

MAGL INHIBITOR, PREPARATION METHOD AND USE THEREOF

FIELD OF TECHNOLOGY

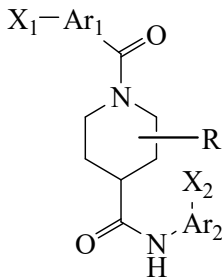
[0001] The present invention relates to the field of medicine and in particular to a MAGL inhibitor, a preparation method and use thereof.

BACKGROUND

[0002] Monoacylglycerol Lipase (MAGL) is a kind of serine hydrolases which accelerate fat to be decomposed into glycerin and fatty acids, and are highly expressed in human aggressive tumor cells and primary tumor cells. High-level MAGL can maintain high pathogenicity of tumor cells by improving the level of fatty acids. MAGL has become an important target spot for the research and development of antitumor drugs.

SUMMARY

[0003] The present invention provides a compound of Formula I or a



pharmaceutically acceptable salt thereof: I , where, R is H or C_{1-5} alkyl, and the C_{1-5} alkyl is selected from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, neo-butyl, n-pentyl, isopentyl, neo-pentyl, cyclopentyl, or C_{1-5} alkyl substituted by halogen, hydroxy, carboxyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-8} cycloalkyl, C_{3-8} heterocyclyl, C_{3-8} cycloalkoxy, aryl, and heteroaryl; the number of R is 0, 1, 2, 3 or 4;

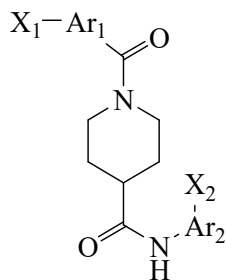
[0004] the Ar₁ and the Ar₂ are respectively and independently selected from C₅₋₁₈ aryl, heteroaryl, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-(C₆₋₁₀ aryl), (5 to 10-membered heteroaryl)-C₁₋₄ alkyl-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-O-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-O-(5 to 10-membered heteroaryl), (5 to 10-membered heteroaryl)-O-(5 to 10-membered heteroaryl), and (5 to 10-membered heteroaryl)-(5 to 10-membered heteroaryl), at any substitution position;

[0005] the X₁ and the X₂ are respectively and independently selected from one or more of H, hydroxy, carboxyl, halogen, acyloxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, heteroaryl, and C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, and heteroaryl that are substituted by hydroxy, carboxyl, halogen and alkyl, at any substitution position.

[0006] In some embodiments, the Ar₁ and the Ar₂ are respectively and independently selected from phenyl, C₅₋₁₈ aryl, heteroaryl, (C₆₋₁₀ aryl)-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-O-(C₆₋₁₀ aryl); the X₁ and the X₂ are respectively and independently selected from one or more of H, hydroxy, halogen, acyloxy, C₁₋₃ alkyl, and C₁₋₃ alkoxy, at any substitution position.

[0007] In some embodiments, the Ar₁ and the Ar₂ are respectively and independently selected from one or more substituents of phenyl, naphthyl, diphenyl ether, indolyl and biphenyl, at any substitution position.

[0008] According to the compound of Formula I or a pharmaceutically acceptable salt thereof, if the R is H, the corresponding structural formula is



II, where, the Ar₁ and the Ar₂ are respectively and independently selected from C₅₋₁₈ aryl, heteroaryl, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄

alkyl-(C₆₋₁₀ aryl), (5 to 10-membered heteroaryl)-C₁₋₄ alkyl-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-O-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-O-(5 to 10-membered heteroaryl), (5 to 10-membered heteroaryl)-O-(5 to 10-membered heteroaryl), and (5 to 10-membered heteroaryl)-(5 to 10-membered heteroaryl), at any substitution position;

[0009] the X₁ and the X₂ are respectively and independently selected from one or more of H, hydroxy, carboxyl, halogen, acyloxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, heteroaryl, and C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, and heteroaryl that are substituted by hydroxy, carboxyl, halogen and alkyl, at any substitution position.

[0010] Specifically, the Ar₁ and the Ar₂ are respectively and independently selected from C₅₋₁₈ aryl, heteroaryl, (C₆₋₁₀ aryl)-C₁₋₄ alkyl, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-(C₆₋₁₀ aryl), (5 to 10-membered heteroaryl)-C₁₋₄ alkyl-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-O-(C₆₋₁₀ aryl), (C₆₋₁₀ aryl)-O-(5 to 10-membered heteroaryl), (5 to 10-membered heteroaryl)-O-(5 to 10-membered heteroaryl), and (5 to 10-membered heteroaryl)-(5 to 10-membered heteroaryl), at any substitution position;

[0011] the X₁ and the X₂ are respectively and independently selected from one or more of H, hydroxy, halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, and C₁₋₃ alkyl and C₁₋₃ alkoxy that are substituted by hydroxy, carboxyl, halogen and alkyl, at any substitution position.

[0012] In some embodiments, the Ar₁ is one or more of phenyl, naphthyl, diphenyl ether and biphenyl, at any substitution position;

[0013] the X₁ is one or more of H, methoxy, hydroxy, F and Cl, at any substitution position;

[0014] the Ar₂ is benzene;

[0015] the X₂ is one or more of H, methyl, dimethyl, methoxy, hydroxy, F and Cl, at any substitution position.

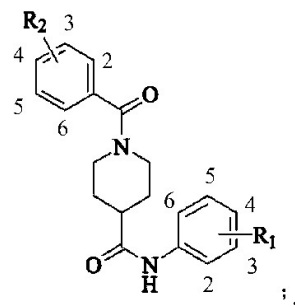
[0016] In a specific embodiment, the Ar₁ has a substitution position of meta-position.

[0017] In some embodiments, the Ar₁ is one or more of benzofuryl, benzimidazolyl, benzoxazolyl, indolyl, benzothiophenyl, quinolyl, isoquinolyl and purinyl, at any substitution position;

[0018] the X₁ is one or more of H, methyl, methoxy, hydroxy, F, Cl and Br, at any substitution position;

[0019] the Ar₂ is phenyl, at any substitution position;

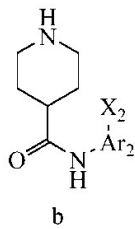
[0020] the X₂ is one or more of H, methyl, dimethyl, methoxy, hydroxy, F and Cl, at any substitution position. In some embodiments, the above Formula I may be



defined as Formula III, as shown in the following formula

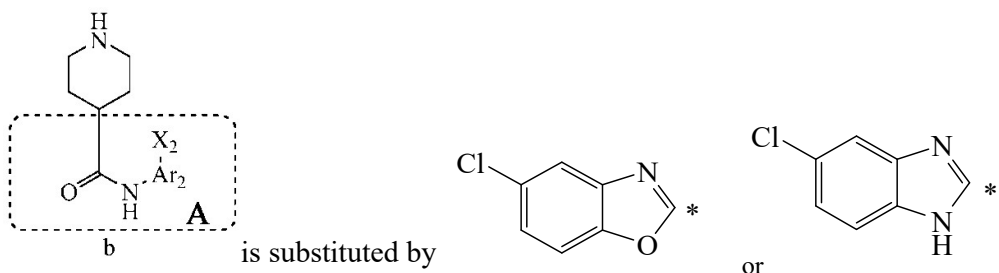
[0021] where, the R₁ is selected from hydroxy, F, Cl, Br, I, methyl, ethyl, propyl, and methoxy; R₂ is selected from hydroxy, F, Cl, Br, I, methyl, ethyl, propyl, methoxy, phenyl, and aryl substituted by hydroxy, F, Cl, Br, I, methyl, ethyl, propyl, and methoxy. The number of the R₁ and the R₂ is 0, 1, 2, 3, or 4; the link mode between the R₁, the R₂ and nucleus is not limited to a single connection of a single bond.

[0022] The present invention provides a compound of Formula b, and

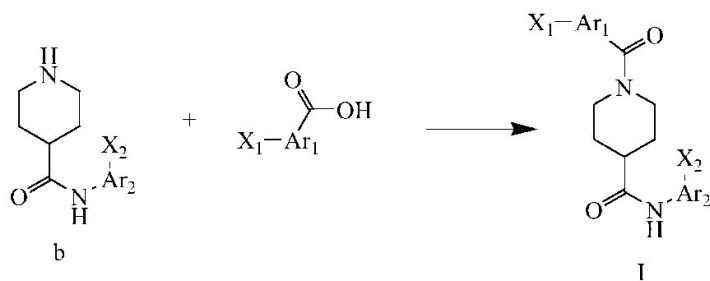


the compound is used for synthesizing the compound of Formula I, where, the Ar₂ and the X₂ are as described in Formula I.

[0023] In some embodiments, a fragment A within the dotted line in



[0024] The present invention provides a method of synthesizing the compound of Formula I, including the following specific

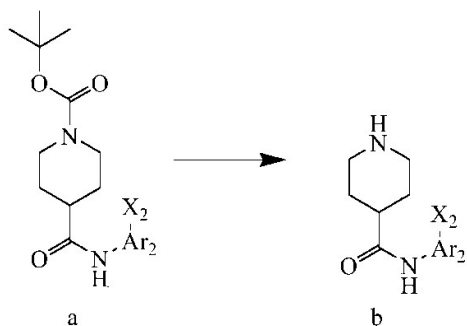


steps: 'b or a salt of b is

reacted with X_1-Ar_1-COOH to obtain **I**; the Ar_1 and the X_1 are described in Formula I.

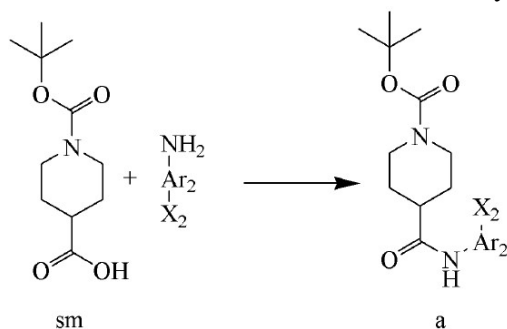
[0025] The **b** or the salt of **b** is reacted with X_1-Ar_1-COOH to obtain **I**; a condensating agent and an alkali are added in this step to facilitate the reaction; where, the condensating agent is selected from HBTU, DMC, HOBT, HOBT/EDCI, HATU, HATU/DIEPA, DCC, CDI, and isopropyl chloroformate; and the structural formula is respectively as follows:

[0026] the **b** or the salt of **b** is obtained by deprotection of **a**;



; the alkali is an organic alkali, such as, N-diisopropylethylamine (DIPEA), diethylamine (DEA) or triethylamine (TEA).

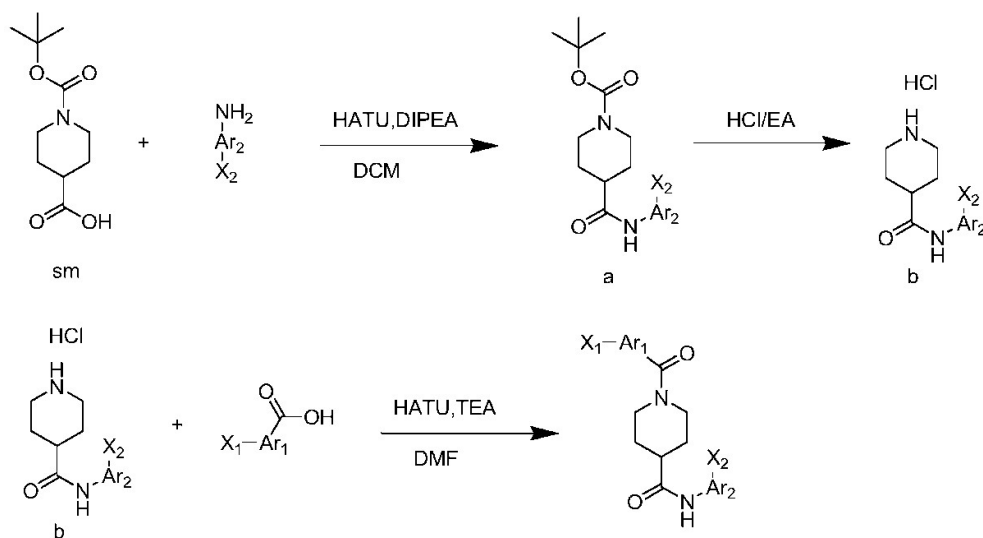
[0027] The a or the salt of a is obtained by reacting sm with $\begin{array}{c} \text{NH}_2 \\ | \\ \text{Ar}_2 \\ | \\ \text{X}_2 \end{array}$ or a salt



thereof;

[0028] where, the sm may be prepared by the prior art, or synthesized by a person skilled in the art without any inventive efforts on the basis of the prior art and through limited tests. A condensating agent and an alkali are added in this step to facilitate the reaction; where, the condensating agent is selected from HBTU, DMC, HOBT, HOBT/EDCI, HATU, HATU/DIEPA, DCC, CDI, and isopropyl chloroformate.

[0029] In some specific embodiments, the following method may be taken:



[0030] where, the reductant is preferably selected from at least one of NaBH_4 , KBH_4 , $\text{NaBH}_4/\text{LiCl}$.

[0031] Unless otherwise specified, solvents selected and used in the above or following steps herein are conventional solvents in the art, and the selection principle

of the solvent is to dissolve reactants, but not participate in reaction, extract products or crystallize the corresponding products therein and separate the same from impurities, such as, water, halogenated hydrocarbons, alkyl amine, fatty hydrocarbons, esters, alcohols, aromatic hydrocarbons, ethers and heterocyclic solvents; specifically selected from, but not limited these solvents: methanol, ethanol, propanol, isopropanol, diethyl ether, ethyl acetate, acetic acid, cyclohexane, dichloromethane, trichloromethane, tetrahydrofuran, pyridine, diethylamine, triethylamine, dimethylformamide, methylbenzene and a mixture of at least two of them.

[0032] a, b and other serial number used herein are convenient for illustrating the general formula, and may be transformed into other number in detailed examples, such as, 1, 2, and 3, which are convenient for description, but free of influencing the structural formula and essence of the reaction equation thereof, and belong to the expression of the general formula and the reaction equation thereof. A person skilled in the art can judge that substituents of each intermediate in all the synthetic routes above are determined according to the structure of a target compound.

[0033] Compounds covered by the general formula of the target compound in general formula I and chiral isomers or cis-trans-isomers as well as a mixture of the isomers in any proportion in a specific substance representative thereof shall be within the scope of the compounds covered by the general formula of the target compound of general formula I and its specific substance representative thereof.

[0034] “At any substitution position” may be construed as any choice in case of a proper valence bond. For example, substitution on a benzene ring, may be one or more of ortho-position, meta-position, and para-position; for example, substitution in a heteroaromatic ring, may be one or more of 2-, 3-, 4-, 5- and other positions. In regard to the selection of substituents, “one or more”, or “a or a plurality of” refers to the number of substituents selected; and the specific number is one, two, three, four...specifically, for example, “Ar₁ is phenyl at any substitution position; X₁ is one or more of F and Cl at any substitution position” includes that the ortho (two), meta (two) and para (one) of phenyl may be substituted by one Cl, two Cl and three Cl or

two meta-positions are respectively substituted by one Cl and one F or one Cl is substituted in the ortho position, while one F is substituted in the para position, and so on.

[0035] Unless otherwise specified, solvents selected and used in the above or following steps herein are conventional solvents in the art, and the selection principle of the solvent is to dissolve reactants, but not participate in reaction, extract products or crystallize the corresponding products therein and separate the same from impurities, such as, water, halogenated hydrocarbons, alkyl amine, fatty hydrocarbons, esters, alcohols, aromatic hydrocarbons, ethers and heterocyclic solvents; specifically selected from, but not limited these solvents: methanol, ethanol, propanol, isopropanol, diethyl ether, ethyl acetate, acetic acid, cyclohexane, dichloromethane, trichloromethane, tetrahydrofuran, pyridine, diethylamine, triethylamine, dimethylformamide, methylbenzene and a mixture of at least two of them.

[0036] Unless otherwise specified, in the above or following reaction herein, when there are excessive amount of reagents, substances capable of reacting with the excessive amount of reagents may be added at the end of the reaction for quenching the reaction. For example, water or saturated ammonium chloride may be used in some examples for quenching.

[0037] Unless otherwise specified, in the above or following reaction herein, the purification way of the product in each step of reaction is selected from extraction, crystallization, solvent removal and column chromatography; and the operations are conventional technologies in the art. Therefore, a person skilled in the art may deal with according to specific conditions.

[0038] The general formula of the present invention and synthesizing method of the general formula may derive these specific substances (not limited thereto). Moreover, under the guidance of the general formula of the present invention and synthesizing method of the general formula, specific compounds obtained by a person skilled in the art without any inventive efforts shall fall within the scope of the present

invention.

[0039] Even though preferred embodiments of the present invention have been displayed and described here, it is obvious for a person skilled in the art that such kind of embodiment is merely provided by examples. Now, a person skilled in the art will envisage of lots of changes, variations and replacements not departing from the present invention. It should be understood that various replacements in embodiments of the present invention may be used for implementing the present invention. The claims annexed are aimed at defining the scope of the present invention such that methods, structures and other equivalent forms within the scope of these claims are covered.

[0040] The present invention provides a pharmaceutical composition, containing the above compound, namely, compounds covered by the general formula of the target compound of Formula I and a specific substance representative thereof, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable pharmaceutical adjuvants.

[0041] The present invention provides a pharmaceutical composition, containing the compound of the present application or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier thereof. The pharmaceutical composition includes but not limited to oral dosage forms, parenteral dosage forms, external formulations and rectal dosage forms. The composition may be a form of liquid, solid, semi-solid, gel or aerosol. In some embodiments, the pharmaceutical composition may be oral troches, capsules, pills, powders, sustained release preparations, solutions and suspensions, sterile solutions, suspensions or emulsions used for parenteral injection, ointments or creams for external use, or suppositories for rectal administration. In other embodiments, the pharmaceutical composition is a unit dosage form suitable for a single administration of an accurate dosage.

[0042] The present invention provides use of all the compounds above or pharmaceutically acceptable salts thereof as well as a pharmaceutical composition

thereof as a monoacylglycerol lipase inhibitor; or use thereof in the preparation of a medicament for treating a disease or a condition having pathological features of metabolic pathways of monoacylglycerol lipase.

[0043] The present invention provides a method for inhibiting monoacylglycerol lipase by all the compounds above or pharmaceutically acceptable salts thereof as well as a pharmaceutical composition thereof. The method includes a method for inhibiting monoacylglycerol lipase in vitro and in vivo. The present invention further provides a method for treating a disease or a condition mediated by monoacylglycerol lipase by using all the compounds above or pharmaceutically acceptable salts thereof as well as a pharmaceutical composition thereof.

