KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY

Title (Name of Technology)

Novel Substituted-1,1-dioxo-benzo[1,2,4] thiadizin-3-ones

Executive Summary

Dr. Churl-Min, Seong, a Senior Research Engineer of Medical-Chemistry Research Center, Korea Research Institute of Chemical Technology (KRICT) has made intensive studies to find a novel serotonin (5-HT6) receptor antagonist and has developed novel substituted-1,1-dioxo-benzo[1,2,4]thiadizin-3-ones.

Recent advances in pharmacology, molecular biology, and genetics on the serotonin system hold out the promise of the development of improved pharmacological treatment for some aspects of neurological diseases. Many currently used treatments of these disorders are thought to act by modulating serotonergic neurons. Thus, a receptor antagonist having excellent binding affinity and selectivity to the serotonin receptor is now concerned.

Korea Research Institute of Chemical Technology (KRICT) intends to enter into a technology transfer or licensing transaction with regard to 5-HT6 receptor antagonist. Terms of the transaction are not set, and interested parties may further discuss the details if they wish to enter into an agreement.

② Industry Sector: 2. Animal health(Pharmaceutical), 3.Biotechnology (Human therapeutics), 8. Non-profit org./Government(Government), 9. Pharmaceutical (Generics)

③ Therapeutic Target: 5. Central Nervous System [Neurological (Migraine), Psychiatric (Anxiety, Depression, Obsessive compulsive disorder, Panic disorder, Schizophrenia)]

④ Development phase: early stage

⑤ Type of business relationship sought (including licensing availability): development collaboration, or non-exclusive or exclusive licensing agreement

Key Technology Highlights

□ **Excellent binding affinity to the 5-HT6 receptor**

The compounds of substituted-l,l-dioxo-benzo [l,2,4] thiadiazin-3-ones according to the present invention have excellent binding affinity to the 5-HT6 receptor.

□ **Excellent selectivity to the 5-HT6 receptor**

The compounds of the present invention have excellent selectivity to the 5 -HT6 receptor over other receptors.

□ **Inhibition of the serotonin(5-HT)-stimulated cAMP**

The compounds of the present invention inhibits the serotonin(5-HT)-stimulated cAMP accumulation.

□ **No rotarod deficits in mice**

The compounds of the present invention of effective don't show any rotarod deficits in mice.

□ **Effect on apomorphine(2 D/D, i.p.)-induced disruption of prepulse inhibition (PPI) in rats.**

The compounds of the present invention have an effect on apomorphine (2 D/D, i.p.)-induced disruption of prepulse inhibition (PPI) in rats.

□ **Strong IP Position**

These technologies have been filed for a patent application in a multitude of countries or have been already patented in Korea. The pending patent applications are anticipated to be patented in the near future.

■ **IP Owner Summary**

Korea Research Institute of Chemical Technology

Ministry of Knowledge Economy Is The Competent Ministry

■ **Personal Description of Researcher**

▫ Name
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Senior Research Engineer
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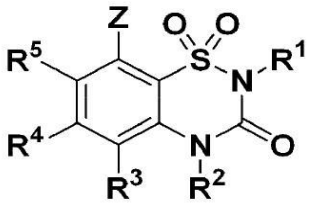
Technology Overview

- **Technology Platform**

The core technology of KRICT is to provide novel substituted-1,1-dioxo-benzo[1,2,4]thiadizin-3-ones or formula 1, which have excellent binding affinity to the 5-HT6 receptor, excellent selectivity to the 5-HT6 receptor over other receptors, inhibition of the serotonin(5-HT)-stimulated cAMP accumulation and an effect on apomorphine(2 D/D, i.p.)-induced disruption of prepulse inhibition (PPI) in rats. Also, the compounds of the present invention of effective dose don't show any rotarod deficits in mice.



wherein, R^1 represents hydrogen, $C_1 - C_{10}$ alkyl, $C_3 - C_{10}$ aryl, $C_3 - C_7$ cycloalkyl, arylalkyl, heteroaryl or heteroarylalkyl, R^2 represents hydrogen, $C_1 - C_{10}$ alkyl, $C_3 - C_{10}$ aryl, heteroaryl, aralkyl, heteroarylalkyl, amino or cyclic amino, R^3 , R^4 and R^5 independently represent hydrogen, halogen, amino, cyclic amino, nitro, cyano, $C_1 - C_{10}$ alkyl, haloalkyl, C_1- C_7 alkoxy, haloalkoxy or piperazinyl or N - methyl piperazinyl, and Z represents saturated mono-, bi-, tricyclic amines containing 1 to 3 nitrogen atoms and 5 to 12 carbon atoms in the ring.

