | 47.9 ± 7.8 |
| $\alpha_{2A}$ | Human Recombinant | 40.7 ± 7.7 |
| $\alpha_{2C}$ | Human Recombinant | 10.8 ± 0.64 |
| Histamine $H_1$ | Guinea Pig whole brain | >1000[a] |
| Muscarine $M_1$ | Human Recombinant | >1000[a] |

Quoted from the reference 2 (MEDCHEM NEWS Vol. 20, No.1, page 23).
Values are means ± SEM of three or more separate experiments.
[a] $IC_{50}$ value

## 2. Antipsychotic Effects

It is thought that the antipsychotic effects of existing therapeutic agents are demonstrated due to the $D_2$ and 5-$HT_{2A}$ receptor antagonisms.[10] We therefore evaluated the antagonisms of lurasidone using rats and mice and compared the results with the existing antipsychotics (**Table 7**). The $D_2$ receptor antagonism was evaluated based on the methamphetamine-induced hyperactivity and apomorphine-induced climbing behavior. As a result, the $ED_{50}$ values of lurasidone's inhibitory action were 2.3 mg/kg, p.o. and 4.1 mg/kg, p.o. respectively. Lurasidone's degree of antagonism against the $D_2$ receptors was nearly equivalent to that of second-generation antipsychotics such as risperidone and olanzapine, stronger than that of clozapine and weaker than that of the first-generation antipsychotic haloperidol. Furthermore, in the observation for the inhibitory action against rats' methamphetamine-induced hyperactivity, the $ED_{50}$ values at one, two, four and eight hours after the lurasidone administration were 2.3, 0.87, 1.6, 5.0 mg/kg, p.o. respectively, thus indicating that lurasidone's effect lasts for eight hours or longer.[1]

**Table 7** Antipsychotic actions of lurasidone and other antipsychotics

| Drugs | $ED_{50}$ (mg/kg, 95% Confidence limits) | | | |
|---|---|---|---|---|
| | MAP-induced hyperactivity in rats | APO-induced climbing behavior in mice | TRY-induced clonic seizure in rats | *p*-CAMP-induced hyperthermia in mice |
| Lurasidone | 2.3 (0.89–6.1) | 4.1 (2.0–8.4) | 5.6 (3.4–9.3) | 3.0 (1.5–5.8) |
| Risperidone | 1.8 (0.86–3.6) | 0.14 (0.047–0.40) | 0.16 (0.044–0.62) | 0.098 (0.039–0.25) |
| Olanzapine | 3.3 (1.5–7.3) | 1.1 (0.35–3.2) | 1.4 (0.59–3.3) | 0.62 (0.31–1.2) |
| Clozapine | 65 (29–140) | 9.5 (3.8–24) | 5.1 (2.6–10) | 5.0 (2.7–9.5) |
| Haloperidol | 0.88 (0.42–1.8) | 0.44 (0.20–1.0) | 14 (6.8–27) | >30 |

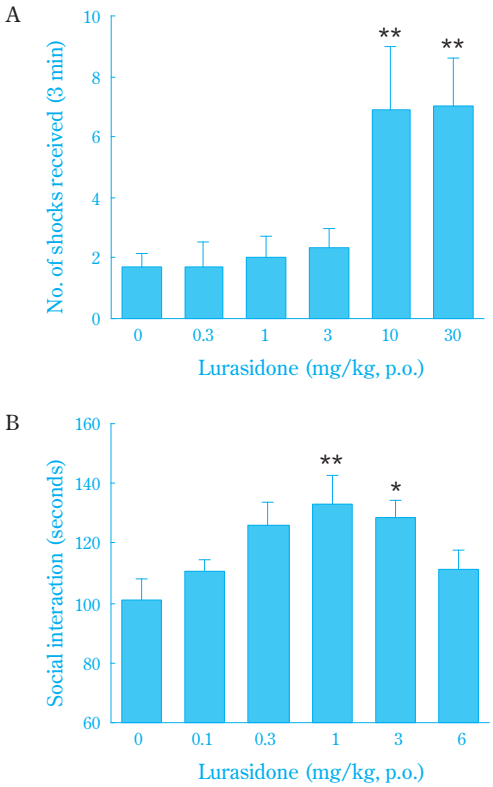
Quoted from the reference 1.
MAP: methamphetamine, APO: apomorphine, TRY: tryptamine, *p*-CAMP: *para*-chloroamphetamine
$ED_{50}$ values and 95% confidence limits in parenthesis were obtained 1 hr after drug administration.