[0044] The condition is selected from: metabolic disorders (e.g., obesity), nephrosis (e.g., acute inflammatory renal injury and diabetic nephropathy), emesis or vomiting (e.g., chemotherapy-induced emesis), nausea (e.g., refractory nausea or chemotherapy-induced nausea), eating disorders (e.g., anorexia or bulimia), neuropathy (e.g., diabetic neuropathy, pellagra neuropathy, alcoholic neuropathy, beriberi neuropathy), neurodegenerative conditions [multiple sclerosis (MS), Parkinson's disease (PD), Huntington's disease, dementia, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), epilepsy, frontotemporal dementia, sleep disorders, Creutzfeldt-Jakob Disease (CJD) or prion disease], schizophrenia, depressive disorders, bipolar disorders, fremitus, dyskinesia, dystonia, spasticity, touretti's syndrome, abstinence syndromes [alcohol abstinence syndrome, antidepressant withdrawal syndrome, antipsychotic withdrawal syndrome, benzodiazepine withdrawal syndrome, Cannabis sativa abstinence syndrome, neonatal abstinence syndrome, nicotine abstinence syndrome, or opiates abstinence syndrome], traumatic brain injury, non-traumatic brain injury, spinal cord injury, epileptic seizure, conditions associated with abnormal cell growth or proliferation [e.g., benign tumors or cancers, such as, benign skin tumors, brain tumors, papilloma, prostate tumors, brain tumors (glioblastoma, medullo-epithelioma, medulloblastoma, neuroblastoma, astrocytoma, astroblastoma, ependymoma, oligodendroglioma, choroid plexus tumor,

neuroepithelioma, epiphyseal tumor, ependyoblastoma, malignant meningioma, sarcosis, melanoma and schwannoma), melanoma, metastatic tumor, renal cancer, bladder cancer, cerebral cancer, glioblastoma (GBM), gastrointestinal cancer, leukemia or blood cancer], inflammatory conditions [for example, appendicitis, bursitis, colitis, irritable bowel syndrome, ulcerative colitis, urocystitis, dermatitis, phlebitis, rhinitis, tendinitis, amygdalitis, vasculitis, acne vulgaris, chronic prostatitis, glomerulonephritis, hypersensitivity, IBS, pelvic inflammatory diseases, sarcoidosis, HIV encephalitis, rabies, brain abscess, neuroinflammation, central nervous system (CNS) inflammation], immune system conditions (e.g., transplant rejection or celiac disease), post-traumatic stress disorder (PTSD), acute stress disorder, panic disorder, substance-induced anxiety, obsessive-compulsive disorder (OCD), agoraphobia, specific phobia, social phobia, anxiety disorder, attention deficit disorder (ADD); attention deficit hyperactivity disorder (ADHD); pains [e.g., acute pain, chronic pain, inflammatory pain, visceralgia, post-surgical pain, migraine, low back pain, arthralgia, stomachache, stethalgia, post-mastectomy pain syndrome, menstrual pain, endometriosis pain, physical trauma-induced pain, headache, sinus headache, tension headache, arachnoiditis, herpes virus pain, diabetic pain, and pain induced by a condition selected from the following: osteoarthritis, rheumatoid arthritis, spondylitis, gout, labor pain, musculoskeletal diseases, dermatosis, toothache, heartburn, burn, sunburn, snake bite, venomous snake bite, spider bite, insect bites, neurogenic bladder, interstitial cystitis, urinary tract infection (UTI), rhinitis, contact dermatitis/hypersensitivity, itching, eczema, pharyngitis, mucositis, enteritis, irritable bowel syndrome (IBS), cholecystitis and pancreatitis; neuropathic pains (e.g., nervous lumbago, complex regional pain syndrome, pillar prosopalgia, causalgia, toxic neuropathy, reflex sympathetic dystrophy, diabetic neuropathy, chronic chemotherapeutant-induced neuropathy, or ischialgia)]; demyelinating diseases [e.g., multiple sclerosis (MS), Devic's disease, CNS neuropathy, central pontine myelinolysis, syphilitic myelopathy, leukoencephalopathy, leukodystrophy, Guillain-Barre syndrome, chronic inflammatory demyelinated polyneuropathy, anti-myelin-associated glycoprotein peripheral neuropathy, Charcot-Marie-Tooth

Disease, peripheral neuropathy, myelerosis, optic neuropathy, progressive inflammatory neuropathy, optic neuritis, and transverse myelitis] as well as cognitive impairments [e.g., Down's syndrome-associated cognitive impairment, Alzheimer's disease-associated cognitive impairment, PD-associated cognitive impairment, mild cognitive impairment (MCI), dementia, post-chemotherapy cognitive impairment (PCCI) and postoperative cognitive dysfunction (POCD)].

[0045] The present invention provides use of a MAGL inhibitor in the preparation of a medicament for treating a disease associated with the MAGL inhibitor.

[0046] In some embodiments, the disease associated with the MAGL inhibitor is pain, migraine, irritable bowel syndrome or ulcerative colitis.

[0047] The pain in the above use is traumatic pain or pathologic pain. Further, the pathologic pain is inflammatory pain or endogenous pain. Furthermore, the pathologic pain is biogenic inflammatory pain, chemogenic inflammatory pain, blood-derived pain, immunogenic pain, endocrine-derived pain, metabolic lesion-caused pain, neuropathic pain or cardiogenic pain.

[0048] In the above use, the pain is transient pain, acute pain or chronic pain.

[0049] In the above use, the pain is nervous system pain, cardiovascular system pain, blood system pain, respiratory system pain, digestive system pain, endocrine system pain, urinary system pain, motor system pain or immune system pain.

[0050] In the above use, the migraine is common migraine, typical migraine and cluster migraine.

[0051] In the above use, the irritable bowel syndrome is constipation-type irritable bowel syndrome, diarrhea-type irritable bowel syndrome, and alternating constipation-diarrhea irritable bowel syndrome.

[0052] The MAGL inhibitor of the present invention can reduce the mice

writhing times caused by acetic acid, extend latent time and delay a thermal stimulus pain threshold of mice pain induced by hot plate. The present invention has a significant analgesic effect.

[0053] In some embodiments, the MAGL inhibitor of the present invention can significantly delay the blood coagulation time of a migraine model, increase the times of tail suspension activity, and significantly increase the 5-HT level in brain tissues. The present invention shows a significant therapeutic effect on migraine.

[0054] The MAGL inhibitor of the present invention can significantly decrease the AWR scoring of an irritable bowel syndrome, reduce the 5-HT level of colon and blood serum. The above result hints that the present invention has a significant therapeutic effect on irritable bowel syndrome. Therefore, it is proved that such kind of compound has the bioactivity of preventing and treating irritable bowel syndrome.

[0055] The MAGL inhibitor of the present invention can significantly increase the colon length in an ulcerative colitis model and reduce total number of hematochezia, and decrease the IL-1 content.

[0056] **Some chemical terms**

[0057] Unless otherwise specified, all the scientific and technological terms herein have the meanings the same as those understood by a person skilled in the art of the subject of the claims. Unless otherwise specified, all the patents, patent applications and disclosure materials referenced in the full text herein are incorporated by reference herein in its entirety.

[0058] It should be understood that the above sketch and the following detailed description are exemplary and only used for explanation, but not construed as limiting the subject of the present application. Unless otherwise specified, a plural form is also included in case of using the singular in this present application. It should be further noted that unless otherwise specified, the “or”, “either” denotes “and/or”. Furthermore, the term, “comprise” and its other forms used herein, for example,

“include”, “contain” and “have” are non-restrictive descriptions.

[0059] Definitions on standard chemical terms may be found in references (including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A(2000) and B (2001), Plenum Press, New York). Unless otherwise specified, conventional methods within the technical scope of the art, for example, mass spectrometry, NMR, IR and UV/Vis spectroscopy and a pharmacology method are used. Unless otherwise specified, terms used in the related description of analytical chemistry, organic synthetic chemistry, medicine and pharmaceutical chemistry are known in the art. Standard technologies may be used in chemical synthesis, chemical analysis, medicament preparation, formulation and delivery as well as treatment on a patient. For example, reaction and purification may be implemented by means of a manufacturer's instruction for a kit, or according to a way commonly known in the art or by the description of the present application. Generally, the above technology and method may be implemented according to the description of multiple summary and more detailed literatures cited and discussed in the description by a conventional method known very well in the art. In this description, a person skilled in the art may choose a group and a substituent to provide a stable structural portion and a compound.

[0060] The term “alkyl” used herein refers to saturated linear or branched hydrocarbon. Exemplary alkyl includes, but not limited to, linear or branched hydrocarbons having 1-6, 1-4 or 1-3 carbon atoms, and respectively called C₁₋₆ alkyl, C₁₋₄ alkyl and C₁₋₃ alkyl herein. Exemplary alkyl includes, but not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neo-pentyl, hexyl, and the like.

[0061] The C₁₋₄ alkyl herein includes C₁₋₃ alkyl, C₁₋₂ alkyl, C₂₋₃ alkyl and C₂₋₄ alkyl; specific examples include but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl and neo-butyl.

[0062] Alkoxy is, namely, alkyloxy. The C₁₋₃ alkoxy herein includes C₁₋₂ alkoxy and C₂₋₃ alkoxy; and specific examples include but not limited to, methoxy, ethoxy, propoxy and isopropoxy.

[0063] The term “cycloalkyl” used herein refers to saturated or partially unsaturated hydrocarbons, e.g., a monocyclic 5-8 membered ring system or a bicyclic 8-12 membered ring system. The C₃₋₈ cycloalkyl herein includes 3-8, 3-6, 4-6, 6-8, 3-7 or 5-8 carbon atoms, which is called C₃₋₈ cycloalkyl, C₃₋₆ cycloalkyl, or C₄₋₆ cycloalkyl herein, and only has different forms but same meanings. Exemplary cycloalkyl includes, but not limited to cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.

[0064] For example, the term “heterocyclyl” used herein contains a monocyclic 5-8 membered ring system or a bicyclic 8-12 membered ring system having one or more hetero atoms (such as, one to three hetero atoms, e.g., N, O or S). For example, the C₃₋₈ heterocyclyl herein represents a monocyclic or polycyclic group having 3 to 8 atoms, which contains C₃₋₆ heterocyclyl, C₄₋₈ heterocyclyl, C₅₋₈ heterocyclyl, C₄₋₇ heterocyclyl, C₃₋₇ heterocyclyl, C₆₋₈ heterocyclyl, and has at least one ring containing 1, 2, 3, or 4 heterocyclic atoms selected from N, O or S; the ring is not aromatic. Examples of heterocyclyl include but not limited to morpholinyl, sulfomorpholinyl, furyl, piperazinyl, piperidyl, pyranyl, pyrrolidyl, tetrahydropyranyl, tetrahydrofurfuryl and 1,3-dioxane.

[0065] C₃₋₈ cycloalkoxy, is namely cycloalkyloxy, and the cycloalkyl is paraphrased the same as that of the above cycloalkyl.

[0066] The term “aryl” used herein refers to an aromatic mono- or poly-carboatomic ring group having 6 to 12 carbon atoms of at least one aromatic ring. The C₆₋₁₀ aryl herein contains C₆₋₈ aryl, C₆₋₁₀ aryl, C₆₋₉ aryl, C₇₋₁₀ aryl, C₈₋₁₀ aryl, C₆ aryl, C₇ aryl, C₈ aryl, C₉ aryl, and C₁₀ aryl. Specific examples include but not limited to phenyl, phenyl substituted by mono- or poly- hydrocarbyl, pentalenyl, indenyl, naphthyl, and azulenyl. The phenyl of mono- or poly- hydrocarbyl includes but not

limited to tolyl, ethyl phenyl, dimethyl phenyl, propyl phenyl, isopropyl phenyl, methyl ethyl phenyl, trimethyl phenyl, butyl phenyl, methyl propyl phenyl, methyl isopropyl phenyl, diethyl phenyl, dimethyl ethyl phenyl, tetramethyl phenyl, tert-butyl phenyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl and 1H-indenyl.

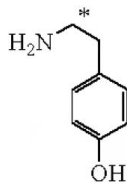
[0067] The C₅₋₁₈ aryl herein includes C₆₋₁₀ aryl, C₁₁₋₁₂ aryl, C₁₃₋₁₅ aryl and C₁₆₋₁₈ aryl, such as, pentyl phenyl, methyl butyl phenyl, methyl isobutyl phenyl, methyl tert-butyl phenyl, ethyl propyl phenyl, ethyl isopropyl phenyl, methyl propyl phenyl, methyl isopropyl phenyl, trimethyl ethyl phenyl, pentamethyl phenyl, and the like.

[0068] The heteroaryl or heteroaryl ring or “heteromatic group” described herein refers to a monocyclic aromatic 5-8 membered ring system or a bicyclic 8-12 membered ring system having one or more hetero atoms (such as, one to three hetero atoms, e.g., N, O or S). 5 to 10-membered heteroaryl described herein contains 5 to 9-membered heteroaryl, 5 to 8-membered heteroaryl, 5 to 7-membered heteroaryl, 5 to 6-membered heteroaryl, 6 to 10-membered heteroaryl, 6 to 9-membered heteroaryl, 6 to 8-membered heteroaryl, 7 to 10-membered heteroaryl, 7 to 9-membered heteroaryl, 8 to 10-membered heteroaryl, 9 to 10-membered heteroaryl, 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, and 10-membered heteroaryl. If possible, the heteroaryl ring may be linked to the adjacent group via C or N. Examples include but are not limited to: furyl, thienyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, pyrimidyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl; examples of 8-12 membered bicycloheteroaryl include but are not limited to: benzofuryl, isobenzofuryl, benzo[b]thienyl, benzo[c]thienyl, isoindolyl, benzo[d]isoxazolyl, benzo[c]isoxazolyl, benzo[d]oxazolyl, benzo[d]isothiazolyl, benzo[c]isothiazolyl, benzo[d]thiazolyl, benzo[d]imidazolyl, benzo[d]imidazolyl, and benzo[d][1,2,3]triazolyl, oxazolyl, thiazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,4-oxadiazole-5-yl, 1,2,4-oxadiazole-3-yl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazole-5-yl, 1,2,4-thiadiazole-3-yl, 1,2,5-thiadiazolyl,

1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, indolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzisothiazolyl, imidazo[1,2- α]pyridyl, pyridazinyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, pyridyl and benzoisoxazolyl.

[0069] “One or more substituents of benzene, naphthalene...” or “one or more of benzene, naphthalene...” described herein refer to one or two or three of phenyl, naphthyl...

[0070] The term “acyloxy”, namely, “acyl oxy” refers to a group —O-C(=O)-R; R is selected from H and substituted or unsubstituted C₁₋₅ alkyl, and the unsubstituted C₁₋₅ alkyl is selected from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, neo-butyl, n-pentyl, iso-pentyl, neo-pentyl, and cyclopentyl; the substituted C₁₋₅ alkyl is C₁₋₅ alkyl substituted by halo, hydroxy, amino, carboxyl, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkoxy, aryl, and heteroaryl. In



some embodiments, the R is n-propyl or

[0071] Halogen, the term used herein, “halo” or “halogen” refers to F, Cl, Br or I.

[0072] When a substituent is described by a conventional chemical formula written from left to right, the substituent also includes chemically equivalent substituents obtained by writing from right to left. For example, CH₂O is equivalent to OCH₂.

[0073] The “compound” described herein refers to including all the stereoisomers, geometrical isomers, tautomers and isotopes. The compound of the present application may be asymmetrical, for example, having one or more stereoisomers. Unless otherwise specified, all the stereoisomers include, for example, enantiomers and diastereoisomers. The compound having asymmetrically substituted carbon atoms in the present application may be separated in an optically active pure

form or in a racemic form. The optically active pure form may be split from a racemic mixture, or synthesized by chiral raw materials or chiral reagents. The compound of the present application further includes a form of tautomer. The form of tautomer is derived from an exchange of a single bond and adjacent double bonds accompanied with a proton migration. The compound of the present application further includes atoms of all the isotopes whatever it is an intermediate or a final compound. Atoms of isotopes include the same atomic number, but have different mass number. For example, isotopes of H include deuterium and tritium. That is, the compound of the present application includes compounds whose partial or complete hydrogen (H) atoms are replaced by tritium (T) and/or deuterium (D), and also includes compounds whose partial or complete ^{12}C are replaced by ^{13}C and/or ^{14}C ; as well as compounds replaced between other isotopes (e.g., N, O, P, and S), for example, ^{14}N and ^{15}N ; ^{18}O and ^{17}O ; ^{31}P and ^{32}P ; ^{35}S and ^{36}S , and the like. The compound described herein may have one or more stereoisomeric centers; and each stereoisomeric center may exist in a R or an S configuration or a combination thereof. Similarly, the compound described herein may have one or more double bonds; and each double bond may exist in an E (trans-) or Z (cis-) configuration or a combination thereof. A specific stereoisomer, regioisomer, diastereoisomer, enantiomer, or an epimer should be construed as including all the possible isomers, such as, stereoisomer, constitutional isomer, diastereoisomer, enantiomer or epimer and a mixture thereof. Therefore, the compound described herein includes all the configurationally different stereoisomers, constitutional isomers, diastereoisomers, enantiomers or epimers and the corresponding mixtures thereof. A person skilled in the art knows the technology used for transforming a specific stereoisomer or keeping a specific stereoisomer the same, and the technology for splitting a stereoisomer mixture, and may choose a proper method based on a specific situation. See, for example, Fumiss et al.(eds.), VOGEL'S ENCYCLOPEDIA OF PRACTICAL ORGANIC CHEMISTRY 5.sup.TH ED., Longman Scientific and Technical Ltd., Essex, 1991, 809-816; and Heller, *Acc. Chem. Res.* 1990, 23, 128.

[0074] The term “optional/arbitrary” or “optionally/arbitrarily” refers that the subsequently described event or situation may occur or may not occur, and the description includes occurrence of the event or situation and not occurrence of the event or situation.

[0075] **Some pharmaceutical terms**

[0076] The term “treating” used herein and other similar synonyms include relieving, alleviating or improving a disease or a condition, inhibiting a disease or a condition, for example, blocking the development of a disease or a condition, relieving a disease or a condition, making a disease or a condition improved, relieving a symptom caused by a disease or a condition, or suspending a symptom of a disease or a condition, preventing other symptoms, improving or preventing a potential metabolism reason for a symptom; further, the term includes a purpose of prevention. The term further includes obtaining a treatment effect and/or prevention effect. The treatment effect refers to healing or improving a potential disease treated. Furthermore, the healing or improvement of one or more physiological symptoms related to a potential disease is also a treatment effect, for example, even though a patient may be still influenced by a potential disease, the improved condition of the patient is observed. In term of a prevention effect, a patient having the risk of suffering from a specific disease is administered the composition, or even if no disease diagnosis is made, the composition is administered to the patient appearing one or more physiological symptoms of the disease.

