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(54) Titre : APPLICATION ANTI-CORONAVIRUS DE L'INHIBITEUR DE LA POLY ADP-RIBOSE POLYMERASE
(54) Title: APPLICATION OF POLY ADP-RIBOSE POLYMERASE INHIBITORS IN CORONA VIRUS RESISTANCE

(57) **Abrégé/Abstract:**

Provided is application of a poly ADP ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof in the preparation of antiviral agents or in the preparation of medicines for the treatment of diseases caused by viruses, wherein the viruses are β -coronaviruses. Also provided is application of a compound represented by formula III and/or a compound represented by formula IV or a pharmaceutically acceptable salt thereof in the preparation of antiviral agents or in the preparation of medicines for treatment of diseases caused by viruses, the viruses being HIV, HPV, EBV, IFV and/or coronaviruses. The poly ADP ribose polymerase inhibitor comprises a compound represented by formula III and/or a compound represented by formula IV or a pharmaceutically acceptable salt thereof, and can achieve a lower effective concentration for inhibiting viruses and a higher antiviral activity while ensuring low toxicity and high safety when being used in human bodies, so that in the application to the clinical treatment of diseases caused by coronaviruses, the present inhibitor can effectively inhibiting the viruses.



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Abstract:

Provided is application of a poly ADP ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof in the preparation of antiviral agents or in the preparation of medicines for the treatment of diseases caused by viruses, wherein the viruses are -coronaviruses. Also provided is application of a compound represented by formula III and/or a compound represented by formula IV or a pharmaceutically acceptable salt thereof in the preparation of antiviral agents or in the preparation of medicines for treatment of diseases caused by viruses, the viruses being HIV, HPV, EBV, IFV and/or coronaviruses. The poly ADP ribose polymerase inhibitor comprises a compound represented by formula III and/or a compound represented by formula IV or a pharmaceutically acceptable salt thereof, and can achieve a lower effective concentration for inhibiting viruses and a higher antiviral activity while ensuring low toxicity and high safety when being used in human bodies, so that in the application to the clinical treatment of diseases caused by coronaviruses, the present inhibitor can effectively inhibiting the viruses.

Abstract

The present invention provides an application of a polyADP-ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof in the preparation of antiviral agents or in the preparation of drugs for the treatment of diseases caused by viruses, wherein the viruses are viruses of the genus β coronaviruses. The present invention also provides the application of the compounds shown in Equation III and/or the compounds shown in Equation IV or their pharmaceutically acceptable salts in the preparation of antiviral agents or in the preparation of drugs for diseases caused by viruses, which are HIV, HPV, EBV, IFV and/or viruses of the coronavirus family. The polyADP-ribose polymerase inhibitors mentioned in the present invention include the compounds shown in Equation III and/or the compounds shown in Equation IV or their pharmaceutically acceptable salts, which have a lower effective concentration and a higher antiviral activity in the inhibition of viruses, ensuring less toxicity and higher safety when used in humans. Therefore, it can play an effective role in suppressing the virus when it is applied to the clinical treatment of diseases caused by coronavirus.

Application of Poly ADP-ribose Polymerase Inhibitors in Corona Virus Resistance

This application requires priority for Chinese patent application 2020101117554 filed on 2020/2/24. This application refers to the full text of the above Chinese patent application.

Technical Field

The invention belongs to the field of biomedical technology, especially involving drugs with poly (ADP-ribose) polymerase inhibitors as the main component and their pharmaceutically acceptable salts as well as drug compositions and kit kits containing them, for application against coronavirus diseases.

Background Technology

Coronavirus (CoV) is an enveloped single-stranded positive-sense RNA virus that can infect humans and a variety of animals, has respiratory, gastrointestinal and nervous system tropism, can cause serious diseases in livestock and companion animals (such as pigs, cattle, chickens, dogs, cats) and can cause diseases ranging from the common cold to severe acute respiratory syndrome in humans. The ninth report of the International Committee on Taxonomy of Viruses divided coronaviruses into four groups: α 、 β 、 γ and δ according to their evolutionary characteristics, of which the hosts of groups α and β were mainly mammals, and groups γ and δ were mainly found in birds and birds.