Formula 1

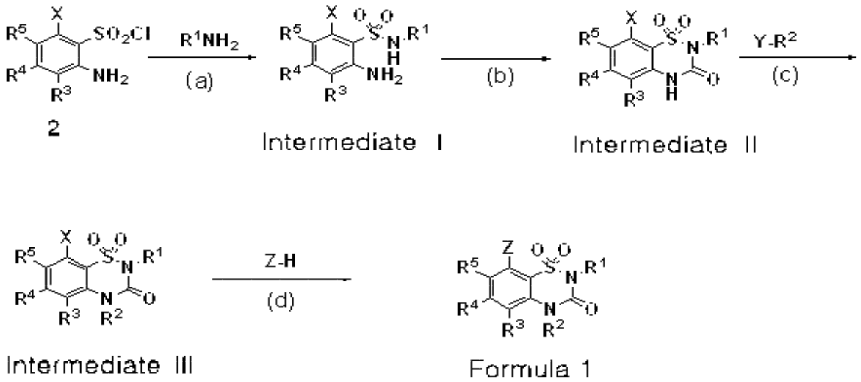
Background and unmet needs: Although the function of serotonin (5-HT) in the central nervous system is still being clarified, various studies have indicated 5-HT has been implicated in the aetiology of many disease states and may be particularly important in mental illness, such as depression, anxiety, schizophrenia, eating disorders, obsessive compulsive disorder (OCD), migraine and panic disorder. During the last decade, multiple 5-HT receptor subtypes have been characterized. Initially, receptor subtypes were characterized using pharmacological tools only. Most recently, the 5-HT6 receptor has been cloned from rat cDNA based on its homology to previously cloned G-protein-coupled receptors

Until selective ligands were developed, exploration of 5-HT6 pharmacology was largely dependent on the use of nonselective agents. In the absence of selective ligands for the receptor, functional studies have been carried out using an antisense approach. 5-HT6 specific antisense produced a specific behavioural syndrome of yawning, stretching and chewing, but had no other discernable action in rats. The nonselective ligands were useful for investigating the pharmacology of 5-HT6 systems in preparations where other 5-HT receptors were absent (e.g., cAMP assays); however, owing to their lack of selectivity, they were of limited value for most other pharmacological studies.

Recent advent of selective agents has greatly benefited 5-HT6 studies, and this field of research has recently exploded. The development of more selective ligands may therefore lead to treatments with increased efficacy and reduced side effects. Alternatively, selective ligands may form completely novel therapies. The bisaryl sulfonamides Ro 04-6790 , Ro 63-0563 were identified as very selective 5-HT6. Shortly thereafter, MS-245, SB-271046, SB-357134 were reported. The problems associated with these antagonists were their low penetration of the CNS or low bioavailability.

Discovery and Achievements: The inventors made an effort to develop a 5-HT6 antagonist having excellent binding affinity and selectivity, and has completed the present invention by discovering that benzothiadiazine derivatives are 5-HT6 antagonists having very excellent binding strength and selectivity compared to sulfonamide or sulfonic structures disclosed in the prior art.