[0077] The term “effective amount”, “therapeutically effective amount” or “pharmaceutically effective amount” used herein refers to an amount of at least one active substance (e.g., the compound of the present application) which is enough to relieve one or more physiological symptoms of the disease or condition treated to some extent after taking. The result may be reduction and/or relieving of a sign, a symptom or a cause of a disease, or any other change required in biosystem. For example, the "effective amount" for treatment refers to an amount of the composition including the compound disclosed herein required by providing a significant relieving

effect of a disease/condition clinically. A technology, for example, a dose escalation test, may be used to determine an effective amount suitable for any individual case.

[0078] The term, “taking”, “applying”, “administering”, or the like used herein refers to methods capable of delivering a compound or a composition to a site demanded for biological action. These methods include but not limited to oral, duodenum, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intra-arterial injection or infusion), external or rectal administration. A person skilled in the art knows application technologies capable of being used for the compound and method described herein, for example, those discussed in Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

[0079] The term “acceptable” used specific to the formulation, composition or component herein refers that the general health condition of a subject receiving treatment will be not harmfully influenced for a long time.

[0080] The term “pharmaceutically acceptable” used herein refers to a substance (e.g., a carrier or a diluent) not affecting bioactivity or properties of the compound of the present application, and non-toxic relatively; namely, the substance may be applied to an individual and free of causing undesirable biological reaction or free of interacting with any component contained in the composition via an undesirable way.

[0081] The term “pharmaceutical composition” used herein refers to a mixture of mixing the compound of the present application with at least one pharmaceutically acceptable substance. The pharmaceutically acceptable substance includes but not limited to a carrier, a stabilizer, a diluent, a dispersant, a suspending agent, a thickener and/or an excipient.

[0082] The term “carrier” used herein refers to a relatively non-toxic substance which helps to introduce the compound of the present application into cells

or tissues.

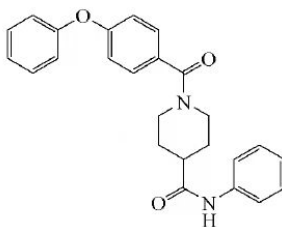
[0083] The term “pharmaceutically acceptable salt” used herein refers to a salt which retains the biopotency of free acids and free alkali of a designated compound, and is free of adverse effect in biology or other aspects. The compound of the present application further includes a pharmaceutically acceptable salt. The pharmaceutically acceptable salt refers to a form where a base group in a parent compound is transformed into a salt. The pharmaceutically acceptable salt includes but not limited to base groups, such as, salts of inorganic or organic acids of amido (amino). The pharmaceutically acceptable salt of the present application may be synthesized by a parent compound, namely, a basic group in a parent compound is reacted with 1-4 equivalent amount of acids in a solvent system. A proper salt is enumerated in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p.1418 and Journal of Pharmaceutical Science, 66, 2(1977).

[0084] Unless otherwise specified, the salt in the present application refers to an acidic salt formed by an organic/inorganic acid, and a basic salt formed by an organic/inorganic base. Additionally, a zwitter-ion (inner salt) will be formed when the basic functional group of the compound in the general formula is pyridine or imidazole (but not limited thereto) and the acidic functional group is carboxylic acid (but not limited thereto); the inner salt is also included in the salt of the present application.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0085] The specific compound representative of the present invention may be synthesized by the synthesizing method of the general formula disclosed herein. The present invention will be further described by reference to detailed embodiments, but the present invention is not limited thereto. Furthermore, under the guidance of the general formula, synthesizing method of the general formula and detailed embodiments of the present invention, a person skilled in the art may obtain other

specific compounds without any inventive effort, and these compounds fall within the scope of the present invention.



MAGLZ-II-01

Example 1 Synthesis of

[0086] Preparation of an intermediate a:

[0087] N-Boc-4 piperidine formic acid (458.6 mg, 2 mmol, 1eq) was dissolved into 15 ml DCM; DIPEA (0.7 ml, 4 mmol, 2eq) and HATU (912 mg, 2.4 mmol, 1.2eq) were added, and stirred for 10 min at room temperature. Phenylamine (0.365 ml, 4 mmol, 2eq) was added and stirred for 12 min at room temperature, then washed with water twice, and washed twice by 0.1 M diluted hydrochloric acid, then distilled under reduced pressure to remove the solvent to obtain an intermediate a without purification.

[0088] Preparation of an intermediate b:

[0089] The intermediate a was dissolved into 10 ml ethyl acetate, and 2 ml HCl/EA solution was added and stirred for 24 h at room temperature to separate out a white solid, then the white solid was subjected to suction filtration and washed by ethyl acetate to obtain an intermediate b, namely, white solid 347.5 mg (72.4%).

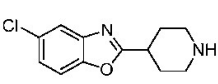
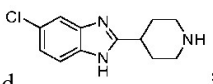
[0090] Preparation of MAGLZ-II-01:

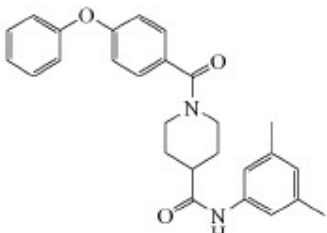
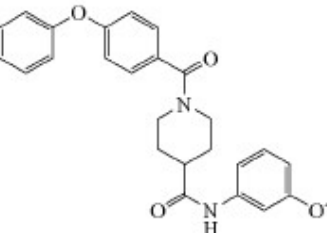
[0091] The intermediate b (120 mg, 0.5 mmol, 1.5eq) was dissolved into 10 ml DMF, and TEA (0.23 ml, 1.65 mmol, 5eq) was added and stirred for 30 min at room temperature, then HATU (152 mg, 0.4 mmol, 1.2eq) and 4-phenoxybenzoic acid (71.4 mg, 0.33 mmol, 1eq) were added and stirred for 2 h at room temperature for full reaction; a saturated sodium chloride solution was added to the reaction solution, and ethyl acetate was used for extraction for 3 times, and organic phases were combined,

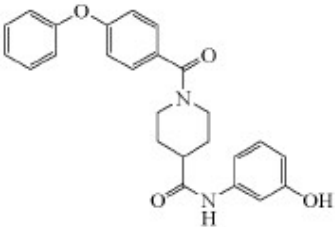
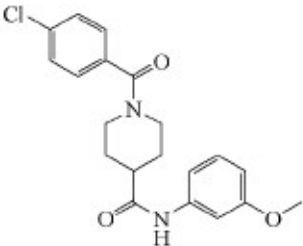
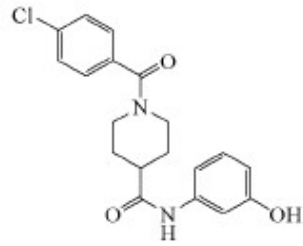
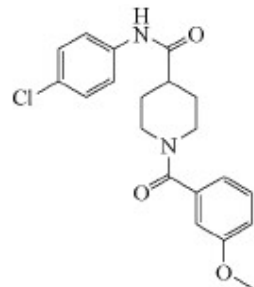
and washed with a saturated sodium chloride solution for 3 times, and dried by anhydrous sodium sulfate, separated and purified by column chromatography (petroleum ether/ethyl acetate=1:1) to obtain a target compound, a light yellow solid 102.4 mg (76.8%).

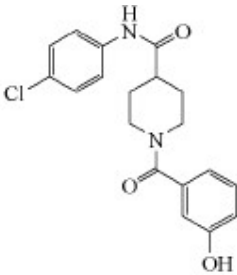
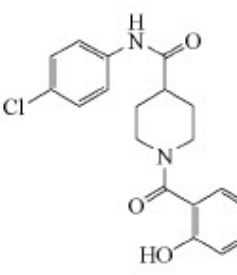
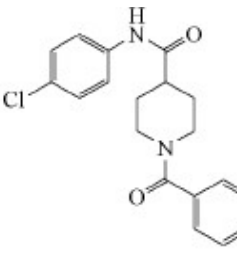
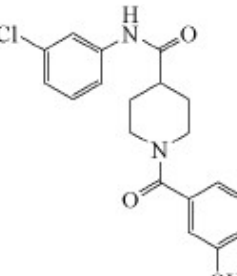
[0092] ^1H NMR (CDCl₃)
 δ (ppm):7.80-7.88(m,1H),7.47-7.54(m,2H),7.29-7.39(m,5H),6.96-7.19(m,6H),2.79-3.05(m,2H),2.45-2.58(m,1H),1.65-2.06(m,6H). The MS result is equivalent to the theoretical value.

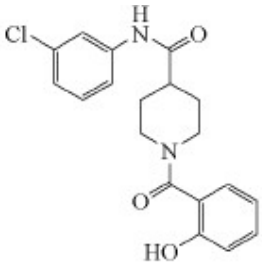
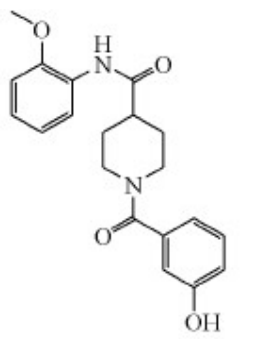
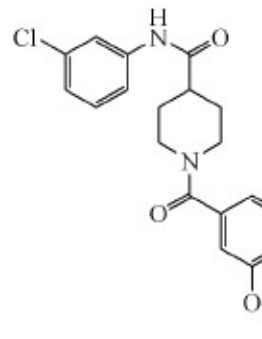
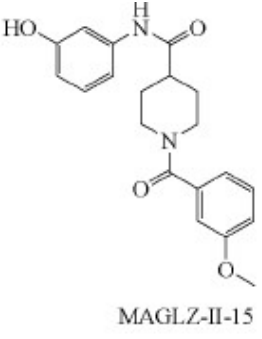
[0093] Preparation processes of Examples 2-23 were based on the synthesizing method of the general formula and similar to those of Example 1, where,

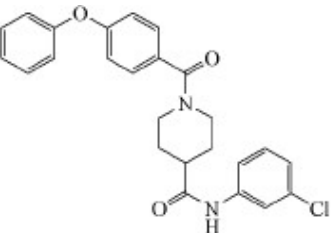
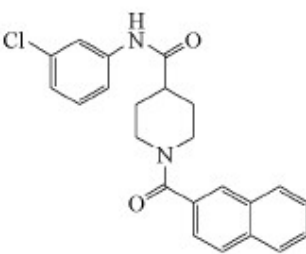
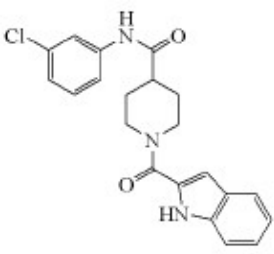
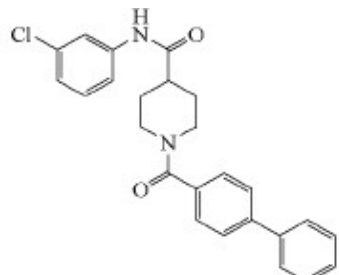
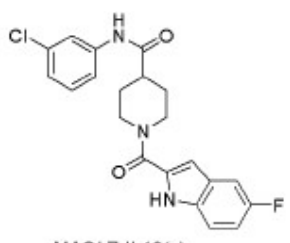
b in Examples 22 and 23 was changed into  and . The MS result of each target product is equivalent to the theoretical value; and the NMR result is as follows:

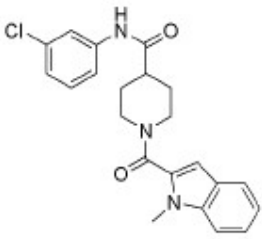
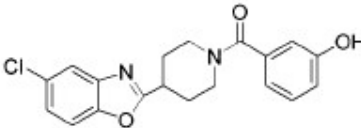
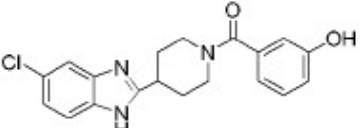
No.	Target product No.	Characterization data
Example 2	 MAGLZ-II-02	^1H NMR (CDCl ₃) δ (ppm):7.32-7.42(m,4H),7.11-7.20(m,3H),6.95-7.07(m,4H),6.74(s,1H),2.79-3.05(m,2H),2.43-2.56(m,1H),2.27(s,6H),1.71-2.07(m,6H).
Example 3	 MAGLZ-II-03	^1H NMR(300 MHz, DMSO-d ₆) δ (ppm): 9.92 (s,1H), 7.40-7.47(m,4H), 7.32-7.34 (m,1H), 7.07-7.23 (m,5H), 7.00-7.05 (m,2H), 3.78-4.68 (m,2H), 3.72 (s,3H), 2.78-3.17 (m,2H), 2.57-2.68 (m,1H), 1.74-1.93 (m,2H), 1.53-1.68 (m,2H);

Example 4	 MAGLZ-II-04	¹ H NMR(DMSO-d ₆) δ (ppm): 9.83(s,1H),9.37(s,1H),7.40-7.46(m,4H),7.17-7.25(m,2H),7.08-7.13(m,2H),7.00-7.06(m,3H),6.93-6.99(m,1H),6.38-6.45(m,1H),2.88-2.92(m,1H),2.68-2.75(m,3H),2.56-2.66(m,1H),1.75-1.93(m,2H),1.50-1.65(m,2H)
Example 5	 MAGLZ-II-05	¹ H NMR(CDCl ₃) δ (ppm):7.32-7.44(m,5H),7.17-7.25(m,1H),6.92-6.99(m,1H),6.65-6.71(m,1H),3.80(s,3H),2.73-3.31(m,4H),2.46-2.56(m,1H),1.78-1.97(m,4H).
Example 6	 MAGLZ-II-06	¹ H NMR(DMSO-d ₆) δ (ppm):9.82(s,1H),9.38(s,1H),7.42-7.55(m,4H),7.16-7.20(m,1H),7.01-7.09(m,1H),6.93-6.99(m,1H),6.39-6.45(m,1H),2.68-2.91(m,4H),2.55-2.64(m,1H),1.80-2.02(m,2H),1.53-1.65(m,2H).
Example 7	 MAGLZ-II-07	¹ H NMR(CDCl ₃) δ (ppm):7.70(s,1H),7.42-7.52(m,2H),7.21-7.37(m,3H),6.92-6.98(m,2H),3.81(s,3H),2.80-2.99(m,4H),2.45-2.55(m,1H),1.99-2.12(m,2H),1.78-1.89(m,2H).

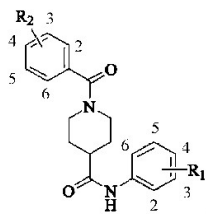
Example 8	 MAGLZ-II-08	¹ H NMR(DMSO-d ₆) δ (ppm):10.08(s,1H),9.68(s,1H),7.60-7.66(m,2H),7.32-7.38(m,2H),7.20-7.28(m,1H),6.73-6.86(m,3H),2.67-2.93(m,3H),2.57-2.66(m,1H),1.68-2.00(m,3H), 1.52-1.65(m,2H).
Example 9	 MAGLZ-II-09	¹ H NMR(DMSO-d ₆) δ (ppm):10.02(s,1H),9.72(s,1H),7.60-7.66(m,2H),7.31-7.37(m,2H),7.18-7.25(m,1H),7.08-7.13(m,1H),6.81-6.89(m,2H),3.98-4.13(m,2H),2.85-2.97(m,2H),2.54-2.66(m,1H),1.75-1.86(m,2H), 1.52-1.66(m,2H).
Example 10	 MAGLZ-II-10	¹ H NMR(DMSO-d ₆) δ (ppm): 10.10(s,1H),9.87(s,1H),7.61-7.66(m,2H),7.33-7.38(m,2H),7.23-7.29(m,2H),6.77-6.83(m,2H),2.86-3.02(m,2H),2.54-2.85(m,3H),1.77-1.87(m,2H),1.52-1.62(m,2H).
Example 11	 MAGLZ-II-11	¹ H NMR(DMSO-d ₆) δ (ppm): 10.08(s,1H), 9.62(s,1H),7.82(t,1H,J=3Hz),7.44-7.50(m,1H),7.32(t,1H, J=6Hz), 7.24 (t,1H,J=6Hz), 7.07-7.12(m,1H), 6.74-6.86(m,3H), 2.89-2.98(m,2H), 2.60-2.74 (m,1H), 2.49-2.58 (m,2H), 1.82-1.91 (m,2H), 1.52-1.64 (m,2H);

Example 12	 MAGLZ-II-12	¹H NMR(DMSO-d₆) δ (ppm): 10.15(s,1H),9.79(s,1H),7.835(t,1H,J=1.5Hz),7.42-7.48(m,1H),7.32(t,1H,J=6Hz),7.18-7.26(m,1H),7.06-7.13(m,2H),6.80-6.89(m,2H),2.69-2.89(m,4H),2.55-2.65(m,1H),1.69-1.93(m,2H),1.49-1.67(m,2H).
Example 13	 MAGLZ-II-13	¹H NMR(DMSO-d₆) δ (ppm): 9.64(s,1H),9.07(s,1H),7.87-8.00(m,1H),7.24(t,1H,J=7.8Hz),6.99-7.13(m,2H),6.72-6.94(m,4H),3.83(s,3H),2.62-3.16(m,4H),1.43-1.95(m,5H).
Example 14	 MAGLZ-II-14	¹H NMR(DMSO-d₆) δ (ppm): 10.12(s,1H),7.83(t,1H,J=1.92Hz),7.43-7.50(m,1H),7.30-7.39(m,2H),7.07-7.11(m,1H),7.00-7.04(m,1H),6.91-6.96(m,2H),3.79(s,3H),2.67-3.30(m,4H),2.58-2.67(m,1H),1.76-1.95(m,2H),1.53-1.66(m,2H).
Example 15	 MAGLZ-II-15	¹H NMR(DMSO-d₆) δ (ppm): 9.68(s,1H),9.23(s,1H),7.32-7.42(m,1H),7.15-7.20(m,1H),6.90-7.06(m,5H),6.40-6.48(m,1H),3.80(s,3H),2.68-3.20(m,4H),2.56-2.68(m,1H),1.76-1.79(m,2H),1.54-1.66(m,2H).