As of February 2020, there are currently seven known coronaviruses can infect humans, including human coronavirus 229E (HCoV-229E), NL63 (HCoV-NL63), HKU1 (HCoV-HKU1), OC43 (HCoV-OC43), and Middle East respiratory syndrome coronavirus (MERS-CoV), which cause symptoms of upper respiratory tract infection, and severe acute respiratory syndrome (SARS) -related coronaviruses: coronavirus SARS-CoV (severe acute respiratory syndrome coronavirus) and SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2). Coronavirus causes 15% to 30% of respiratory infections in people each year, causing more severe disease in newborns, the elderly, and other susceptible populations, who have a higher incidence of lower respiratory tract infections. Among them, the mortality rates of SARS-CoV and MERS-CoV, coronavirus with high mortality, were as high as 10% and 36%, respectively. The novel coronavirus SARS-CoV-2, which mainly broke out in Hubei, China from 2019 to early 2020, caused more than 70,000 infections and could lead to severe COVID-19

pneumonia (novel coronavirus pneumonia), with a severe rate in the range of 15 – 30% and a fatality rate of about 2%, again aroused great attention to coronavirus. However, there is no approved specific drug for the treatment of coronavirus infections, and even for patients with severe acute respiratory tract infections caused by SARS-CoV, SARS-CoV-2, and MERS-CoV infections, symptomatic treatment is mainly used to reduce patient complications in clinical practice. Therefore, there is an urgent need to develop effective drugs to treat coronavirus infections.

Small molecule compounds are a hot topic in antiviral drug candidates. Exploring the new uses of existing drugs has become an important way of drug research and development. Because candidate drugs have pharmacodynamic testing, functional targets and clinical safety data, which are conducive to further toxicological evaluation, pharmacokinetic evaluation and preparation research and development, they can greatly reduce R & D risks, shorten R & D time and R & D costs, and have broad application prospects.

At present, most of the clinical first-line treatments for coronavirus infections are broad-spectrum antivirals, such as the anti-HIV drugs lopinavir/ritonavir (Crizil), abidol, and the anti-Ebola virus drug repassivir. Abidol (also known as Arbidol) is a broad-spectrum antiviral drug that mainly treats upper respiratory tract infections caused by influenza A and B viruses, and has been shown to have some inhibitory activity against SARS-CoV and MERS-CoV coronavirus in recent years. On February 4, 2020, the latest research results of Li Lanjuan's team showed in vitro cell experiments that abidol could effectively inhibit coronavirus by 60-fold at concentrations of 10 to 30 micromoles compared with the drug-untreated control group, and significantly inhibit the cytopathic effect of the virus on cells. However, judging from the current data, concentrations of 10 to 30 micromoles are difficult to achieve in current clinical treatment. «In the novel coronavirus pneumonia diagnosis and treatment program (trial sixth edition), the recommended dosage of abidol is 200 mg three times a day. However, according to the package insert of "Abidol Tablets (Manosu)", after a single oral dose of Abidol 200 mg, 400 mg and 600 mg in subjects, the peak concentrations were 614.1 ± 342.5 ng/mL, 904.2 ± 355.6 ng/mL and 975.1 ± 661.0 ng/mL, respectively, which were only equivalent to 1-2 micromolar levels and much lower than the in vitro inhibitory concentrations, and it was speculated that it could only exert limited in vivo antiviral activity. At the same time, the package insert shows that the incidence of adverse events of Abidol is about 6.2%, mainly manifested as nausea, diarrhea, dizziness and increased

serum transaminases, and in the human bioequivalence trial of domestic Abidol preparations that requires vigilance at the same time, some healthy subjects experienced bradycardia (the heart rate of some healthy subjects was less than 60 beats/min after 3 hours of medication, and the heart rate decreased between 2 and 24 beats/min). The relationship of this event to the drug is unknown. In addition, it should be used with caution or as directed by a physician in pregnant and lactating women and those with severe renal insufficiency. The significance of this drug for patients with sinus node disease or dysfunction is not clear, so it is currently recommended that this product be carefully considered in this population. According to the above data, it is speculated that even existing drugs listed as recommended treatments are not the best choice for the treatment of coronavirus due to their low antiviral activity, insufficient clinical evidence and safety issues.

