DESCRIPTION

TITLE OF THE INVENTION:

THERAPEUTIC AGENT AND PROPHYLACTIC AGENT FOR FUNCTIONAL GASTROINTESTINAL DISORDERS AND XEROSTOMIA

TECHNICAL FIELD

[0001] The present invention relates to a therapeutic agent and a prophylactic agent for functional gastrointestinal disorders (FGIDs). The present invention also relates to a therapeutic agent and a prophylactic agent for xerostomia (dry mouth).

[0002] According to Rome IV diagnostic criteria (hereinafter, sometimes referred to as "Rome IV"), functional gastrointestinal disorders are also called disorders of gut - brain interaction, and are considered to be a group of disorders that manifest gastrointestinal symptoms related to gastrointestinal motility abnormalities, visceral hyperesthesia, etc. (NON-PATENT DOCUMENT 1).

[0003] Adult functional gastrointestinal disorders include esophageal disorders, gastroduodenal disorders, bowel disorders, centrally mediated disorders of gastrointestinal pain gallbladder and sphincter of Oddi disorders, and anorectal disorders (NON-PATENT DOCUMENTS 1 and 2). For example, esophageal disorders include functional heartburn, gastroduodenal disorders include functional dyspepsia, and bowel disorders include irritable bowel syndrome (IBS), functional constipation, and opioid-induced constipation.

[0004] The onset and pathological conditions of functional gastrointestinal disorders are considered to be closely related to physiological functions such as gastrointestinal motility, sensation, and microflora, psychological factors such as stress, and genetics, and environmental factors, etc. (NON-PATENT DOCUMENT 1). Patients with functional gastrointestinal disorders have chronic or recurrent gastrointestinal symptoms (for example, upset stomach, stomach pain, diarrhea or constipation, etc.), and such patients have decreased quality of life (QOL) due to restricted daily activities.

[0005] Xerostomia is dryness of oral cavity result from the insufficient saliva secretion due to various causes. When the saliva secretion decreases, objective symptoms such as bad breath are observed in addition to unpleasant subjective symptoms such as masticatory disorders, dysgeusia, and dry mouse, and tongue coating and periodontal disease are observed. When the decrease in the amount of saliva secreted is severe, decayed teeth, angular cheilitis, etc., are observed in the patients. Therefore, the QOL of patients with xerostomia decreases (NON-PATENT DOCUMENT 3).

PRIOR ART DOCUMENTS

[NON-PATENT DOCUMENTS]

[0006] NON-PATENT DOCUMENT 1: Rome IV (Functional Gastrointestinal Disorders, 4th Edition), 2016, Rome Foundation, INC.

NON-PATENT DOCUMENT 2: Gastroenterology, 2016, Vol. 150, No. 6, p. 1257-1261

NON-PATENT DOCUMENT 3: Advances in Clinical Experimental Medicine, 2016, Vol. 25, No. 1, p. 199-206

NON-PATENT DOCUMENT 4: Pharmacological Reviews, 1998, Vol. 50, No. 2, p. 279-290

NON-PATENT DOCUMENT 5: British Journal of Pharmacology, 2006, Vol. 148, No. 5, p. 565-578

NON-PATENT DOCUMENT 6: Trends in Pharmacological Sciences, 2017, Vol. 38, No. 9, p. 837-847

NON-PATENT DOCUMENT 7: Nature, 2012, Vol. 482, p. 552-556

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0007] As described above, functional gastrointestinal disorders and xerostomia decrease the patient's quality of life. Therefore, therapeutic agents and prophylactic agents for functional gastrointestinal disorders and xerostomia are desired.

[0008]An object of the present invention is to provide a novel therapeutic agent or prophylactic agent for functional gastrointestinal disorders. Another object of the present invention is to provide a novel therapeutic agent or prophylactic agent for xerostomia.

MEANS OF SOLVING THE PROBLEMS

[0009] As a result of intensive studies, the inventors discovered that an azabenzimidazole compound represented by the following formula [1], or a pharmaceutically acceptable salt thereof, or a solvate thereof (sometimes herein referred to as a "compound of the present invention") is useful for the prevention and treatment of functional gastrointestinal disorders and xerostomia, and achieved the present invention.

[0010] That is, for the present invention, the following (Item 1) to (Item 14) can be mentioned.

(Item 1)

A therapeutic agent or prophylactic agent for a functional gastrointestinal disorder,

(d) when W is W-3,

if B is B-1, U^1 is CR^{41} wherein R^{41} is as defined above, and U^2 is a nitrogen atom, then Y is Y-1, Y-2, Y-3, or Y-4, and preferably Y-1, Y-2, or Y-3.

[0076] The compound of the present invention can be prepared from a known compound or an easily synthesizable intermediate, for example, according to the following method, Examples described below, or a known method. In the preparation of the compound of the present invention, in the case where a starting material has a substituent that affects the reaction, the reaction is generally carried out after protecting the starting material with a suitable protective group in advance by a known method. The protective group can be removed by a known method after the reaction.

[0077] The azabenzimidazole compound according to the present invention may be used as it is for pharmaceuticals, and can also be used in the form of a pharmaceutically acceptable salt or solvate, or a solvate of the salt, according to a known method. Examples of pharmaceutically acceptable salts include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid, salts with organic acids such as acetic acid, malic acid, lactic acid, citric acid, tartaric acid, maleic acid, succinic acid, fumaric acid, p-toluenesulfonic acid, benzenesulfonic acid, and methanesulfonic acid, salts with alkali metals such as lithium, potassium, and sodium, salts with alkaline earth metals such as magnesium and calcium, and salts with an organic base such as ammonium salts. These salts can be formed by methods well known in the art.