Example 16	 MAGLZ-II-16	¹ H NMR(DMSO-d ₆) δ (ppm): 10.13(s,1H), 7.79-7.88(m,1H),7.41-7.48(m,5H),7.29-7.36(m,1H),7.17-7.24(m,1H),7.07-7.12(m,3H),7.01-7.05(m,3H),2.56-3.29(m,4H),1.46-1.99(m,5H)
Example 17	 MAGLZ-II-17	¹ H NMR(DMSO-d ₆) δ (ppm): 10.14(s,1H),7.97-8.04(m,4H),7.81-7.87(m,1H), 7.57-7.62(m,2H),7.44-7.54(m,2H),7.29-7.38(m,1H),7.06-7.14(m,1H),3.65-4.66(m,2H),2.88-3.22(m,2H),2.64-2.71(m,1H),1.62-1.97(m,4H).
Example 18	 MAGLZ-II-18	¹ H NMR(DMSO-d ₆) δ (ppm): 11.58(s,1H), 10.17(s,1H),7.82-7.88(m,1H),7.58-7.65(m,1H),7.40-7.50(m,2H),7.29-7.37(m,1H),7.15-7.23(m,1H),7.01-7.13(m,2H),6.78-6.82(m,1H),4.44-4.58(m,2H),3.00-3.26(m,2H),2.66-2.74(m,1H),1.86-2.00(m,2H),1.58-1.74(m,2H).
Example 19	 MAGLZ-II-19	¹ H NMR(DMSO-d ₆) δ (ppm): 10.16(s,1H),7.83-7.86(m,1H),7.69-7.78(m,4H),7.47-7.52(m,4H),7.37-7.46(m,2H),7.33(t,1H, J=8.04),7.07-7.13(m,1H),3.67-4.61(m,2H),2.89-3.16(m,2H),2.61-2.69(m,1H),1.82-1.99(m,2H),1.56-1.69(m,2H).
Example 20	 MAGLZ-II-18(a)	[M+H] ⁺ 401.2.

Example 21	 MAGLZ-II-18(c)	¹H NMR(300 MHz, DMSO-d₆) δ (ppm): 10.17(s,1H),7.83-7.87(t,1H),7.59-7.65(d,1H), 7.50-7.56(d,1H),7.45-7.49(m,1H),7.30-7.37(t, 1H),7.23-7.30(t,1H),7.11-7.14(m,1H),7.07-7.11(m,1H),6.67(s,1H),3.77(s,3H),2.63-2.76(m,2 H),1.98-2.06(s,1H),1.85-1.97(d,2H),1.57-1.73 (m,2H),1.15-1.28(m,2H). MS: [M+Na]⁺: 418.2.
Example 22	 MAGLZ-II-30	¹H NMR(300 MHz, DMSO-d₆) δ (ppm): 9.68 (s,1H), 7.83-7.84(d,1H), 7.73-7.75 (d,1H), 7.40-7.43 (m,1H), 7.21-7.25 (t,1H), 6.81-6.84 (m,1H), 6.78-6.80 (d,1H), 6.75-6.76 (m,1H), 4.40 (d,1H), 3.67 (s,1H), 3.21 (s,2H),3.09-3.15 (m,1H), 2.11-2.15 (m,2H), 1.75-1.78 (m,2H); [M+Na]⁺379.1
Example 23	 MAGLZ-II-31	¹H NMR(300 MHz, DMSO-d₆) δ (ppm): 12.48 (s,1H), 9.73 (s,1H), 7.56-7.62(t,1H), 7.50-7.56 (d,1H), 7.24-7.29 (t,1H), 7.18-7.20 (m,1H), 6.80-6.87 (m,3H), 4.50 (d,1H), 3.71 (d,1H), 2.03-2.10 (m,2H), 1.71-1.81 (m,2H);3.21 (s,2H), 3.02-3.17 (m,1H),2.03-2.10 (m,2H), 1.71-1.81 (m,2H); [M+H]⁺356.1

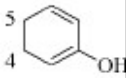
[0094] The target products synthesized in Examples 24-30 are described on the basis of the following structural formula:



, where, the R₁ is selected from hydroxy, F, Cl, Br, I, methyl, ethyl, propyl, and methoxy; R₂ is selected from hydroxy, F, Cl, Br, I, methyl, ethyl, propyl, methoxy, phenyl, and aryl substituted by hydroxyl, F, Cl, Br, I, methyl, ethyl, propyl, and methoxy. The number of R₁ and R₂ is 0, 1, 2, 3 or 4; the link mode between the R₁, the R₂ and nucleus is not limited to a single bond.

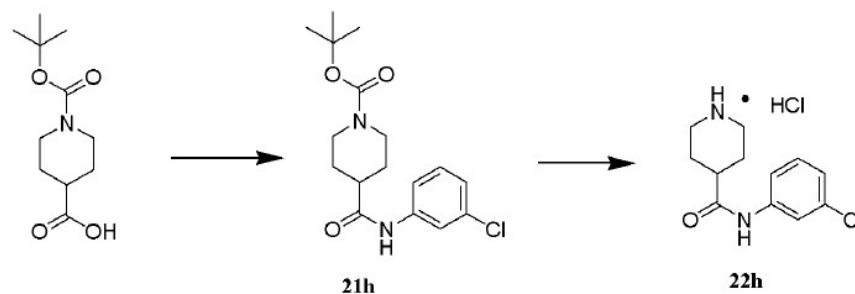
Example	Compound	R ₁	R ₂	Characterization data
Example 24	MAGLZ-II-20	3-Cl	4-OH	¹ H NMR(300 MHz, DMSO-d ₆) δ (ppm): 10.12 (s,1H), 9.83 (s,1H), 7.81-7.84 (m,1H), 7.42-7.49 (m,1H), 7.29-7.36 (m,1H), 7.22-7.28 (m,2H), 7.06-7.12 (m,1H), 6.77-6.83 (m,2H), 2.89-2.90 (m,2H), 2.73-2.74 (m,2H), 2.55-2.67 (m,1H), 1.77-1.89 (m,2H), 1.50-1.65 (m,2H); [M+H] ⁺ 359.1
Example 25	MAGLZ-II-21	3-Cl	4-Cl	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.12 (s,1H), 7.81-7.84 (m,1H), 7.49-7.55 (m,2H), 7.41-7.48 (m,3H), 7.29-7.36 (m,1H), 7.07-7.12 (m,1H), 3.16-3.19 (m,2H), 2.79-3.11 (m,2H), 2.58-2.69 (m,1H), 1.71-1.95 (m,2H), 1.52-1.68 (m,2H); [M+H] ⁺ 377.08

Example 26	MAGLZ-II-22	3-Cl, and 4-Cl	3-OH	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.24 (s,1H), 9.67 (s,1H),8.00-8.03 (m,1H), 7.47-7.58 (m,2H), 7.24 (t,1H, J = 7.5 Hz), 6.80-6.86 (m,1H), 6.74-6.80 (m,2H), 2.88-2.91 (m,2H), 2.69-2.74 (m,2H), 2.56-2.67 (m,1H), 1.72-1.93 (m,2H), 1.50-1.63 (m,2H); [M+H] ⁺ 393.08
Example 27	MAGLZ-II-23	3-Cl and 5-Cl	3-OH	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.27 (s,1H), 9.67 (s,1H), 7.94-7.97 (m,1H), 7.67-7.70 (m,2H), 7.25-7.28 (m,1H), 6.72-6.85 (m,3H), 2.88-2.91 (m,2H), 2.73-2.74 (m,2H), 2.56-2.67 (m,1H), 1.73-1.92 (m,2H), 1.48-1.63 (m,2H); [M+H] ⁺ 393.08
Example 28	MAGLZ-II-24	3-Cl, and 4-Cl		¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.24 (s,1H), 7.95-8.02 (m,5H), 7.57-7.60 (m,2H), 7.48-7.54 (m,3H), 2.89 (s,2H), 2.73 (s,2H), 2.61-2.65 (m,1H), 1.74-1.90 (m,2H), 1.57-1.67 (m,2H); [M+H] ⁺ 427.09
Example 29	MAGLZ-II-25	3-Cl and 5-Cl		¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.28 (s,1H), 7.95-8.00 (m,4H), 7.68-7.69 (d,2H), 7.57-7.60 (m,2H), 7.49-7.52 (m,1H), 7.25-7.26 (t,1H), 2.89 (s,2H), 2.73 (s,2H), 2.59-2.63 (m,1H), 1.73-1.91 (m,2H), 1.58-1.65 (m,2H); [M+H] ⁺ 427.09

Example 30	MAGLZ-II-26	3-F	3-OH	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.16 (s,1H), 9.69 (s,1H), 7.58-7.65 (m,1H), 7.27-7.38 (m,2H), 7.24 (t,1H, J = 7.5 Hz), 6.73-6.90 (m,4H), 2.71-3.12 (m,4H), 2.56-2.68 (m,1H), 1.73-1.93 (m,2H), 1.49-1.65 (m,2H); [M+H] ⁺ 343.15
Example 31	MAGLZ-II-27	3-F and 4-Cl	3-OH	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.30 (s,1H), 9.76 (s,1H), 7.76-7.81 (m,1H), 7.47-7.53 (t,1H), 7.32-7.36 (m,1H), 7.21-7.27 (t,1H), 6.74-6.85 (m,3H), 2.66-2.89 (m,4H), 2.63-2.73 (m,1H), 1.76-1.85 (m,2H), 1.54-1.57 (m,2H); [M+H] ⁺ 377.10
Example 32	MAGLZ-II-29	3-Cl		¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.13 (s,1H), 9.93 (s,1H), 7.82-7.87 (m,3H), 7.72-7.75 (d,1H), 7.44-7.47 (m,1H), 7.37-7.40(m,1H),7.29-7.34 (t,1H), 7.07-7.15 (m,3H), 2.64-3.02 (m,4H), 2.60-2.64 (m,1H), 1.82-1.85 (m,2H), 1.56-1.68 (m,2H); [M+Na] ⁺ 431.12
Example 33	MAGLZ-II-11 (a)	3-Cl	2-F and 5-OH	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.17 (s,1H), 9.68 (s,1H), 7.82 (s,1H), 7.43-7.45 (d,1H), 7.29-7.35 (t,1H), 7.06-7.09 (m,2H), 6.79-6.82 (m,1H), 6.67 (s,1H), 2.84-2.89 (d,2H), 2.68-2.73 (d,2H), 2.61-2.62 (m,1H), 1.76-1.93 (m,4H); [M+Na] ⁺ 399.1

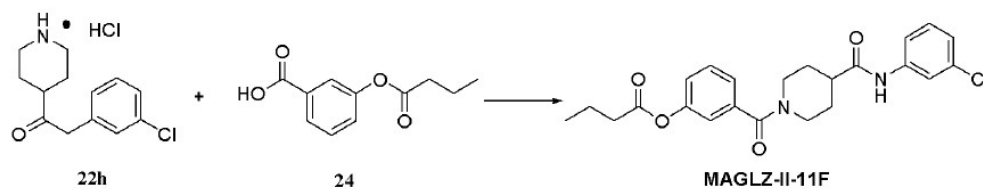
[0095]

Example 34 Preparation of MAGLZ-II-11F:



[0096] A raw material N-Boc-4-piperidine formic acid (20) (229.3 mg, 1 mmol) was dissolved into 10 mL CH₂Cl₂, DIPEA (0.35 mL, 2 mmol) and HATU (456 mg, 1.2 mmol) were added, and stirred for 10 min at room temperature, then 3-chloroaniline (0.21 mL, 2 mmol) was added and stirred for 6 h at room temperature, washed with water for three times, and washed by 10% diluted hydrochloric acid for three times, and dried by anhydrous Na₂SO₄, subjected to rotary evaporation to remove CH₂Cl₂, thus obtaining an intermediate 21 h without further purification.

[0097] The intermediate 21 h was dissolved into 10 mL EtOAc, and 4M HCl/EtOAc solution (2 mL) was added and stirred for 12 h at room temperature to separate out a white solid, then the white solid was subjected to suction filtration, and a filter cake was washed with EtOAc to obtain an intermediate 22 h, namely, a white solid (188.1 mg and yield: 68.4%).



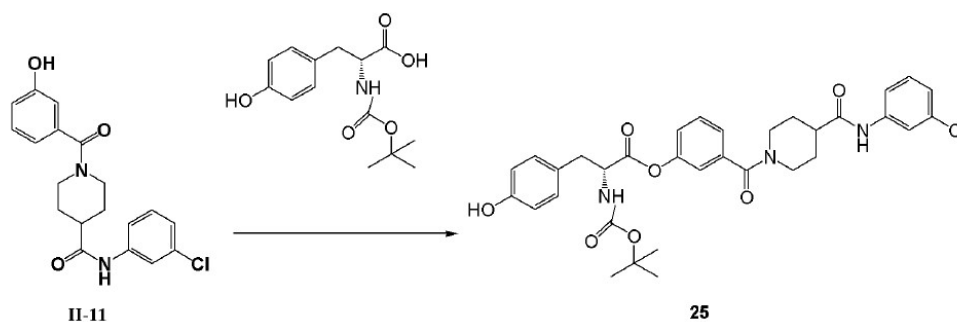
[0098] The intermediate 24 (62.5 mg, 0.3 mmol) was dissolved into anhydrous DMF, HATU (136.8 mg, 0.36 mmol) and TEA (151.8 mg, 1.5 mmol) were added and stirred for 30 min at room temperature, then the hydrochloride intermediate 22 h (107.33 mg, 0.39 mmol) was added and stirred for 12 h at room temperature to stop the reaction; then a saturated salt solution was added and EtOAc was used for extraction for three times, organic phases were combined and washed for three times

with a saturated salt solution and dried by anhydrous Na_2SO_4 , then separated and purified by column chromatography (petroleum ether: ethyl acetate =1:1) to obtain a yellow solid (94.9 mg and yield: 74.1%).

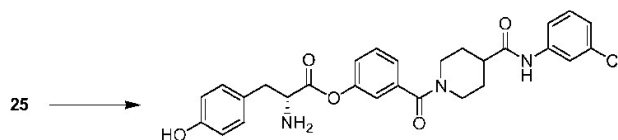
[0099] Characterization data:

[00100] ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.65 (s, 1H), 7.40-7.45 (t, 1H), 7.34-7.36 (d, 2H), 7.23-7.28 (d, 1H), 7.14-7.16 (m, 2H), 7.07-7.10 (m, 1H), 2.96 (s, 1H), 2.88 (s, 1H), 2.52-2.58 (t, 2H), 2.04 (s, 1H), 1.74-1.86 (m, 2H), 1.59 (s, 4H), 1.24-1.28 (m, 3H), 1.02-1.07 (t, 3H); $[\text{M}+\text{Na}]^+$: 451.2.

[00101] Example 35 Synthesis of MAGLZ-II-11J



[00102] A raw material N-Boc-L-tyrosine (0.5 mmol, 140.5 mg) was dissolved into 10 mL anhydrous CH_2Cl_2 , and the intermediate II-11 (179.5 mg, 0.5 mmol) and DMAP (0.1 mmol, 12.2 mg) were added, reacted and cooled to 0°C , then dissolved into DCC (0.55 mmol, 113.4 mg) of 3 mL anhydrous CH_2Cl_2 , and stirred for 10 min, and reacted to room temperature, then the above materials were stirred for 12 h at room temperature; the reaction was incomplete, after the reaction was stopped, suction filtration was performed, and a filter liquor was rotary dried, and added with 20 mL CH_2Cl_2 and washed with a saturated salt solution for three times, and dried by anhydrous sodium sulfate. The above product was separated and purified by column chromatography (dichloromethane: methanol=100:1) to obtain an intermediate 25, namely, a white solid (52.6 mg, yield: 16.9%).



[00103]

MAGLZ-II-11J

[00104] The intermediate 25 (37 mg) was dissolved into 10 mL EtOAc, and 4M HCl/EtOAc solution (2 mL) was added and stirred for 12 h at room temperature to separate out a white solid, then the white solid was subjected to suction filtration and a filter cake was washed with EtOAc, and the filter cake was added with 10 mL sodium bicarbonate and extracted with EtOAc for three times, then, organic phases were combined and washed with a saturated salt solution for three times and dried by anhydrous sodium sulfate, then subjected to rotary evaporation to remove EtOAc, thus obtaining a light white solid (12 mg and yield: 40%).

[00105] Characterization data of MAGLZ-II-11J: ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 11.95 (s, 1H), 10.14 (s, 1H), 7.83 (s, 1H), 7.54-7.56 (d, 1H), 7.48-7.51 (t, 1H), 7.44-7.46 (d, 1H), 7.28-7.34 (m, 2H), 7.10-7.12 (m, 2H), 7.04-7.07 (d, 2H), 6.69-6.71 (d, 2H), 4.40-4.49 (m, 1H), 4.26-4.30 (t, 1H), 4.00-4.06 (m, 2H), 3.61 (s, 1H), 3.07-3.14 (d, 2H), 2.89-2.98 (d, 2H), 2.60-2.65 (m, 1H), 1.58-1.78 (m, 4H); $[\text{M}+\text{Na}]^+544.17$.

[00106] Example 36: MAGL enzyme analysis

[00107] A kit for screening the MAGL inhibitor from Cayman was used; according to the specification, an ethanol solution of 4-nitrophenylacetic acid served as a MAGL substrate, and the substrate had a final concentration of 236UM. 150 μL 1Xassay buffer, 10 μL recombinant human protein MAGL and 10 μL different concentrations of MAGL inhibitors (six points within 1 nM to 1000 nM) were added to per well of a 96-well plate. JZL195 (a positive control inhibitor) served as a positive control well, after incubation for 5 min at room temperature, per well was added with 10 μL MAGL substrate, and 86 wells were vibrated for 10 s and placed for 10 min at room temperature, then an absorbance was detected at 410 nm. 100% inhibition control wells (150 μL 1Xassay buffer, 10 μL MAGL and 10 μL DMSO

were added per well of the 96-well plate, and three repeated wells were set) and background wells (160 μ L 1X assay buffer and 10 μ L DMSO were added per well, and three repeated wells were set) were further set. Graphad Prism 5.0 was taken to calculate IC₅₀ curves fitting each inhibitor. Specific values are shown in Table 2.