Additionally, the 5-HT$_{2A}$ receptor antagonism was evaluated based on the inhibitory action against tryptamine-induced seizures and *p*-chloroamphetamine (*p*-CAMP)-induced hyperthermia. The ED$_{50}$ values of lurasidone's inhibitory action were 5.6 mg/kg, p.o. and 3.0 mg/kg, p.o., respectively. The degree of lurasidone's antagonism against 5-HT$_{2A}$ receptors was nearly equivalent to that of clozapine, stronger than that of haloperidol, and weaker than that of risperidone and olanzapine.

The above results indicated that the lurasidone had D$_2$ and 5-HT$_{2A}$ receptor antagonisms, thereby possessing an antipsychotic effect similar to the existing drugs.

### 3. Mood-Stabilizing Effect

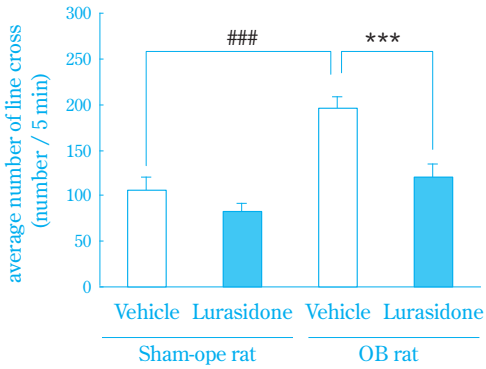
It has been reported that the 5-HT$_{1A}$ and 5-HT$_7$ receptors are involved in anxiety and depressive symptoms.[11),12)] Because lurasidone acts as a partial agonist on 5-HT$_{1A}$ receptors and as an antagonist against 5-HT$_7$ receptors, it was expected that it would possess anxiolytic and antidepressant effects. Therefore, we evaluated its anxiolytic effects through the Vogel conflict test and the social interaction test using rats. In the Vogel conflict test, lurasidone (0.3–30 mg/kg) increased the number of shocks dose-dependently and its minimum effective dose was 10 mg/kg (**Fig. 6A**). In the social interaction test, lurasidone (1 and 3 mg/kg) significantly increased the social interaction time compared to vehicle control (**Fig. 6B**).




A) Effect on the number of shocks in Vogel's test. Each column shows mean ± SEM of 11 to 22 rats.
B) Effect on social interaction in Lister hooded rats. Each column represents mean ± SEM of 10 pairs of rats.

*$P$<0.05; **$P$<0.01: significantly different from vehicle group (Dunnett's test).
Quoted from the reference 1.

**Fig. 6** Anxiolytic-like activities of lurasidone in the Vogel conflict test (A) and social interaction test (B).




Repeated treatment of lurasidone (3 mg/kg/day p.o., 2 weeks) significantly reduced olfactory bulbectomy(OB)-induced hyperactivity, but did not affect the activity in sham-operated rats. Each column represents mean ± SEM of 10 to 14 rats.

###$P$<0.001: significantly different from vehicle treatment in sham-operated rat (Student's t test).

***$P$<0.001: significantly different from vehicle treatment in olfactory bulbectomy rat (Student's t test).
Quoted from the reference 1.

**Fig. 7** Effect of lurasidone on olfactory bulbectomy(OB)-induced hyperactivity.

Moreover, we evaluated the inhibitory action against the spontaneous hyperactivity of olfactory bulbectomized rats in order to investigate lurasidone's antidepressant agent-like action. Two weeks of treatment with lurasidone (3 mg/kg) significantly suppressed this hyperactivity (**Fig. 7**).

The results suggested that lurasidone possesses anxiolytic- and antidepressant-like effects at doses near the level needed for antipsychotic effects.