In addition to Abidol, other antiviral drugs are also undergoing in vitro screening and clinical trials against novel coronavirus. But there is evidence that not all antiviral drugs are effective against novel coronavirus. Among them, the anti-AIDS drug Kelizhi is not effective in the treatment of pneumonia caused by novel coronavirus infection, and has toxic and side effects, and is no longer recommended to continue to use. Redexivir, which is undergoing clinical studies, also carries a serious risk of hepatotoxicity. Therefore, according to the existing evidence and experience, the treatment of coronavirus has its particularity, and it is still necessary to develop drugs with independent intellectual property rights, innovative mechanism of action, good efficacy and safety.

Poly (ADP-ribose) polymerases (PARP) play an important role in DNA damage repair and apoptosis, and are also involved in a series of cellular processes including infection and immune regulation. This protein family consists of 17 members, including PARP1, PARP2, etc. Industry development of PARP inhibitors was initially hoped to exert anticancer effects by blocking DNA damage repair in highly mutated cancer cells, thereby using the accumulation of "toxic damage" and "synergistic lethality" effects. Currently, there are four PARP inhibitors marketed worldwide, olaparib, niraparib, rukaparib, and talazoparib. At the same time, several PARP inhibitors at home and abroad have entered the clinical study stage, including fluzoparib, furosemide, simepride, IMP4297, BGB-290, ABT-888 and so on.

According to the literature, PARP may be closely related to viral invasion, integration, replication and capsid protein formation. In 2001, Hyo Chol Ha et al. reported that PARP-1

enzyme plays a key role in HIV-1 replication, integration and transcription during HIV viral replication, and PARP inhibitors were mentioned to help inhibit HIV virus infection in Proc Natl Acad Sci U S A. 2001; 98 (6): 3364 – 8; it was also reported that PARP-1 could also inhibit the nuclear localization of PARP-1 by participating in the transcriptional expression of NF-KB stimulator gene in the inflammatory pathway, thereby inhibiting the NF-KB transcriptional pathway and achieving the effect of inhibiting viral replication. Finally, PARP-1 can induce apoptosis of immune cells, including T cells, so inhibition of PARP-1 may block the integration of HIV in host cells, so as to achieve the effect of treating AIDS. Similar findings have been shown in HPV, EBV, HSV, etc. Tempera et al demonstrated in 2010 that PARP1 inhibitors inhibit Epstein-Barr virus (J Virol. 2010; 84 (10): 4988 – 97.). In 2012, Grady et al demonstrated that PARP1 inhibitors inhibited HSV virus (J Virol. 2012; 86 (15): 8259 – 68.). In 2017, Matthew E. Grunewald et al proposed that the capsid protein of coronavirus is ADP ribosylation modified and speculated that some isoforms of PARP are involved in coronavirus capsid protein formation (Virology. 2018, 517: 62 – 68), but it does not further explain which PARP isoform selectivity is extremely important, nor does it suggest whether PARP inhibitors can inhibit viral replication or capsid protein formation. On the other hand, 2016, Chad. V. Kuny et al. published an article discussing the role of PARP enzymes in virus-host interactions. Among them, PARP13 can degrade viral reverse RNA and thus block viral replication, and PARP10, 12, 13, and 14 can inhibit viral replication through interferon production (PLoS pathogens, 2016, 12 (3): e1005453). In 2019, Matthew E. Grunewald mentioned in his article that PARP enzymes function as both antiviral and immunomodulatory agents, confirming that the presence of PARP12 and PARP14 can inhibit viral invasion and replication (PLoS pathogens, 2019, 15 (5): e1007756). It can be seen that some subtypes of PARP enzymes instead inhibit viral infection. At present, the function of PARP is inconclusive at home and abroad, and the inhibitory effect of PARP inhibitors on various viruses is not clear.