Table 2 Activity data

Compound No. MAGLX	IC ₅₀ (μ M)
MAGLZ-II-01	0.045
MAGLZ-II-02	0.027
MAGLZ-II-03	0.749
MAGLZ-II-04	ND
MAGLZ-II-05	4.07
MAGLZ-II-06	1.96
MAGLZ-II-07	0.576
MAGLZ-II-08	1.34
MAGLZ-II-09	10.8
MAGLZ-II-10	0.662
MAGLZ-II-11	0.096
MAGLZ-II-12	ND
MAGLZ-II-13	0.926
MAGLZ-II-14	0.333

MAGLZ-II-15	ND
MAGLZ-II-16	0.018
MAGLZ-II-17	0.015
MAGLZ-II-18	0.670
MAGLZ-II-19	2.82
MAGLZ-II-18 (c)	0.0026
MAGLZ-II-18 (a)	2.15
MAGLZ-II-20	9.92
MAGLZ-II-21	ND
MAGLZ-II-22	1.77
MAGLZ-II-23	4.03
MAGLZ-II-24	0.275
MAGLZ-II-25	0.139
MAGLZ-II-26	12.2
MAGLZ-II-27	2.90
MAGLZ-II-29	0.252
MAGLZ-II-30	0.011
MAGLZ-II-31	ND

MAGLZ-II-11 (a)	2.15
MAGLZ-II-11F	0.126
MAGLZ-II-11J	1.60

[00108] Example 37 Tissue distribution test on the MAGL inhibitor of the present invention

[00109] Detection reagent: MAGLZ-II-11, MAGLZ-II-16, and MAGLZ-II-17;

[00110] test object: mice;

[00111] administration dose: 16 mg/kg (formulation concentration: 8 mg/ml);

[00112] administration mode: subcutaneous injection;

[00113] sampling time: sampling was performed 1, 2, and 5 hours later after administration;

[00114] test tissues: brain, heart, liver, spleen, lung, kidney, pancreas, and blood;

[00115] experimental results indicate that:

[00116] 3 test substances are distributed in the brain detected, where, the content of MAGLZ-II-16 in the brain is up to the highest, MAGLZ-II-17 is ranking the second, and MAGLZ-II-11 is the lowest (see Table 3).

Table 3 Tissue distribution diagram

Time/h	MAGLZ-II-01	MAGLZ-II-02	MAGLZ-II-11	MAGLZ-II-16	MAGLZ-II-17
1.0	0	0	0	0	2.9
2.0	0.6	1.2	1.6	32.8	9.4

5.0	0.9	3.7	1.3	16.9	4.8
-----	-----	-----	-----	------	-----

[00117] Example 38 Effect of the MAGL inhibitor of the present invention on reserpine-induced mice depression

[00118] 1) Basic information

[00119] Species: ICR mouse

[00120] Microbiological level: SPF

[00121] Quantity and sex of the animals purchased: male: 75; female: 75

[00122] Quantity and sex of the animals used: male: 75; female: 75

[00123] Body weight: 13-18 g when accepted

[00124] 2) Animal grouping

[00125] Group design: there were 50 pieces for each batch of animals and 3 batches in total; each batch of animals were randomly divided into 5 groups; low, middle and high-dose groups of the samples for test, blank control group and model group; a sample for test was tested per batch.

[00126] 3) Test method

[00127] 3.1 Animals were administrated via subcutaneous injection per day with doses of 4, 8 and 16 mg/kg for 6 d in total. 2 h later after the final administration, each animal was subcutaneously injected with 4 mg/kg reserpine except the blank control group; afterwards, indicators, such as, awakening, finger contact, fear, head touch, autonomic activity, upright and eyelid closure were determined 2 h later.

[00128] 4) Statistical analysis

[00129] Data statistics and analysis were completed via a computer by SPSS 17.0 software and office 2016, and data statistics was inspected by Kruskal-Wallis. If the Kruskal-Wallis inspection result is significant ($P \leq 0.05$), multiple comparison

inspection is further performed by a Mann-Whitney U nonparametric test method.

[00130] 5) Results are shown in Tables 4A, 4B and 4C

Table 4A

Group	Awakenin g	Finger contact	Head touch	Fear	Autonom ic activity	Upright	Eyelid closure
Blank control group	4±0	4±0	4±0	4±0	4±0	4±0	4±0
Model group	2.2±1.40* *	1.2±0.98* *	1.4±0.92* *	0.2±0.60* *	0±0**	0±0**	1.2±1.33 **
MAGL-II-11- L	3±1.61	1.6±1.50	1±1.34	0±0	0.8±1.60	0.8±1.6 0	1.2±0.98
MAGL-II-11- M	2.6±1.56	1.8±1.66	1.8±1.40	0±0	0.8±1.60	0.8±1.6 0	1.4±1.28
MAGL-II-11- H	3.2±1.33	2±1.79	2.6±1.56	0.2±0.60	1.8±1.66* *	1±1.61* *	2±1.26

Note: a comparison between the model group and the blank group: * $P<0.05$, ** $P<0.01$; a comparison between the administration group and the model group: * $P<0.05$, ** $P<0.01$.

Table 4B

Group	Awakeni ng	Finger contact	Head touch	Fear	Autonomi c activity	Upright	Eyelid closure
Blank control group	4±0	4±0	4±0	4±0	4±0	4±0	4±0
Model group	3.5±1.32 **	3.5±1.32 **	3.58±1.10 **	0.25±0.66 **	0.58±0.85 **	0±0**	1.83±0.44 **

MAGL-II-17 -L	4±0	4±0	3.75±0.66	3.5±1.32	0.5±0.87	0.25±0.66	2.25±0.66
MAGL-II-17 -M	4±0	4±0	4±0	0±0	1.5±1.66	1±1.41	1±1.00
MAGL-II-17 -H	4±0	4±0	3.75±0.66	0±0	0.25±0.66	0±0	0.25±0.66

Note: a comparison between the model group and the blank group: * $P<0.05$, ** $P<0.01$; a comparison between the administration group and the model group: * $P<0.05$, ** $P<0.01$.

Table 4C

Group	Awakeni ng	Finger contact	Head touch	Fear	Autonomi c activity	Upright	Eyelid closure
Blank control group	4±0	4±0	4±0	4±0	4±0	4±0	4±0
Model group	1.6±1.2**	1.2±0.98* *	0±0**	0±0**	0.2±0.6**	0±0**	0±0**
MAGL-II-16-L	2±0	1.4±0.92	0.4±0.8	0±0	0±0	0±0	0±0
MAGL-II-16- M	1.8±0.6	1.2±0.98	0.8±0.98*	0±0	0.2±0.6	0±0	0±0
MAGL-II-16- H	2±0	1.6±0.8	0.8±0.98*	0±0	0.6±0.6*	0.4±1.2	0±0

Note: a comparison between the model group and the blank group: * $P<0.05$, ** $P<0.01$; a comparison between the administration group and the model group: * $P<0.05$, ** $P<0.01$.

[00131] 5.1) MAGLZ-II-11:

[00132] Nonparametric test

[00133] Each indicator of the Kruskal-Wallis test has a statistic difference ($P < 0.05$);

[00134] Comparison of difference between groups

[00135] Mann-Whitney U test

[00136] The comparison between the model group and the blank control group shows a statistic difference ($P < 0.05$), indicating a good modeling result; the comparison between the low/middle/high-dose group and the model group shows no statistic difference ($P > 0.05$); the comparison between the high-dose group and the model control group (autonomic activity and upright) shows a statistic difference ($P < 0.01$, $P < 0.05$); the variation trend of the indicator is consistent with the blank control.

[00137] 5.2) MAGLZ-II-17: each indicator of the Kruskal-Wallis test has a statistic difference ($P < 0.05$); Mann-Whitney U test

[00138] The comparison between the model group and the blank control group shows a statistic difference ($P < 0.05$), indicating a good modeling result;

[00139] the comparison between the low-dose group and the model group shows no statistic difference ($P > 0.05$);

[00140] the comparison between the middle-dose group (eyelid closure) and the model group shows a statistic difference ($P < 0.05$); but the mean value is less than that of the model group; and other indicators show no statistic difference ($P > 0.05$);

[00141] the comparison between the high-dose group (eyelid closure) and the model group shows a statistic difference ($P < 0.01$); but the mean value is less than that of the model group; and other indicators show no statistic difference ($P > 0.05$);

[00142] 5.3) MAGLZ-II-16: each indicator of the Kruskal-Wallis test has a statistic difference ($P < 0.05$); Mann-Whitney U test

[00143] The comparison between the model group and the blank control group

shows a statistic difference ($P<0.05$), indicating a good modeling result;

[00144] the comparison between the low-dose group and the model group shows no statistic difference ($P>0.05$);

[00145] the comparison between the middle-dose group (head touch) and the model group shows a statistic difference ($P<0.05$); but the mean value is greater than that of the model group and has a trend change the same as that of the blank control group; and other indicators show no statistic difference ($P>0.05$);

[00146] the comparison between the high-dose group (head touch and autonomic activity) and the model group shows a statistic difference ($P<0.05$); but the mean value is greater than that of the model group and has a trend change the same as that of the blank control group; and other indicators show no statistic difference ($P>0.05$).

[00147] 6) Conclusion

[00148] 6.1) MAGLZ-II-11 has a certain effect on reserpine-induced depression under this test condition.

[00149] 6.2) MAGLZ-II-16 has a certain effect on reserpine-induced depression under this test condition.

[00150] 6.3) MAGLZ-II-17 may enhance the effect on reserpine-induced depression under this test condition.

[00151] Example 39 Effect of the MAGL inhibitor of the present invention on mice forced swimming test and tail suspension model

[00152] 1 Materials and methods

[00153] 1.1 Experimental animal

[00154] Male ICR mice having a body weight of 18-22 g. The animals were active on a schedule of normal illumination for 12 h and in the dark for 12 h. Environmental temperature and relative humidity were relatively kept for $22\pm 1^{\circ}\text{C}$ and

55±5%.

[00155] 1.2 Experimental method

[00156] 1.2.1 Animal grouping and administration method

[00157] There were 7 groups of laboratory mice, 10 pieces each group, set as a control group (normal saline), a positive control group (fluoxetine hydrochloride capsule, 5 mg/kg), 5 MAGLZ-II series of administration treatment groups: MAGLZ-II-06, MAGLZ-II-07, MAGLZ-II-11, MAGLZ-II-17 and MAGLZ-II-18, respectively, with an administration concentration of 5 mg/kg.

[00158] All medicaments were used once per day via intragastric administration with a dose of 20 mL/kg (body weight), lasting for 10 d. 1 h later after the final administration, the detection of animal behaviors was started.

[00159] 1.2.2 Mice forced swimming test

[00160] Mice forced swimming test was performed according to the method established by Porsolt (Porsolt R D. Behavioural despair in mice: A primary screening test for antidepressants[J]. Arch. Int. Pharmacodyn. 1977, 229). The mice were separately subjected to forced swimming in an open cylindrical container (diameter: 10 cm and height: 25 cm); the container had a water temperature of 25±1 °C and a water depth of 19 cm; the total time that each animal kept still in the course of 6 min was recorded as immobility time (unit: s). Each mouse was judged as still when stopped struggling, kept suspension in water and only made necessary movement to keep the head above the water. Decrease of the immobility time indicates that there is an anti-depression effect.

[00161] 1.2.3 Mice tail suspension test

[00162] The tail suspension test (TST) was performed by the method established by Porsolt, et al. (Porsolt R D, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments[J]. Nature, 1977, 266(5604):730-732). Mice were respectively suspended on the tail portions with tail

suspension clamps at a distance of 10 mm away from the tail portion of the box (250 mm×250 mm×300 mm) and a distance of 5 cm where the head of each mouse was away from the bottom portion. Noise was tested in a dark room having minimum background, and each mouse was suspended for 6 min, and an immobility time was recorded at intervals in the final 4 min. Judgment standard: the mice stopped struggling and kept still completely.

[00163] 1.2.4 Data processing

[00164] All data are shown by $\bar{x} \pm SD$, and the comparison among groups is analyzed by one-way variance.

[00165] 2 Results

[00166] 2.1 Influences of MAGLZ-II series of compounds on forced swimming test

[00167] The test for the influences of MAGLZ-II series of compounds on mice forced swimming test indicates that the positive control medicament, fluoxetine hydrochloride and MAGLZ-II series of compounds may obviously shorten the accumulated immobility time ($P < 0.05$) of mice forced swimming test (Table 5).

Table 5 Influences of the MAGLZ-II series of compounds on mice forced swimming test

Group	Dose (mg/kg)	Number animals (pcs.)	of Accumulated immobility time (S)
Control group	-	10	136.84±46.69
Fluoxetine hydrochloride capsule	5	10	92.64±29.17**
MAGLZ-II-06	5	10	89.23±46.37*
MAGLZ-II-07	5	10	91.31±41.85*

MAGLZ-II-11	5	10	73.57±27.28**
MAGLZ-II-17	5	10	79.38±41.67**
MAGLZ-II-18	5	10	81.71±38.12**

[00168] Note: compared with the control group, *P<0.05 and **P<0.01.

[00169] 2.2 Influences of the MAGLZ-II series of compounds on mice tail suspension test

[00170] Compared with the control group, the MAGLZ-II series of compounds may obviously shorten the accumulated immobility time (P<0.05) of tail suspension mice (Table 6).

Table 6 Influences of the MAGLZ-II series of compounds on mice tail suspension behaviors

Group	Dose (mg/kg)	Number animals (pcs.)	of Accumulated immobility time (S)
Control group	-	10	132.38±44.51
Fluoxetine hydrochloride capsule	5	10	92.19±23.63**
MAGLZ-II-06	5	10	90.73±30.51**
MAGLZ-II-07	5	10	89.66±31.52*
MAGLZ-II-11	5	10	72.81±23.49**
MAGLZ-II-17	5	10	89.87±29.68**
MAGLZ-II-18	5	10	79.68±25.72**

Note: compared with the control group, *P<0.05 and **P<0.01.

[00171] 3 Discussion

[00172] Mice forced swimming test and tail suspension test are comparatively common and classical depression models for animals. Despair, behavior distortion and other conditions of the mice reflected by the model are significant features of in vitro depression simulation; meanwhile, the mice are more sensitive to antidepressants and easy to operate. Therefore, the two models are common screening models for antidepressants. Such two classical depression models for animals are used in this study to further evaluate and verify the anti-depression activity of the MAGLZ-II series of compounds. The results indicate that the MAGLZ-II series of compounds may significantly shorten the accumulated immobility time of the mice forced swimming test and tail suspension test, showing that the MAGLZ-II series of compounds have a specific antidepressant effect.

[00173] Example 40 Influences of the MAGL inhibitor of the present invention on the mice writhing times caused by acetic acid

[00174] 1. Animal grouping and administration

[00175] 200 male ICR mice (20±2) g were divided into 20 groups randomly according to body weight, 10 pieces for each group. The specific grouping conditions are as follows: model group: an equal volume of 0.5% sodium carboxymethylcellulose, ig

[00176] positive control group: 10 mg/kg diclofenac sodium, ig

MAGLZ-II-11 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11 middle-dose group: 15 mg/kg, ig

MAGLZ-II-11 high-dose group: 30 mg/kg, ig

MAGLZ-II-11a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11a middle-dose group: 15 mg/kg, ig

MAGLZ-II-11a high-dose group: 30 mg/kg, ig

MAGLZ-II-18a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18a middle-dose group: 15 mg/kg, ig

MAGLZ-II-18a high-dose group: 30 mg/kg, ig

MAGLZ-II-18 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18 middle-dose group: 15 mg/kg, ig

MAGLZ-II-18 high-dose group: 30 mg/kg, ig

MAGLZ-II-18c low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18c middle-dose group: 15 mg/kg, ig

MAGLZ-II-18c high-dose group: 30 mg/kg, ig

MAGLZ-II-10 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-10 middle-dose group: 15 mg/kg, ig

MAGLZ-II-10 high-dose group: 30 mg/kg, ig

[00177] Each compound was prepared into a suspension by 0.5% sodium carboxymethylcellulose respectively, and then set according to the dose, and each administration group was administered intragastrically; the model group was administered intragastrically an equal volume of 0.5% sodium carboxymethylcellulose.

[00178] 2. Experimental method and data processing

[00179] Mice were intraperitoneally injected with acetic acid to cause a large area and more lasting painful stimuli in deep enterocoelia, causing mice to produce writhing responses. After being administered for 1 h, each dose group was intraperitoneally injected with 0.7% acetic acid-normal saline solution (0.1 ml/10 g).

[00180] The time (pain latent time) that the mice started to appear writhing after being intraperitoneally injected with acetic acid was recorded.

[00181] The writhing response times of each mouse within 20 min were recorded after injecting acetic acid to cause pain, and then, the writhing inhibition ratio of each administration group was calculated.

[00182] Writhing inhibition ratio = [(writhing times of the control group -

writhing times of the administration group)/writhing times of the control group]×100%

[00183] Experimental data is shown by $\bar{x} \pm s$ and subjected to variance analysis by SPSS15.0 software.

[00184] 3. Experimental results

[00185] Experimental results are shown in Table 7.

Table 7 Influences of the MAGL inhibitor of the present invention on the mice writhing times caused by acetic acid

Group	Writhing times	Inhibition ratio (%)	Latent time (s)
Model group	39.3±12.9	—	226.5±38.2
Positive medicament group	24.5±12.9*	37.7	358.5±172.7*
MAGLZ-II-18a low-dose group	24.2±8.5**	38.4	355.5±136.5*
MAGLZ-II-18a middle-dose group	20.8±12.5**	47.1	380.7±130.7**
MAGLZ-II-18a high-dose group	17.8±11.1***	54.7	422.4±137.9***
MAGLZ-II-11 low-dose group	23.4±11.7**	40.5	379.7±129.3**
MAGLZ-II-11 middle-dose group	17.5±9.6***	55.5	408.4±128.2***
MAGLZ-II-11 high-dose group	13.6±13.1***	65.4	467.8±175.6***
MAGLZ-II-11a low-dose	22.6±12.0**	42.5	401.2±168.3**

group				
MAGLZ-II-11a group	middle-dose	18.6±14.6**	52.7	438.9±230.0**
MAGLZ-II-11a group	high-dose	12.5±9.4***	68.2	488.8±172.0***
MAGLZ-II-18 group	low-dose	25.0±13.5*	36.4	318.7±120.2*
MAGLZ-II-18 group	middle-dose	21.8±12.4**	44.5	381.4±127.1**
MAGLZ-II-18 group	high-dose	15.8±15.3**	59.8	410.9±186.5**
MAGLZ-II-18c group	low-dose	28.3±11.9	28.0	263.5±77.7
MAGLZ-II-18c group	middle-dose	24.9±12.2*	36.6	312.7±90.9*
MAGLZ-II-18c group	high-dose	19.9±12.2**	49.4	373.6±114.0**
MAGLZ-II-10 group	low-dose	34.0±9.1	13.5	235.4±59.6
MAGLZ-II-10 group	middle-dose	32.8±11.6	16.5	246.2±69.5
MAGLZ-II-10 group	high-dose	24.8±11.1*	36.9	306.4±90.2*

[00186] Compared with the model group, *P<0.05, **P<0.01 and ***P<0.001.