### 4. Effects on Learning and Memory

Because NMDA receptor antagonists such as phencyclidine (PCP) and ketamine can cause schizophrenic symptoms, in recent years it has been thought that the malfunction of NMDA receptors may be involved in the pathogenesis of schizophrenia.[13)] Based on this hypothesis, we investigated the effects of lurasidone using rats on learning and memory impairments caused by the NMDA receptor antagonists MK-801 and

**Table 8** Effects of lurasidone on rat cognition model

| Task | Model | Lurasidone MED | Reference |
|---|---|---|---|
| Passive avoidance | Normal | Not impaired | 14 |
| | Acute MK-801 | 3 mg/kg, p.o. | |
| Morris water maze | Acute MK-801 | 1 mg/kg, p.o. | 16 |
| Radial arm maze (reference memory) | Acute MK-801 | 1 mg/kg, p.o. | 16 |
| Radial arm maze (working memory) | | improvement tendency | |
| Novel object recognition | Subchronic PCP | 0.1 mg/kg, i.p. | 17, 18 |

PCP. The results are summarized in the table shown below (**Table 8**).

Lurasidone demonstrated a remarkable improvement action toward learning and memory impairments caused by MK-801 (0.05mg/kg, s.c.) in passive-avoidance response tests.[14] Based on the fact that 5-HT$_{1A}$ receptor and 5-HT$_7$ receptor antagonists showed an improvement action in the same models, it was surmised that those receptors might be involved in the improvement action of lurasidone.[15] Similarly, in Morris water maze tests and radial-arm maze tests, lurasidone demonstrated an improvement action toward learning and memory impairments caused by MK-801.[16]

Lurasidone also showed an improvement action toward learning and memory impairments induced by PCP (2mg/kg, i.p. twice/day, 7 days) in novel object recognition tests.[17), 18] Additionally, the fact that this improvement action was inhibited by the a 5-HT$_{1A}$ receptor antagonist and a 5-HT$_7$ receptor agonist suggests that the 5-HT$_{1A}$ receptor agonist action and the 5-HT$_7$ receptor antagonistic action are involved in the improvement action of lurasidone.[17), 18]

Lurasidone, as described above, demonstrated an improvement action on learning and memory impairments caused by NMDA receptor antagonists in several animal models.

### 5. Extrapyramidal Symptoms/Central Nervous System Depressant Action

For the evaluation of side effects, the extrapyramidal symptoms and central nervous system depressant action were evaluated using rats and mice.[1] The catalepsy induction effect was evaluated in order to investigate the extrapyramidal symptoms. As a result, lurasidone did not demonstrate any action until the dose reached 1000 mg/kg, p.o.[1] Moreover, for the evaluation of the central nervous system depressant action, the effects of potentiation of hexobarbital-induced anesthesia, muscle relaxation and inhibition of motor coordination were evaluated, and lurasidone's ED$_{50}$ values were >1000 mg/kg, p.o., >1000 mg/kg, p.o. and 250 mg/kg, p.o., respectively.[1] In animal models, the extrapyramidal symptom induction and central nervous system depressant action of lurasidone were weak.

## Conclusion

We have made the most of our knowledge and techniques accumulated through the research and development of tandospirone, and have thus successfully developed the antipsychotic agent lurasidone hydrochloride having wide-ranging efficacy and a high level of safety.

We believe this new drug is worthy of special mention as a good example of success in drug development by making the most of the structure-activity relationship due to the following reasons: First, the D$_2$ and 5-HT$_{2A}$ receptor antagonisms were successfully added to the compound through the conformational transition of the aryl moiety; and secondly the side-effect parameters (alpha 1, H$_1$ and M$_1$ receptors) were successfully separated by controlling the conformation through the effective conformational transition method, i.e. the introduction of the ring, while maintaining the anxiolytic effect (5-HT$_{1A}$ agonist action) possessed by the original skeletal structure.

We were also able to obtain favorable results from the clinical trial on lurasidone hydrochloride.[19] Subsequently, LATUDA® (lurasidone HCl) was approved by the U.S. Food and Drug Administration (FDA) on October 2010 for the treatment of patients with schizophrenia and launched in the United States in February 2011.[20]

Given the fact that while other drugs having similar efficacies have required an assessment period of more than thirteen months, it was merely ten months for lurasidone hydrochloride, which was an exceptionally "quick approval," and it is obvious that high regard was given to its outstanding efficacy and safety. Additionally,

phase III is currently progressing in Japan. We hope this drug will soon be recognized as one of the new therapeutic approaches for schizophrenia. Furthermore, we strongly hope the knowledge and experience we have acquired through the development of lurasidone will serve as a foundation for the future research and development of new drugs.

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