[0078] For example, in the case where the compound of the present invention is a hydrochloride salt, the hydrochloride salt can be prepared by dissolving the azabenzimidazole compound according to the present invention in a solution of hydrogen chloride in alcohol, a solution of hydrogen chloride in ethyl acetate, a solution of hydrogen chloride in 1,4-dioxane, a solution of hydrogen chloride in cyclopentyl methyl ether, or a solution of hydrogen chloride in diethyl ether.

[0079] Some of the compounds of the present invention may have an asymmetric carbon, and the respective stereo isomers and mixtures thereof are all included in the present invention. The stereo isomers can be prepared, for example, by means of optical resolution from the racemate thereof according to a known method using an optically active acid (for example, tartaric acid, dibenzoyltartaric acid, mandelic acid, 10-camphor sulfonic acid, etc.), utilizing its basicity, or by using an optically active compound prepared in advance as a starting material. In addition, the stereo isomers may also be prepared by optical resolution using a chiral column

for 4 hours. The reaction mixture was cooled to room temperature, then diluted with saturated aq. ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with water and saturated saline and dried over anhydrous sodium sulfate, and then the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (1.0 g).

Reference Example 13: 2'-cyclopropyl-N^4-{[1-(methoxymethyl)cyclohexyl]methyl}-N^4-methyl-6'-(trifluoromethyl)[2,4'-bipyridine]-4,5,6-triamine

A mixture of 6-chloro-N^4-{[1-(methoxymethyl)cyclohexyl]methyl}-N^4-methyl-3-nitropyridin-2,4-diamine (1.0 g), 2-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine (1.1 g), potassium carbonate (1.2 g), $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (95 mg), 1,4-dioxane (12 mL), and water (4.5 mL) was degassed and stirred at 90°C under an argon atmosphere for 2 hours. The reaction mixture was cooled to room temperature, then diluted with water and ethyl acetate, and extracted with ethyl acetate. The organic layer was washed with water and saturated saline, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-cyclopropyl-N^4-{[1-(methoxymethyl)cyclohexyl]methyl}-N^4-methyl-5-nitro-6'-(trifluoromethyl)[2,4'-bipyridine]-4,6-diamine. This compound was mixed with 2-propanol (9.7 mL), water (2.9 mL), ammonium chloride (0.47 g), and zinc powder (0.95 g), and the mixture was stirred at room temperature for 1 hour. The insolubles were filtered off through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the title compound (1.2 g).

Reference Example 14: Ethyl [4-(3-fluoro-4-formylphenoxy)piperidin-1-yl]acetate

[Step 1] Preparation of tert-butyl 4-(3-fluoro-4-formylphenoxy)piperidine-1-carboxylate

PPh_3 (782 mg) was added to a mixture of tert-butyl 4-hydroxypiperidine-1-carboxylate (400 mg), 2-fluoro-4-hydroxybenzaldehyde (175 mg), and THF (10 mL) with stirring at room temperature, and DEAD (1.4 mL) was added to the mixture under ice-cooling. The temperature of the mixture was increased to room temperature, and the mixture was stirred. The reaction mixture was diluted with ethyl acetate and washed sequentially with saturated aq. sodium bicarbonate and saturated saline, and then the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to afford the title compound (175 mg).

[Step 2] Preparation of ethyl [4-(3-fluoro-4-formylphenoxy)piperidin-1-yl]acetate

Hydrogen chloride (4 M in ethyl acetate, 0.68 mL) was added to a solution of tert-butyl 4-(3-fluoro-4-formylphenoxy)piperidine-1-carboxylate (175 mg), obtained in Step 1, in methanol (1.4 mL) with stirring at room temperature, and the mixture was stirred at the same

[0118] [Table 7]

REx	PREx	Compound Name	Data
34	6	2'-Ethoxy-N^4-(3-methoxy-2,2-dimethylpropyl)-N^4-methyl-5-nitro-6'-(trifluoromethyl)[2,4'-bipyridine]-4,6-diamine	MS (ESI+) m/z 458.7 $(M+H)^+$
35	6	2'-Ethoxy-N^4-{[1-(methoxymethyl)cyclobutyl]methyl}-N^4-methyl-5-nitro-6'-(trifluoromethyl)[2,4'-bipyridine]-4,6-diamine	MS (ESI+) m/z 470.2 $(M+H)^+$
36	6	2'-Ethoxy-N^4-{[1-(methoxymethyl)cyclopentyl]methyl}-N^4-methyl-5-nitro-6'-(trifluoromethyl)[2,4'-bipyridine]-4,6-diamine	MS (ESI+) m/z 484.7 $(M+H)^+$
37	6	6'-Cyclopropyl-N^4-{[1-(methoxymethyl)cyclopentyl]methyl}-N^4-methyl-5-nitro-5'-(trifluoromethyl)[2,3'-bipyridine]-4,6-diamine	MS (ESI+) m/z 480.6 $(M+H)^+$
38	6	6'-Cyclopropyl-N^4-{[1-(ethoxymethyl)cyclopentyl]methyl}-N^4-methyl-5-nitro-5'-(trifluoromethyl)[2,3'-bipyridine]-4,6-diamine	MS (ESI+) m/z 494.3 $(M+H)^+$
39	6	2'-Cyclopropyl-N^4-{[1-(methoxymethyl)cyclopentyl]methyl}-N^4-methyl-5-nitro-6'-(trifluoromethyl)[2,4'-bipyridine]-4,6-diamine	MS (ESI+) m/z 480.6 $(M+H)^+$
40	8	2'-Ethoxy-N^4-(3-methoxy-2,2-dimethylpropyl)-N^4-methyl-6'-(trifluoromethyl)[2,4'-bipyridine]-4,5,6-triamine	MS (ESI+) m/z 428.4 $(M+H)^+$