[00187] It can be seen from the experimental results shown in Table 1 that compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a

and MAGLZ-II-18c of the present invention may significantly decrease the mice writhing times caused by acetic acid and extend latent time.

[00188] Example 41 Influences of the MAGL inhibitor of the present invention on the mice pain response induced by hot plate

[00189] Female ICR mice (20±2) g were placed on an intelligent hot plate at 55±0.5℃, and latency (s) that the plantar of mice touched the hot plate until the occurrence of a hind paws licking response served as a pain threshold indicator; the mice (response latency <5 s or >30 s) or jumping mice were eliminated.

[00190] Grouping and administration were the same as those in Example 40.

[00191] The mice were continuously administered intragastrically for 7 consecutive days; the pain threshold of each group of mice was respectively determined once at 30, 60, 90 and 120 min after the final administration; the pain threshold greater than 60 s was calculated by 60 s.

[00192] Experimental results are shown in Table 8.

Table 8 Influences of the MAGL inhibitor of the present invention on the pain threshold of mice pain response induced by hot plate

Pain thresholds of the mice at different periods of time after administration (s)				
Group	30 min	60 min	90 min	120 min
Model group	15.63±7.32	16.85±7.46	15.50±6.11	15.38±6.93
Positive medicament group	22.32±6.76*	24.34±8.19*	22.64±6.48*	22.52±6.91*
MAGLZ-II-11 low-dose group	37.92±8.83***	44.14±7.56***	45.93±8.38***	43.80±6.12***
MAGLZ-II-11 middle-dose group	40.33±8.25***	44.87±5.67***	46.41±5.36***	43.44±5.91***

MAGLZ-II-11 high-dose group	41.43±5.15***	46.16±6.63***	47.22±5.98***	45.49±6.31***
MAGLZ-II-11a low-dose group	36.18±8.50***	43.17±7.43***	42.83±7.34***	42.16±7.05***
MAGLZ-II-11a middle-dose group	38.16±7.00***	45.47±7.03***	43.71±5.87***	42.34±7.04***
MAGLZ-II-11a high-dose group	39.45±6.75***	46.56±6.35***	45.42±6.84***	43.73±5.68***
MAGLZ-II-18a low-dose group	34.62±6.65***	40.29±6.73***	43.98±6.55***	43.56±6.01***
MAGLZ-II-18a middle-dose group	37.51±6.07***	42.42±5.90***	45.86±7.09***	44.38±5.44***
MAGLZ-II-18a high-dose group	40.86±7.17***	46.29±5.27***	48.70±5.73***	47.04±5.54***
MAGLZ-II-18 low-dose group	26.33±7.52**	26.74±7.05**	27.16±7.32**	26.64±10.03**
MAGLZ-II-18 middle-dose group	26.41±7.53**	27.09±7.53**	27.58±7.71**	27.38±9.97**
MAGLZ-II-18 high-dose group	26.73±7.37**	27.22±7.29**	27.86±7.93**	27.62±10.01**
MAGLZ-II-18c low-dose group	23.98±6.89*	24.75±6.91*	25.16±8.87*	24.28±7.17*
MAGLZ-II-18c middle-dose group	26.82±7.99**	28.52±6.18**	28.66±8.73**	27.88±7.74**
MAGLZ-II-18c high-dose group	29.23±7.95**	30.24±7.80**	30.66±8.35**	29.87±7.43**

MAGLZ-II-10 low-dose group	16.37±6.00	17.93±5.75	19.24±4.72	19.14±4.63
MAGLZ-II-10 middle-dose group	16.67±5.97	18.79±5.95	22.43±5.31	20.60±4.64
MAGLZ-II-10 high-dose group	17.73±6.20	19.77±6.73	25.25±7.01*	24.90±5.73*

[00193] Compared with the model group, *P<0.05, **P<0.01 and ***P<0.001.

[00194] Compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a, MAGLZ-II-18, and MAGLZ-II-18c of the present invention may significantly extend pain thresholds of the thermal-stimulus mice.

[00195] Example 42 Influences of the MAGL inhibitor of the present invention on a pain threshold of the mice with inflammatory pain

[00196] Male SD mice (180±20) g were injected with a complete Freund's adjuvant (50 µL/piece) at the right rear plantar of mice, and mice in the control group were injected with the corresponding volume of 0.5% sodium carboxymethylcellulose to establish a paw edema inflammatory pain model. After modeling, the mice were administered for 7 d continuously, and administered intragastrically once per day. Pain thresholds (s) of the mice were respectively determined on the 1st, 3rd and 7th day before administration and after modeling at different periods of time.

[00197] Grouping and administration were the same as those of Example 40.

Table 9 Influences of the MAGL inhibitor of the present invention on the pain thresholds of the mice with inflammatory pain

Group	Pain thresholds of the mice at different periods of time after administration (s)			
	0 d	1 d	3 d	7 d
Control group	12.67±2.52	13.02±3.03	12.91±2.81	12.88±2.88

Model group	12.56±2.50	5.49±0.94 ^{###}	7.06±0.63 ^{###}	8.27±0.57 ^{###}
Positive medicament group	12.71±2.55	6.38±0.91 [*]	8.05±1.23 [*]	9.00±0.91 [*]
MAGLZ-II-11 low-dose group	12.94±2.41	7.55±1.29 ^{***}	9.00±0.73 ^{***}	10.26±1.08 ^{***}
MAGLZ-II-11 middle-dose group	12.80±2.27	7.73±1.10 ^{***}	9.47±0.79 ^{***}	10.93±1.62 ^{***}
MAGLZ-II-11 high-dose group	12.88±2.27	7.99±0.90 ^{***}	9.88±1.34 ^{***}	11.26±1.82 ^{***}
MAGLZ-II-11a low-dose group	12.96±2.44	7.38±1.19 ^{***}	8.87±0.74 ^{***}	9.91±1.05 ^{***}
MAGLZ-II-11a middle-dose group	13.03±2.35	7.58±0.84 ^{***}	9.30±0.75 ^{***}	10.66±1.30 ^{***}
MAGLZ-II-11a high-dose group	12.97±2.32	7.83±1.01 ^{***}	9.55±1.58 ^{***}	11.00±1.61 ^{***}
MAGLZ-II-18a low-dose group	12.73±2.43	6.97±0.87 ^{**}	8.44±1.03 ^{**}	9.56±0.92 ^{**}
MAGLZ-II-18a middle-dose group	12.86±2.25	7.26±0.70 ^{***}	9.01±0.68 ^{***}	10.37±1.49 ^{***}
MAGLZ-II-18a high-dose group	12.85±2.26	7.49±0.79 ^{***}	9.35±1.2 ^{***}	10.37±1.59 ^{***}
MAGLZ-II-18 low-dose group	12.73±2.43 [*]	6.39±0.91 [*]	8.12±1.29 [*]	9.16±1.17 [*]
MAGLZ-II-18 middle-dose group	12.86±2.25 ^{**}	6.62±0.69 ^{**}	8.24±0.73 ^{**}	9.51±1.15 ^{**}
MAGLZ-II-18	12.85±2.26 ^{**}	6.95±0.85 ^{**}	8.49±1.15 ^{**}	9.62±0.93 ^{**}

high-dose group				
MAGLZ-II-18c				
low-dose group	12.75±2.46*	6.36±0.89*	7.98±1.21*	8.95±0.67*
MAGLZ-II-18c				
middle-dose group	12.86±2.07*	6.41±0.91*	8.10±1.30*	8.99±0.92*
MAGLZ-II-18c				
high-dose group	12.85±2.09*	6.44±0.92*	8.17±1.14*	9.05±0.84*
MAGLZ-II-10				
low-dose group	12.71±2.47	5.59±0.89	7.15±0.59	8.33±0.57
MAGLZ-II-10				
middle-dose group	12.77±2.48	5.62±0.84	7.18±0.55	8.36±0.59
MAGLZ-II-10				
high-dose group	12.93±2.26	5.67±0.93	7.95±0.66*	8.93±0.61*

[00198] Compared with the model group, *P<0.05, **P<0.01 and ***P<0.001.

[00199] Compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a, MAGLZ-II-18 and MAGLZ-II-18c of the present invention may significantly extend the pain threshold of the mice with inflammatory pain.

[00200] Example 43 Therapeutical effect of the MAGL inhibitor of the present invention on irritable bowel syndrome rats induced by early maternal separation

[00201] Irritable Bowel Syndrome (IBS) is a kind of common functional disease of stomach and intestine, manifested as chronic abdominal pain, abdominal discomfort and change of bowl evacuation habit, and no obvious intestinal lesion. This experiment is mainly used to discuss the therapeutical effect of the MAGL inhibitor of the present invention on irritable bowel syndrome rats induced by early maternal separation.

[00202] 1. Animal grouping and administration

[00203] 200 SD rats (20 ± 2) g were divided into 20 groups randomly according to body weight, 10 pieces for each group. The specific grouping conditions are as follows:

[00204] blank group: an equal volume of 0.5% sodium carboxymethylcellulose, ig

[00205] model group: an equal volume of 0.5% sodium carboxymethylcellulose, ig

MAGLZ-II-11 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11 middle-dose group: 15 mg/kg, ig

MAGLZ-II-11 high-dose group: 30 mg/kg, ig

MAGLZ-II-11a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11a middle-dose group: 15 mg/kg, ig

MAGLZ-II-11a high-dose group: 30 mg/kg, ig

MAGLZ-II-18a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18a middle-dose group: 15 mg/kg, ig

MAGLZ-II-18a high-dose group: 30 mg/kg, ig

MAGLZ-II-18 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18 middle-dose group: 15 mg/kg, ig

MAGLZ-II-18 high-dose group: 30 mg/kg, ig

MAGLZ-II-18c low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18c middle-dose group: 15 mg/kg, ig

MAGLZ-II-18c high-dose group: 30 mg/kg, ig

MAGLZ-II-10 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-10 middle-dose group: 15 mg/kg, ig

MAGLZ-II-10 high-dose group: 30 mg/kg, ig

[00206] Each compound was prepared into a suspension by 0.5% sodium carboxymethylcellulose respectively, and then set according to the dose, and each administration group was administered intragastrically; the model group was administered intragastrically an equal volume of 0.5% sodium carboxymethylcellulose.

2. Experimental method and data processing

[00207] The newborn SD male rats were separated from the mother rat in lactation period for 3 h every day on the 2nd to the 21st day after the birth of the newborn SD rats, namely, the mother rat in lactation period was taken out of the cage at 8:30 a.m., and then the newborn rats were removed from the initial cage and put to another separate cage, then the cage was transferred to an adjacent room, then the newborn rats were returned to the initial cage 3 h later, namely, at 11:30 such that the newborn rats and the mother rat got together; the newborn rats were weaned on the 22nd day after birth and separated from the initial cage on the 30th day, grouped on the 60th day, and administered, 20 d in total.

[00208] Intragastric administration was performed within the administration period once a day with continuous administration for 20 d.

[00209] End point of the experiment: dissection was performed after finishing the corresponding test indicators of the experiment.

[00210] Test indicators: abdominal withdrawal reflex (AWR); test method: rats were fasted 18 h before the experiment and drank water freely, and narcotized with diethyl ether; then an air sac coated with paraffin oil was inserted into the rats' colorectum for 4.0 cm, and a catheter outside the anus was fixed at the root of the rat tail with an adhesive tape, and connected with an injection syringe and a sphygmomanometer via three links. The rats were put to an organic glass inspection box (20 cm×12 cm×9 cm), after the rats were awake and fully adapted to the environment for 30 min, the experiment was started. 20, 40 and 60 mm Hg of pressure were respectively applied on the rats, and continuous expansion was performed for 20

s each time with a stimulus interval of 4 min; each pressure was performed for 3 times repeatedly for AWR scoring. AWR scoring was performed by a single blind method; scoring standard: 0 points: no obvious behavior change; 1 point: simple head movement only; 2 points: abdominal muscles started to shrink but are not separated from the table top; 3 points: abdominal muscles obviously shrank to flatten or inferior abdominal wall was separated from the table top; 4 points: abdominal wall hunched up or body/pelvis hunched up.

[00211] At the end of the experiment, the animals were dissected and weighed, and narcotized to take blood, then the content of 5-HT in serum was determined by high performance liquid chromatography. Cerebrum was taken on an ice and precooled and cleaned slightly with 0.5% sodium carboxymethylcellulose, and then sucked dry with a filter paper, and placed into a cryogenic tube, and preserved at -20°C for further use, then the content of 5-HT in brain tissues was detected by high performance liquid chromatography.

[00212] Colon histological observation: after the experiment on colectasia, distal colon (5-6 cm away from the anus) of the rat was taken and subjected to conventional HE dyeing to observe the inflammation and damage conditions of the colon wall.

[00213] Data is presented by a mean±SD, and the difference among groups is subjected to statistics with t tests or a one-way ANOVA method, and P<0.05 shows a significant difference.

[00214] 3. Experimental results

[00215] Experimental results are shown in Table 10.

Table 10 Influences of the MAGL inhibitor of the present invention on the AWR scoring and 5-HT of the IBS rats

Group	Quant AWR scoring	Colon (μg/mg)	Serum (μg/ml)
-------	----------------------	------------------	---------------

	ity	20 mm Hg	40 mm Hg	60 mm Hg	5-HT	5-HT
Blank group	10	1.93±0.43	2.78±0.35	3.29±0.25	11.78±1.78	28.55±4.03
Model group	10	2.85±0.28 ^{##} #	3.53±0.22 ^{###}	3.86±0.13 ^{###}	19.76±2.52 ^{###}	38.73±3.42 ^{###}
MAGLZ-II-1						
8c	10	2.28±0.58 [*]	3.20±0.43 [*]	3.61±0.24 ^{**}	16.84±2.87 [*]	34.2±5.37 [*]
Low-dose group						
MAGLZ-II-1						
8c	10	1.79±0.23 ^{**} *	2.87±0.65 ^{**}	3.27±0.51 ^{**}	14.99±2.90 ^{**}	31.88±4.40 ^{**}
Middle-dose group						
MAGLZ-II-1						
8c	10	1.38±0.51 ^{**} *	2.20±0.57 ^{***}	2.96±0.70 ^{***}	14.34±2.40 ^{***}	29.03±5.29 ^{***}
High-dose group						
MAGLZ-II-1						
1a	10	2.12±0.36 ^{**} *	3.02±0.53 [*]	3.58±0.26 ^{**}	16.33±2.78 ^{**}	31.76±5.42 ^{**}
Low-dose group						
MAGLZ-II-1						
1a	10	1.51±0.43 ^{**} *	2.52±0.38 ^{***}	3.27±0.48 ^{***}	14.79±2.73 ^{***}	29.89±5.34 ^{***}
Middle-dose group						
MAGLZ-II-1						
1a	10	1.23±0.50 ^{**} *	2.13±0.48 ^{***}	2.87±0.46 ^{***}	12.65±3.36 ^{***}	24.05±6.17 ^{***}

High-dose

group

MAGLZ-II-1

0

10 2.87±0.39 3.43±0.30 3.79±0.20 21.44±2.72 36.32±3.14

Low-dose

group

MAGLZ-II-1

0

10 2.83±0.47 3.56±0.22 3.80±0.17 20.97±2.24 38.65±2.68

Middle-dose

group

MAGLZ-II-1

0

10 2.89±0.46 3.21±0.35* 3.65±0.17* 18.66±2.38* 33.09±2.31*

High-dose

group

MAGLZ-II-1

1

10 2.50±0.38* 3.00±0.49** 3.60±0.22** 16.24±2.34** 31.75±5.33**

Low-dose

group

MAGLZ-II-1

1

10 2.02±0.57** 2.42±0.41*** 3.03±0.37*** 14.33±2.10*** 29.47±4.91***

Middle-dose

group

MAGLZ-II-1

1

10 1.39±0.30**
* 1.92±0.33*** 2.86±0.26*** 12.00±2.93*** 23.82±6.34***

High-dose

group

MAGLZ-II-1 10 2.59±0.33 3.26±0.39 3.65±0.23* 21.91±2.46 35.73±3.32

8						
Low-dose						
group						
MAGLZ-II-1						
8						
	10	2.29±0.36**	3.01±0.40**	3.3±0.45**	14.89±3.19**	29.12±7.05**
Middle-dose						
group						
MAGLZ-II-1						
8						
	10	1.87±0.36**				
	*		2.6±0.54***	3.09±0.34***	14.33±2.10***	30.86±5.28***
High-dose						
group						
MAGLZ-II-1						
8a						
	10	2.58±0.26*	3.06±0.38**	3.50±0.29**	16.43±2.15**	32.51±5.01**
Low-dose						
group						
MAGLZ-II-1						
8a						
	10	2.35±0.40**	3.02±0.51**	3.39±0.34***	14.64±2.17***	30.20±5.59***
Middle-dose						
group						
MAGLZ-II-1						
8a						
	10	1.96±0.46**				
	*		2.60±0.58***	3.00±0.54***	13.90±1.13***	29.44±4.37***
High-dose						
group						

[00216] Compared with the blank group, #P<0.05, ##P< 0.01, ###P< 0.001;

[00217] and compared with the model group, *P<0.05, **P<0.01 and ***P<0.001.

[00218] It can be seen from the experimental results shown in Table 10 that

compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a, MAGLZ-II-18 and MAGLZ-II-18c of the present invention may significantly decrease the AWR scoring, and the 5-HT level in colon and serum.

[00219] Example 44 Influences of the MAGL inhibitor of the present invention on reserpine-induced mice migraine

[00220] 1. Animal grouping and administration

[00221] 210 male ICR mice (20±2) g were divided into 21 groups randomly according to body weight, 10 pieces for each group. The specific grouping conditions are as follows: blank group: an equal volume of 0.5% sodium carboxymethylcellulose, ig

[00222] model group: an equal volume of 0.5% sodium carboxymethylcellulose, ig

[00223] positive control group: 0.5 mg/kg Zolmitriptan, ig

MAGLZ-II-11 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11 middle-dose group: 15 mg/kg, ig

MAGLZ-II-11 high-dose group: 30 mg/kg, ig

MAGLZ-II-11a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11a middle-dose group: 15 mg/kg, ig

MAGLZ-II-11a high-dose group: 30 mg/kg, ig

MAGLZ-II-18a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18a middle-dose group: 15 mg/kg, ig

MAGLZ-II-18a high-dose group: 30 mg/kg, ig

MAGLZ-II-18 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18 middle-dose group: 15 mg/kg, ig

MAGLZ-II-18 high-dose group: 30 mg/kg, ig

MAGLZ-II-18c low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18c middle-dose group: 15 mg/kg, ig

MAGLZ-II-18c high-dose group: 30 mg/kg, ig

MAGLZ-II-10 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-10 middle-dose group: 15 mg/kg, ig

MAGLZ-II-10 high-dose group: 30 mg/kg, ig

[00224] Each compound was prepared into a suspension by 0.5% sodium carboxymethylcellulose respectively, and then set according to the dose, and each administration group was administered intragastrically; the model group was administered intragastrically an equal volume of 0.5% sodium carboxymethylcellulose.