In summary, it is urgent to seek drugs that can effectively inhibit the virus at lower effective concentrations and higher antiviral activity when ensuring high medication safety and less side effects, so as to apply them to clinical treatment of coronavirus diseases.

Invention Contents

The technical problem to be solved by the present invention is that, in order to overcome

such problems as the high effective concentration of drugs used in the existing technology for the treatment of coronavirus diseases that can function, the antiviral activity is not strong enough to exert the antiviral activity in vivo when used in clinical practice, a poly (ADP-ribose) polymerase (PARP) inhibitor or its pharmaceutically acceptable salt, and the drug composition and kit containing it are provided for the application in antiviral, such as coronavirus, and the antiviral can be the use of the PARP inhibitor of the present invention as an antiviral agent or the use of the PARP inhibitor to treat diseases caused by the virus. The poly (ADP-ribose) polymerase inhibitors or pharmaceutically acceptable salts thereof, and drug compositions and kit kits thereof are more effective in inhibiting viruses when applied to the clinic for the treatment of coronavirus induced diseases, provided that they have less toxicity and higher safety when used in humans.

After a large number of experiments, the invention accidentally finds that poly (ADP-ribose) polymerase inhibitors or their pharmaceutically acceptable salts can significantly inhibit coronavirus replication in vitro. The invention is the first to demonstrate that poly (ADP-ribose) polymerase inhibitors or pharmaceutically acceptable salts can inhibit coronavirus infection of host cells and coronavirus replication and can be used for disease treatment against coronavirus infection, which is of great significance for the prevention, control and treatment of coronavirus infection, especially coronavirus SARS-CoV-2.

In order to solve the technical problems mentioned above, the first aspect of the invention provides a poly (ADP-ribose) polymerase inhibitor or its pharmaceutically acceptable salt for use in preparing antiviral agents or in preparing drugs for the treatment of diseases caused by viruses, which are viruses of the genus Betacoronavirus.

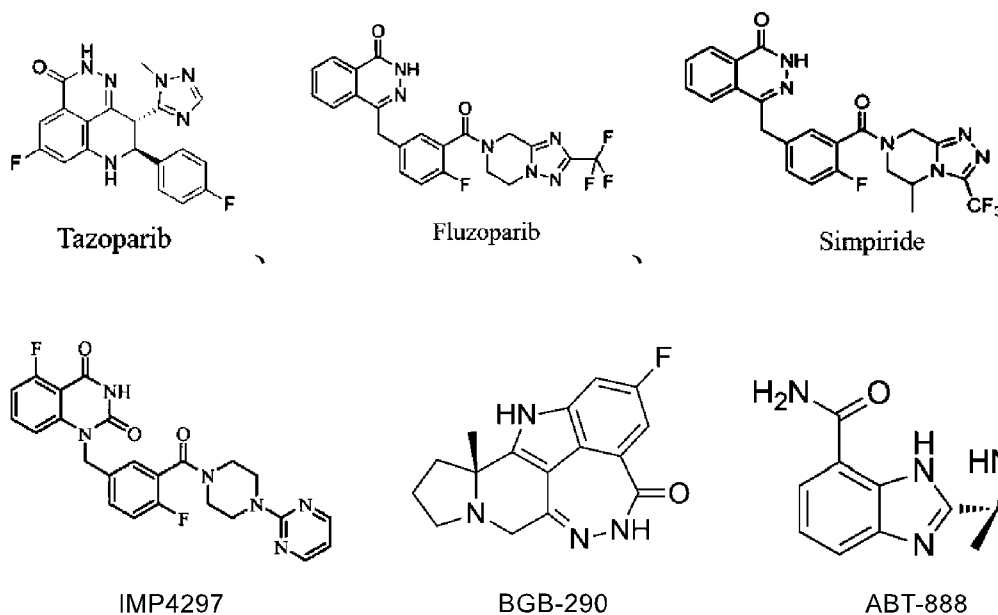
In the present invention, the SARS-associated coronavirus is the coronavirus causing severe acute respiratory syndrome (SARS). The diseases caused by SARS-related coronavirus are symptoms or diseases caused by viral infections, which are mainly reflected in respiratory diseases in the early stage and are clinically characterized by fever, fatigue, dry cough, cough, accelerated breathing or acute respiratory distress syndrome, shortness of breath, etc., and a few patients are accompanied by nasal congestion, runny nose, sore throat and other symptoms. Imaging findings showed varying degrees of lung changes such as multiple spots and ground-glass opacities, and the main mode of transmission of the virus was close droplet transmission or contact with respiratory secretions of patients. Gastrointestinal symptoms such