Fig. 1. Preparation of 1,1-dioxo-benzo[1,2,4]thiadizin-3-one



wherein, $R^1 - R^5$ and Z are same as the aforementioned definition in Formula 1, and X is a fluorine, chlorine, bromine, iodine or trifluoroacetate, and Y is chlorine, bromine, iodine, methanesulfonate orp-toluenesulfonate

First, in the **step (a),** the intermediate I may be obtained by reaction of the compound 2 and a suitable amine in the presence of a base. The compound 2 used as starting material, 2-aminosulfonylchlorides may be commercially available or where they are not commercially available, may be prepared by the procedure described herein or by the analogous procedures for known compounds from the art of organic synthesis. The base is preferably triethylamine and, the reaction is conveniently conducted in an inert solvent, such as 1.4-dioxane or tetrahydrofuran, at the room temperature

In the **step (b),** the cyclization of the intermediates I prepared in the step (a) provides the corresponding intermediates II(l,l-dioxo-l,4-dihydro-benzo[1,2,4] thiadiazin-3-ones) with high yield. The cyclization is conducted by reaction of the intermediates I and phosgen(COCl), preferably, di-, tri-phosgen. The reaction is conveniently carried out in an inert solvent such as 1.4-dioxane or tetrahydrofuran under the refluxing condition. Then, in the **step (c),** the intermediate lll(2,4-substituted-benzo[l,2,4] thiadiazin-3-ones) is obtained by substitution on the intermediate II prepared in the above step (b) in the presence of a base. In the **step (d),** substituted-l,l-dioxo-benzo[l,2,4]thiadiazin-3-ones represented by formula 1 is obtained by neucleophilic substitution reaction of the intermediate m prepared in the step (c) and a appropriate amine.

Fig. 2. Inhibitory effect of compounds according to the example of the present invention and methiothepin on cAMP accumulation mediated by 5-HT6 receptor of human HeLa cell.

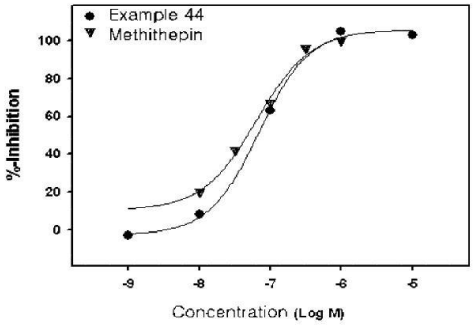
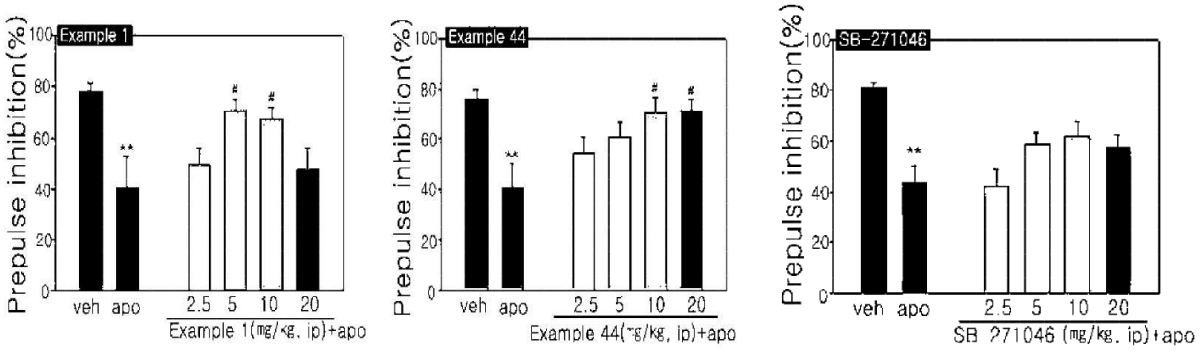


Fig. 3. Inhibitory effect of compounds according to the example of the present invention (50 D/D, i.p.) on hyperactivity of a rat induced by apomorphine (2 D/D, i.p.).



Patents and Publications

KRICT have patents issued or filed for application in many countries such as U.S., Japan, Europe and Korea with regrad to novel substituted-1,1-dioxo-benzo[1,2,4]thiadizin-3-ones.

TABLE. List of Patents

Country	Status	Patent, Publication or Appln. No.
PCT	-	WO 2007/108569
Korea	Granted	10-0787130
Europe	Pending	06732718
JAPAN	Pending	2009501336