[00225] 2. Experimental method and data processing

[00226] The blank control group was subcutaneously injected with normal saline, and the rest groups of mice were subcutaneously injected with a reserpine solution (0.2 mg/kg), 10 d in total; if the mice showed eye closure, squat and reduced activity, diarrhea, less food-intake, back arching and other typical reserpine symptoms after being injected with reserpine, the modeling was believed successful.

[00227] The mice in the blank control group and model group were administered intragastrically via a solvent from the 5th day after modeling, and the rest groups of mice were respectively administered corresponding medicaments and doses for intragastric administration for 10 consecutive days; 1 h later after the final administration, the mice were weighed; blood was taken at inner canthus to detect blood coagulation time; whole blood was taken, and cerebrum was taken on an ice and preserved at -20°C for the subsequent experiment.

[00228] End point of the experiment: model administration was continued for 10 d, detection and blood taking were performed 1 h later after the final administration on the 10th day, thus finishing the experiment.

[00229] Test indicator: the mice were weighed once every two days after the beginning of the experiment.

[00230] Behavioral test: tail suspension activity was performed; the position 1 cm away from the tail of the mice was glued by an adhesive tape on the 9th day of the test, and the adhesive tape was penetrated by a steel needle, and hung in a dark box such that the mice were hung upside down; then the mice struggling times (total number of overturning from hanging) within 2 min were observed.

[00231] The mice were weighed 1 h later after the final administration; blood of inner canthus was taken via a capillary to detect the blood coagulation time.

[00232] Blood was taken to detect the content of 5-HT in serum via high-performance liquid chromatography. Cerebrum was taken on an ice and precooled and cleaned slightly with 0.5% sodium carboxymethylcellulose, and then sucked dry with a filter paper, and placed into a cryogenic tube, and preserved at -20°C for further use, then the content of 5-HT in brain tissues was detected by high performance liquid chromatography.

[00233] 5-HT test method: a sample was precipitated with 10% perchloric acid solution according to 1:1, and then centrifuged to take supernatant for test. Chromatographic conditions: the chromatographic column is a SHIMADZU VP-ODS C₁₈ column (250*4.6 mm, 5 μm), the mobile phase is a methanol-0.01 mol/L potassium acetate buffer solution (10:90, V/V, PH is adjusted to 4.00 with 0.2 mol/L citric acid) for gradient elution; the column temperature is 25°C, flow rate is 1.00 ml/min and test wavelength is 275 nm.

[00234] Data is presented by a mean±SD, and the difference among groups is subjected to statistics with t tests or a one-way ANOVA method, and P<0.05 shows a significant difference.

[00235] **3. Experimental results**

[00236] Experimental results are shown in Tables 11-13.

Table 11 Influences of the MAGL inhibitor of the present invention on blood coagulation time

Grouping	Dose	Blood coagulation time (S)
Normal group	-	352.50±37.48
Model group	-	115.38±24.05***
Zolmitriptan	0.5 mg/kg	185.12±38.86###
MAGLZ-II-18a low-dose group	7.5 mg/kg	137.25±67.22
MAGLZ-II-18a middle-dose group	15 mg/kg	191.50±63.66##
MAGLZ-II-18a high-dose group	30 mg/kg	252.25±30.99###
MAGLZ-II-11 low-dose group	7.5 mg/kg	222.5±35.52###
MAGLZ-II-11 middle-dose group	15 mg/kg	326.88±45.9###
MAGLZ-II -11 high-dose group	30 mg/kg	336.88±33.09###
MAGLZ-II-10 low-dose group	7.5 mg/kg	113.25±23.31
MAGLZ-II-10 middle-dose group	15 mg/kg	125.25±19.31
MAGLZ-II -10 high-dose group	30 mg/kg	148.00±30.23 [#]
MAGLZ-II-11a low-dose group	7.5 mg/kg	136.75±33.22
MAGLZ-II-11a middle-dose group	15 mg/kg	256.88±42.93###
MAGLZ-II-11a high-dose group	30 mg/kg	300.63±45.26###
MAGLZ-II-18c low-dose group	7.5 mg/kg	148.00±30.23 [#]
MAGLZ-II-18c middle-dose	15 mg/kg	198.63±21.36###

group

MAGLZ-II -18c high-dose group 30 mg/kg 237.13±28.75^{###}

MAGLZ-II-18 low-dose group 7.5 mg/kg 186.5±51.71^{##}

MAGLZ-II-18 middle-dose group 15 mg/kg 212.63±46.02^{###}

MAGLZ-II -18 high-dose group 30 mg/kg 241.5±41.63^{###}

[00237] Compared with the model group, [#]P<0.05, ^{##}P<0.01, ^{###}P<0.001.

[00238] It can be seen from the experimental results shown in Table 11 that compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a, MAGLZ-II-18 and MAGLZ-II-18c of the present invention may significantly extend the blood coagulation time.

Table 12 Influences of the MAGL inhibitor of the present invention on the times of tail suspension

Grouping	Dose	Times
Normal group	-	22.38±3.38
Model group	-	8.38±2.62 ^{***}
Zolmitriptan	0.5 mg/kg	18.13±3.94 ^{###}
MAGLZ-II-18a low-dose group	7.5 mg/kg	11.38±2.67 [#]
MAGLZ-II-18a middle-dose group	15 mg/kg	13.38±2.67 ^{##}
MAGLZ-II-18a high-dose group	30 mg/kg	18.50±2.00 ^{###}
MAGLZ-II-10 low-dose group	7.5 mg/kg	9.25±2.66
MAGLZ-II -10 middle-dose group	15 mg/kg	10.63±1.19 [#]
MAGLZ-II -10 high-dose group	30 mg/kg	11.63±1.85 [#]

MAGLZ-II-11 low-dose group	7.5 mg/kg	14.13±1.89 ^{###}
MAGLZ-II -11 middle-dose group	15 mg/kg	16.13±1.73 ^{###}
MAGLZ-II -11 high-dose group	30 mg/kg	23.00±3.59 ^{###}
MAGLZ-II-11a low-dose group	7.5 mg/kg	16.13±3.68 ^{###}
MAGLZ-II-11a middle-dose group	15 mg/kg	19.88±4.09 ^{###}
MAGLZ-II-11a high-dose group	30 mg/kg	20.75±4.98 ^{###}
MAGLZ-II-18c low-dose group	7.5 mg/kg	10.13±2.3 ^{##}
MAGLZ-II -18c middle-dose group	15 mg/kg	12.75±2.6 ^{##}
MAGLZ-II -18c high-dose group	30 mg/kg	15.88±3.8 ^{###}
MAGLZ-II-18 low-dose group	7.5 mg/kg	11.88±4.02 ^{###}
MAGLZ-II -18 middle-dose group	15 mg/kg	13.75±4.56 ^{###}
MAGLZ-II -18 high-dose group	30 mg/kg	16.51±4.38 ^{###}

[00239] Compared with the model group, [#]P<0.05, ^{##}P<0.01, ^{###}P<0.001.

[00240] It can be seen from the experimental results shown in Table 12 that compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a, MAGLZ-II-18 and MAGLZ-II-18c of the present invention may significantly increase the times of the tail suspension activity.

Table 13 Influences of the MAGL inhibitor of the present invention on a brain tissue 5-hydroxytryptamine

Grouping	Dose	5-HT (nmol/g)
Normal group	-	3.36±0.4
Model group	-	0.88±0.23 ^{***}
Zolmitriptan	0.5 mg/kg	1.93±0.37 ^{###}

MAGLZ-II-18a low-dose group	7.5 mg/kg	1.21±0.17 ^{##}
MAGLZ-II-18a middle-dose group	15 mg/kg	1.65±0.18 ^{###}
MAGLZ-II-18a high-dose group	30 mg/kg	2.76±0.34 ^{###}
MAGLZ-II-10 low-dose group	7.5 mg/kg	0.85±0.20
MAGLZ-II -10 middle-dose group	15 mg/kg	1.05±0.14
MAGLZ-II -10 high-dose group	30 mg/kg	0.90±0.21 [#]
MAGLZ-II-11 low-dose group	7.5 mg/kg	1.54±0.27 ^{###}
MAGLZ-II -11 middle-dose group	15 mg/kg	2.10±0.22 ^{###}
MAGLZ-II -11 high-dose group	30 mg/kg	3.63±5.34 ^{###}
MAGLZ-II-11a low-dose group	7.5 mg/kg	1.35±0.38 ^{##}
MAGLZ-II-11a middle-dose group	15 mg/kg	1.86±0.29 ^{###}
MAGLZ-II-11a high-dose group	30 mg/kg	2.97±0.28 ^{###}
MAGLZ-II-18c low-dose group	7.5 mg/kg	1.14±0.22 [#]
MAGLZ-II -18c middle-dose group	15 mg/kg	1.37±0.34 ^{##}
MAGLZ-II -18c high-dose group	30 mg/kg	1.79±0.32 ^{###}
MAGLZ-II-18 low-dose group	7.5 mg/kg	1.13±0.45 [#]
MAGLZ-II -18 middle-dose group	15 mg/kg	1.54±0.54 ^{###}
MAGLZ-II -18 high-dose group	30 mg/kg	2.08±0.59 ^{###}

[00241] Compared with the model group, [#]P<0.05, ^{##}P<0.01, ^{###}P<0.001.

[00242] It can be seen from the experimental results shown in Table 13 that compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a, MAGLZ-II-18 and MAGLZ-II-18c of the present invention may significantly increase the level of 5-HT in the brain tissue of reserpine-induced low 5-HT model mice.

[00243] **Example 45 Study on the effect of the MAGL inhibitor on mice ulcerative colitis**

[00244] **1. Animal grouping and administration**

[00245] Healthy male SPF-level BALB/c mice (8-week old and body mass: (20±2) g).

[00246] The mice were quarantined for 7 d after entering to a room, and healthy male mice were selected as subject animals. Major examination contents within the quarantine period include but not limited to: whether to be consistent with the quantity and body indicators of the animals required during application, general state, and body weight; animals not passing through the above quarantine items were not brought into the test.

[00247] Modeling: the mice were randomly divided into 21 groups at the end of the quarantine, 10 pieces for each group. The mice in the normal group drank normal water freely, and the rest groups of mice drank 1.0%-1.5% DSS solution freely for modeling, 7 d later after modeling, the mice in the modeling group drank normal water freely for 7 d, and 14 d served as a modeling period for four continuous periods, and the mice in the modeling group were administered at the same time.

[00248] Blank group: an equal volume of 0.5% sodium carboxymethylcellulose, ig

[00249] Model group: an equal volume of 0.5% sodium carboxymethylcellulose, ig

[00250] Positive control group: Mesalazine (100 mg/kg), ig

MAGLZ-II-11 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11 middle-dose group: 15 mg/kg, ig

MAGLZ-II-11 high-dose group: 30 mg/kg, ig

MAGLZ-II-11a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-11a middle-dose group: 15 mg/kg, ig

MAGLZ-II-11a high-dose group: 30 mg/kg, ig

MAGLZ-II-18a low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18a middle-dose group: 15 mg/kg, ig

MAGLZ-II-18a high-dose group: 30 mg/kg, ig

MAGLZ-II-18 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18 middle-dose group: 15 mg/kg, ig

MAGLZ-II-18 high-dose group: 30 mg/kg, ig

MAGLZ-II-18c low-dose group: 7.5 mg/kg, ig

MAGLZ-II-18c middle-dose group: 15 mg/kg, ig

MAGLZ-II-18c high-dose group: 30 mg/kg, ig

MAGLZ-II-10 low-dose group: 7.5 mg/kg, ig

MAGLZ-II-10 middle-dose group: 15 mg/kg, ig

MAGLZ-II-10 high-dose group: 30 mg/kg, ig

[00251] Each compound was prepared into a suspension by 0.5% sodium carboxymethylcellulose respectively, and then set according to the dose, and each administration group was administered intragastrically; the model group was administered intragastrically an equal volume of 0.5% sodium carboxymethylcellulose.

[00252] 2. Test process and method

[00253] End point of the experiment: experimental administration was performed for four periods, and dissection was performed on the 3rd and 4th day of the recovery period of the 4th period.

[00254] Test indicators: the mice were weighed twice a week after the beginning of the administration; diarrhea and hematochezia of the mice were observed,

and times of hematochezia were recorded.

[00255] At the end of the experiment, the mice were dissected and weighed, and narcotized to take blood, then serum was preserved at -80°C. Spleen was taken and weighed to calculate the spleen index. The content of IL-1 β in serum was detected via ELISA. Colorectum was cut and taken to measure the length of colorectum, then immobilized by formaldehyde and dyed by HE to detect the pathological change.

Data is presented by a mean $\pm$ SD, and the difference among groups is subjected to statistics with t tests or a one-way ANOVA method, and P<0.05 shows a significant difference.

[00256] 3. Result and discussion

[00257] Experimental results are shown in Table 14.

Table 14 Influences of the MAGL inhibitor of the present invention on the colon length, hematochezia times and IL-1 content of ulcerative colitis mice

Group	Qua	Colon	length	Total	times	of IL-1	content
	ntity	(cm)		hematochezia	within	(pg/mL)	
				the four periods			
Blank group	10	8.22 $\pm$ 1.45		0 $\pm$ 0		35.36 $\pm$ 5.92	
Model group	10	5.70 $\pm$ 0.78 ^{###}		38.60 $\pm$ 2.80 ^{###}		55.53 $\pm$ 3.62 ^{###}	
Mesalazine (100 mg/kg)	10	6.66 $\pm$ 0.68 ^{**}		32.80 $\pm$ 4.96 ^{**}		48.33 $\pm$ 6.49 ^{**}	
MAGLZ-II-11 low-dose group	10	6.88 $\pm$ 0.89 ^{**}		32.00 $\pm$ 4.94 ^{**}		44.57 $\pm$ 10.32 ^{**}	
MAGLZ-II-11 middle-dose group	10	7.26 $\pm$ 0.67 ^{***}		27.20 $\pm$ 5.39 ^{***}		41.40 $\pm$ 9.50 ^{***}	
MAGLZ-II-11 high-dose group	10	7.68 $\pm$ 0.75 ^{***}		24.80 $\pm$ 5.43 ^{***}		33.83 $\pm$ 7.14 ^{***}	

MAGLZ-II-18a low-dose group	10	6.51±0.90*	33.60±5.83**	47.32±9.06*
MAGLZ-II-18a middle-dose group	10	7.06±1.20**	29.90±8.95**	43.77±10.69**
MAGLZ-II-18a high-dose group	10	7.72±0.92***	27.90±7.28***	36.22±4.31***
MAGLZ-II-18c low-dose group	10	6.25±1.17	43.10±7.59	48.08±13.18
MAGLZ-II-18c middle-dose group	10	6.47±0.71*	43.20±5.31*	44.09±9.13**
MAGLZ-II-18c high-dose group	10	6.65±0.67**	31.80±6.6**	45.10±8.88**
MAGLZ-II-11a low-dose group	10	7.21±1.10**	28.80±7.04**	42.01±13.92**
MAGLZ-II-11a middle-dose group	10	7.20±0.97**	29.10±7.14**	40.70±8.50***
MAGLZ-II-11a high-dose group	10	7.56±0.74***	27.90±3.73***	38.61±10.98***
MAGLZ-II-10 low-dose group	10	5.92±0.66	38.40±5.02	51.81±7.86
MAGLZ-II-10 middle-dose group	10	5.72±0.60	38.20±7.83	50.83±7.79
MAGLZ-II-10 high-dose group	10	6.35±0.61*	35.15±4.52*	47.25±6.37*
MAGLZ-II-18 low-dose group	10	6.44±0.64*	32.80±4.64**	46.15±9.65*

MAGLZ-II-18 middle-dose group	10	6.37±0.39*	33.90±4.77*	49.01±5.65*
MAGLZ-II-18 high-dose group	10	6.73±0.63**	32.80±4.37**	46.98±7.56**

[00258] Compared with the blank group, #P<0.05, ##P<0.01, ###P<0.001;

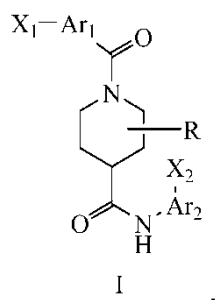
[00259] and compared with the model group, *P<0.05, **P<0.01 and ***P<0.001.

[00260] Compared with the model group, the MAGLZ-II-11, MAGLZ-II-11a, MAGLZ-II-18a, MAGLZ-II-18 and MAGLZ-II-18c of the present invention may significantly increase the colon length, reduce the total times of hematochezia and decrease the IL-1 content.

[00261] The present invention has been described by the above examples; any equivalent replacement is apparent and contained in the present invention.

CLAIMS

1. A compound of Formula I or a pharmaceutically acceptable salt thereof:



wherein R is H or C₁₋₅ alkyl, and the C₁₋₅ alkyl is selected from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, neo-butyl, n-pentyl, isopentyl, neo-pentyl, cyclopentyl, or C₁₋₅ alkyl substituted by halogen, hydroxy, carboxyl, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, and heteroaryl; the number of R is 0, 1, 2, 3 or 4;

Ar₁ is selected from the group consisting of diphenyl ether, benzofuryl, benzimidazolyl, benzoxazolyl, benzothiophenyl, quinolyl, isoquinolyl and purinyl;

Ar₂ are C₅₋₁₈ aryl;

X₁ and X₂ are respectively and independently one or more substituents selected from the group consisting of H, hydroxy, carboxyl, halogen, acyloxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, heteroaryl, and C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, and heteroaryl that are substituted by hydroxy, carboxyl, halogen and alkyl, at any substitution position.

2. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein the X₁ and the X₂ are respectively and independently one or more substituents selected from the group consisting of H, hydroxy, carboxyl, halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, heteroaryl, and C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ cycloalkyl, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, aryl, and heteroaryl that are substituted by hydroxy, carboxyl, halogen and alkyl, at any substitution position.

3. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein the X₁ and the X₂ are respectively and independently one or more substituents selected from the group consisting of H, hydroxy, halogen, acyloxy, C₁₋₃ alkyl, and C₁₋₃ alkoxy, at any substitution position.

4. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein the Ar₁ is one or more substituents selected from the group consisting of diphenyl ether, indolyl and biphenyl, at any substitution position.