as diarrhea, acute gastroenteritis in infants and neonates, and rarely neurological syndromes may also be present. Many complications may occur in the later stage, including uncorrectable metabolic acidosis and bleeding and coagulation dysfunction, respiratory failure, fulminant myocarditis to heart failure, liver and kidney failure and other multiple organ failure and septic shock. Critically ill patients mostly present with dyspnea and/or hypoxemia one week after onset, and in severe cases rapidly progress to acute respiratory distress syndrome, septic shock, uncorrectable metabolic acidosis and coagulopathy, and multiple organ failure. These diseases are expected to be treated with PARP inhibitors of the present invention. In addition, some virus carriers do not experience the above symptoms, and PARP inhibitors described in this invention can also be used to inhibit viral replication and spread so as to avoid new cases of disease or transmission of the virus by the virus carriers. In a scheme, the viruses of the genus Betacoronavirus are those causing acute respiratory syndrome such as SARS-associated coronavirus; preferably, the SARS-associated coronavirus is SARS-CoV (severe acute respiratory syndrome coronavirus) and/or SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

In a protocol, the poly (ADP-ribose) polymerase inhibitors are those directed against PARP 1 and/or PARP2.

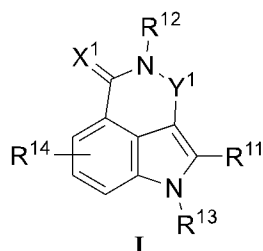
In a scheme, the poly (ADP-ribose) polymerase inhibitor is a solvent complex of substance A, its pharmaceutically acceptable salt, its solvent complex, or its pharmaceutically acceptable salt;

Substance A described was selected from Tazoparib, Fluzoparib, Simpiride, IMP4297, BGB-290, ABT-888, PARP inhibitors as described in CN1342161A, PARP inhibitors as described in CN1788000A, PARP inhibitors as described in CN103242273A, PARP inhibitors as described in CN101415686A, and one or more of PARP inhibitors as described in CN101578279A; this is only an example and does not exclude the possibility that Substance A could be selected from other compounds not listed here.

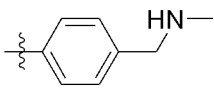


In the present invention, the term "selected from one or more of ..." includes the combination of the listed compounds. In some embodiments of the present invention, the combination of two or more compounds results in a better therapeutic effect.

In a scheme, the PARP inhibitors described in CN1342161A are compounds shown in Equation I;



Among them, R¹¹ is H, halogen, cyanide, alkyl of C₁ ~ C₄, alkene of C₂ ~ C₄, alkynyl of C₂ ~ C₄, naphthyl of C₃ ~ C₄, "containing 1 ~ 2 heteroatoms, heteroatoms selected from one or more of O, N and S, 3 ~ 6 membered" heteroalkyl groups, aryl of C₆ ~ C₁₀, "containing 1 ~ 2 heteroatoms, heteroatoms selected from one or more of O, N and S, 5 ~ 10 membered" heteroaryl groups, alkyl groups of C₁ ~ C₄ replaced by one or more R¹¹⁻¹, alkene groups of C₂ ~ C₄ replaced by one or more R¹¹⁻¹, alkynyl groups of C₂ ~ C₄ replaced by one or more R¹¹⁻¹, naphthyl groups of C₃ ~ C₄ replaced by one or more R¹¹⁻¹, and containing 1 ~ 2 heteroatoms replaced by one or more R¹¹⁻¹. The heteroatoms are selected from one or more heterocyclic alkyl groups in O, N and