5. The compound of Formula I or a pharmaceutically acceptable salt thereof according to claim 1, wherein if the R is H.

6. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein the X₁ and the X₂ are respectively and independently one or more substituents selected from the group consisting of H, hydroxy, halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₈ heterocyclyl, C₃₋₈ cycloalkoxy, and C₁₋₃ alkyl and C₁₋₃ alkoxy that are substituted by hydroxy, halogen and alkyl, at any substitution position.

7. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein,

the Ar₁ is diphenyl ether or biphenyl, at any substitution position;

the X₁ is one or more of H, methoxy, hydroxy, F and Cl, at any substitution position;

the Ar₂ is phenyl, at any substitution position; and

the X₂ is one or more of H, methyl, dimethyl, methoxy, hydroxy, F and Cl, at any substitution position.

8. The compound or a pharmaceutically acceptable salt thereof according to claim 5, wherein the Ar₁ has a substitution position of meta-position.

9. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein,

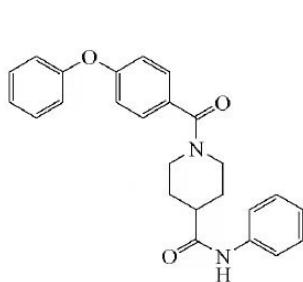
the Ar₁ is benzofuryl, benzimidazolyl, benzoxazolyl, benzothiophenyl, indolyl, quinolyl, isoquinolyl or purinyl, at any substitution position;

the X₁ is one or more substituents selected from the group consisting of H, methyl, methoxy, hydroxy, F, Cl and Br, at any substitution position;

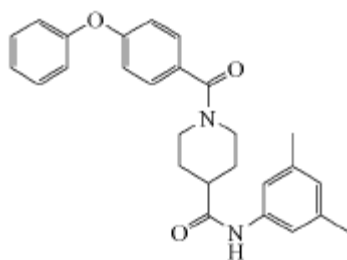
the Ar₂ is phenyl, at any substitution position;

the X₂ is one or more substituents selected from the group consisting of H, methyl, dimethyl, methoxy, hydroxy, F and Cl, at any substitution position.

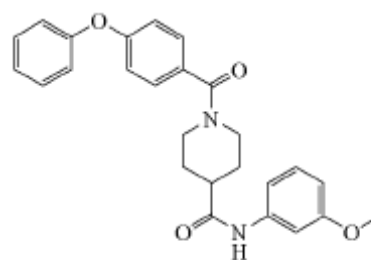
10. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



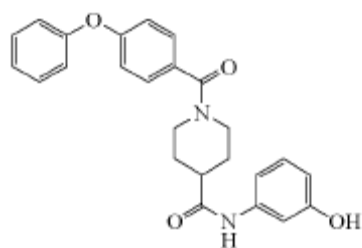
MAGLZ-II-01



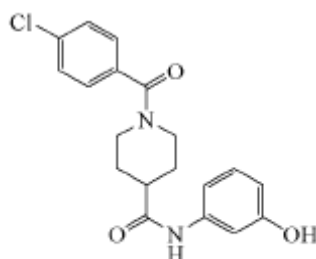
MAGLZ-II-02



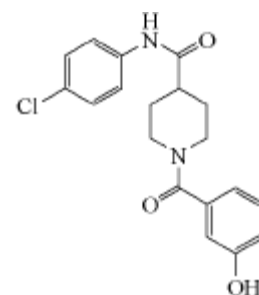
MAGLZ-II-03



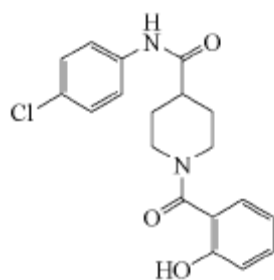
MAGLZ-II-04



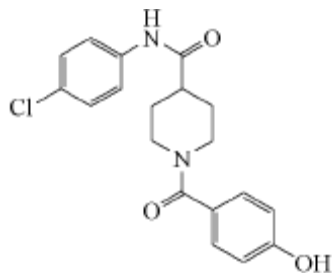
MAGLZ-II-06



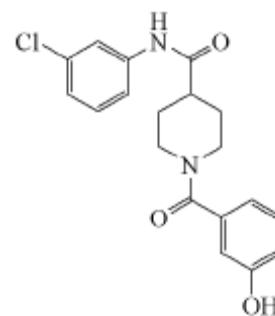
MAGLZ-II-08



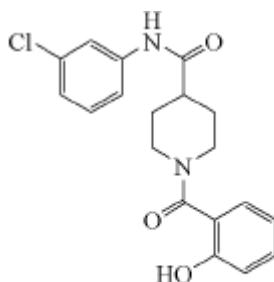
MAGLZ-II-09



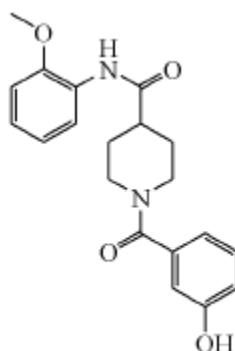
MAGLZ-II-10



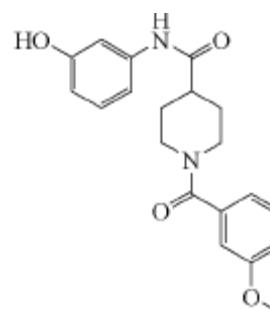
MAGLZ-II-11



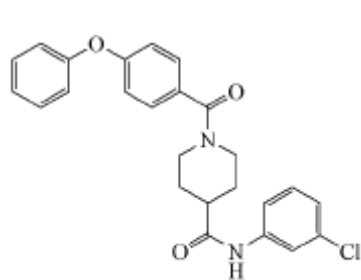
MAGLZ-II-12



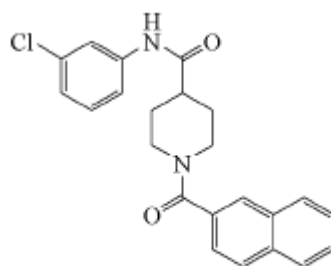
MAGLZ-II-13



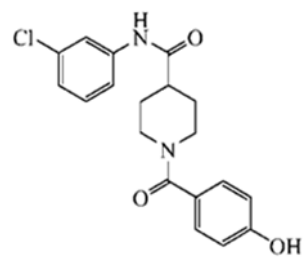
MAGLZ-II-15



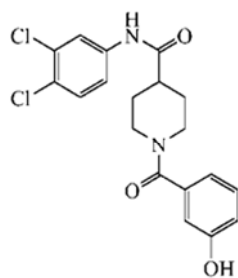
MAGLZ-II-16



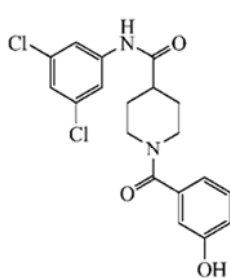
MAGLZ-II-17



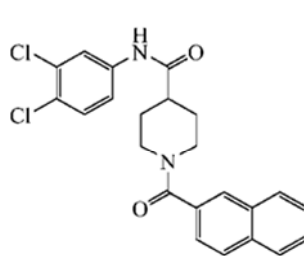
MAGLZ-II-20



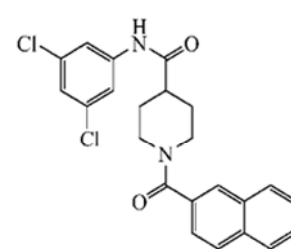
MAGLZ-II-22



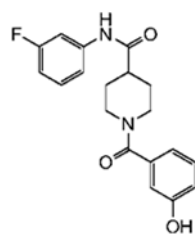
MAGLZ-II-23



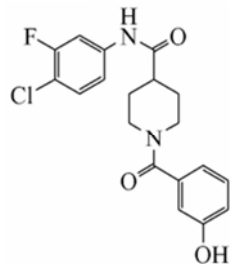
MAGLZ-II-24



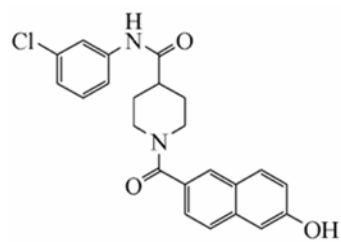
MAGLZ-II-25



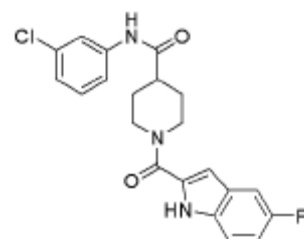
MAGLZ-II-26



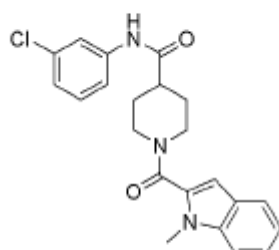
MAGLZ-II-27



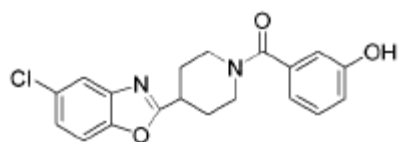
MAGLZ-II-29



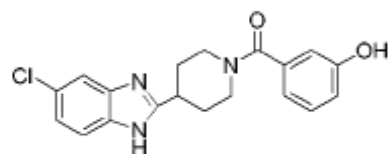
MAGLZ-II-18(a)



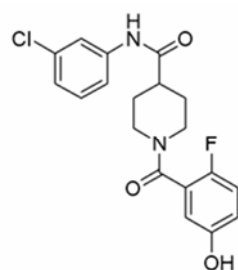
MAGLZ-II-18(c)



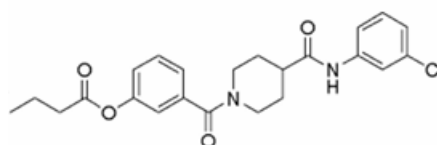
MAGLZ-II-30



MAGLZ-II-31

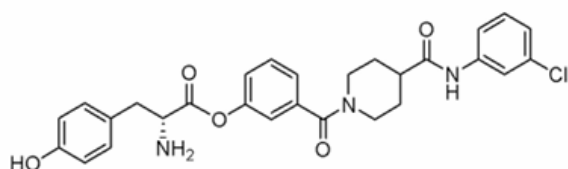


MAGLZ-II-11(a)

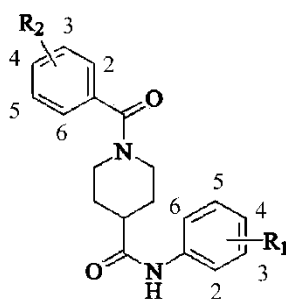


MAGLZ-II-11F

and

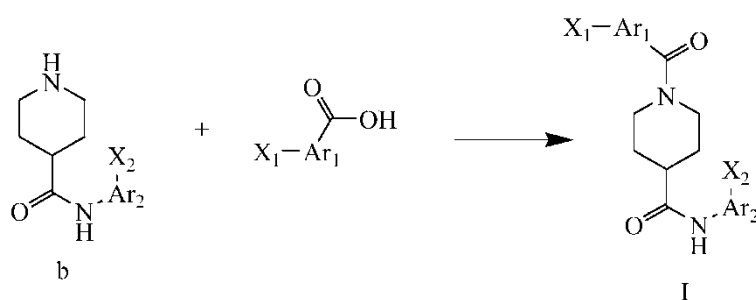


MAGLZ-II-11J



11. A compound of Formula III or a pharmaceutically acceptable salt thereof, wherein the R_1 is selected from hydroxy, F, Cl, Br, I, methyl, ethyl, propyl, and methoxy; the R_2 is selected from I, ethyl, and propyl; the number of the R_1 and the R_2 is 0, 1, 2, 3, or 4; the link mode between the R_1 , the R_2 and nucleus is not limited to a single connection via a single bond.

12. A method of synthesizing the compound of Formula I, comprising the following specific



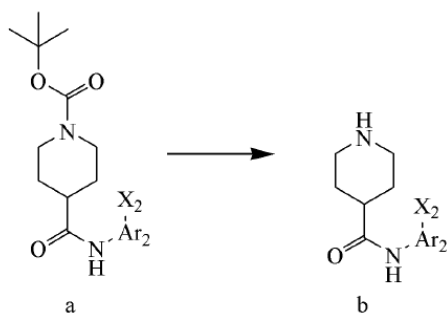
steps:

reacted with X_1-Ar_1-COOH to obtain I; the X_1 , the X_2 , the Ar_1 and the Ar_2 are as described in claim 1.

13. The synthesizing method according to claim 12, wherein the b or the salt of b is reacted

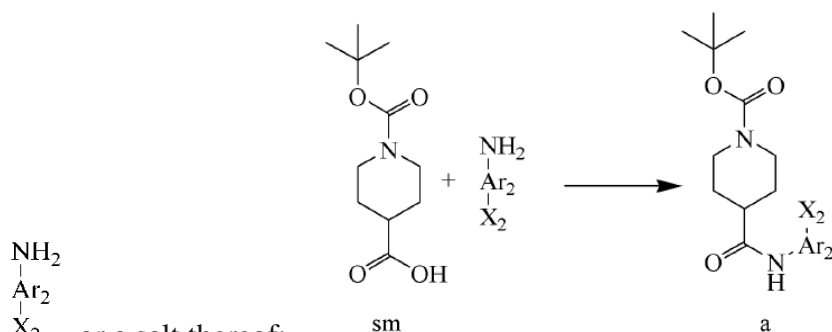
with $\text{X}_1-\text{Ar}_1-\text{COOH}$ to obtain I; a condensating agent and an alkali are added in this step to facilitate the reaction; wherein, the condensating agent is selected from HBTU, DMC, HOBT, HOBT/EDCI, HATU, HATU/DIEPA, DCC, CDI, and isopropyl chloroformate.

14. The synthesizing method according to claim 12, wherein the b or the salt of b is obtained



by deprotection of a;

15. The synthesizing method according to claim 12, wherein the a or the salt of a is obtained



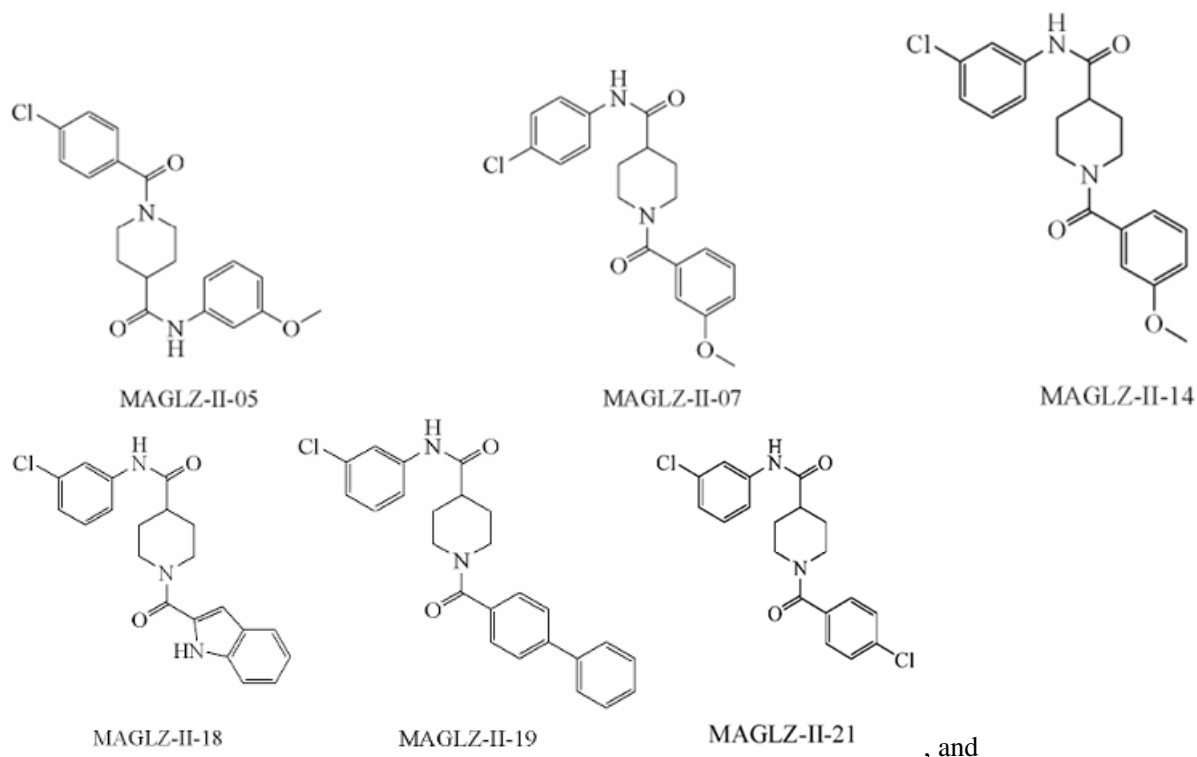
by reacting sm with $\text{NH}_2-\text{Ar}_2-\text{X}_2$ or a salt thereof;

16. A pharmaceutical composition, comprising the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-11, and a pharmaceutically acceptable carrier.

17. Use of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-11 in the preparation of a medicament for treating a MAGL-mediated disease or condition, wherein the MAGL-mediated disease or condition is selected from the group consisting of: metabolic disorders, nephrosis, emesis or vomiting or nausea, eating disorders, neuropathy, schizophrenia, depressive disorders, bipolar disorders, fremitus, dyskinesia, abstinence syndromes, traumatic brain injury, non-traumatic brain injury, spinal cord injury, epileptic seizure, conditions associated with abnormal cell growth or proliferation [such as, benign tumors or cancers], inflammatory conditions, immune system conditions, irritable bowel syndromes, ulcer colonitis, acute stress disorders, substance-inducing anxiety,

obsessive-compulsive disorders, anxiety disorders; attention deficiency disorders, attention deficit hyperactivity disorders, pains, migraine, demyelinating diseases, and cognitive impairments.

18. Use of a compound or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a MAGL-mediated disease or condition, wherein the compound is selected from the group consisting of:



the MAGL-mediated disease or condition is selected from the group consisting of: metabolic disorders, nephrosis, emesis or vomiting or nausea, eating disorders, neuropathy, schizophrenia, depressive disorders, bipolar disorders, fremitus, dyskinesia, abstinence syndromes, traumatic brain injury, non-traumatic brain injury, spinal cord injury, epileptic seizure, conditions associated with abnormal cell growth or proliferation [such as, benign tumors or cancers], inflammatory conditions, immune system conditions, irritable bowel syndromes, ulcer colitis, acute stress disorders, substance-inducing anxiety, obsessive-compulsive disorders, anxiety disorders; attention deficiency disorders, attention deficit hyperactivity disorders, pains, migraine, demyelinating diseases, and cognitive impairments.