S, 3-6 membered heterocyclic alkyl groups, the  groups of C₆ ~ C₁₀ replaced by

one or more R^{11-1} (described as aryl groups of $C_6 \sim C_{10}$ such as phenyl groups; described as aryl groups of $C_6 \sim C_{10}$ replaced by one R^{11-1} containing 1-2 heteroatoms replaced by one or more R^{11-1} , and the heteroatoms are selected from one or more heteroaryl groups in O, N and S, 5-10 membered heteroaryl groups, $-C(=O)-R^{11-2}$, $-C(=O)-O-R^{11-3}$ or $-C(=O)-NR^{11-4}R^{11-5}$;

R^{11-1} is independently halogen, hydroxyl, carboxyl, nitro, amino, alkyl of $C_1 \sim C_4$, or alkyl of $C_1 \sim C_4$ substituted by one or more $NR^{11-1-1}R^{11-1-2}$ (described as "alkyl of $C_1 \sim C_4$ " e.g. methyl); R^{11-1-1} and R^{11-1-2} are independently hydrogen or alkyl of $C_1 \sim C_4$ (e.g. methyl);

R^{11-2} , R^{11-3} , R^{11-4} , and R^{11-5} are alkyl of H, $C_1 \sim C_4$, alkyl of $C_2 \sim C_4$, alkyl of $C_2 \sim C_4$, naphthyl of $C_3 \sim C_4$, "containing 1 ~ 2 heteroatoms, heteroatoms are selected from one or more of O, N, and S, 3 ~ 6 membered" heteroalkyl of $C_6 \sim C_{10}$, and "containing 1 ~ 2 heteroatoms. The heteroatoms were selected from one or more of the "heteroaryl groups of 5 ~ 10 elements," alkyl groups of $C_1 \sim C_4$ replaced by one or more R^{11-2-1} , alkyl groups of $C_2 \sim C_4$ replaced by one or more R^{11-2-1} , alkynyl groups of $C_2 \sim C_4$ replaced by one or more R^{11-2-1} , naphthyl groups of $C_3 \sim C_4$ replaced by one or more R^{11-2-1} , "containing 1 ~ 2 heteroatoms replaced by one or more R^{11-2-1} , and heteroatoms were selected from one or more of the "heteroalkyl groups of 3 ~ 6 elements" in O, N, and S, aryl groups of $C_6 \sim C_{10}$ replaced by one or more R^{11-2-1} , or "containing 1 ~ 2 heteroatoms replaced by one or more R^{11-2-1} . The heteroatoms are selected from one or more heteroaryl groups in O, N and S, which are 5 ~ 10 elements;

R^{11-2-1} is independently halogen, hydroxyl, carboxyl, nitro, amino, or alkyl from C_1 to C_4 ;

Y^1 is - (CRY1-1RY1-2) (CRY1-3RY1-4) n- or -N = C (RY1-5) -;

N is 0 or 1;

R^{Y1-1} , R^{Y1-2} and R^{Y1-5} are independently alkyl groups of H, $C_1 \sim C_4$, alkene groups of $C_2 \sim C_4$, alkynyl groups of $C_2 \sim C_4$, naphthyl groups of $C_3 \sim C_4$, "containing 1 ~ 2 heteroatoms, heteroatoms selected from one or more of O, N and S, 3 ~ 6 membered" heteroalkyl groups of $C_6 \sim C_{10}$, "containing 1 ~ 2 heteroatoms, heteroatoms selected from one or more of O, N and S, 5 ~ 10 membered" heteroaryl groups of $C_1 \sim C_4$ substituted by one or more R^{Y1-1-1} , alkene groups of $C_2 \sim C_4$ substituted by one or more R^{Y1-1-1} , alkynyl groups of $C_2 \sim C_4$ substituted by one or more R^{Y1-1-1} , naphthyl groups of $C_3 \sim C_4$ substituted by one or more R^{Y1-1-1} , and "containing 1 ~ 2 heteroatoms of C_4 substituted by one or more R^{Y1-1-1} . The heteroatoms are selected from one or more heterocyclic alkyl groups of 3 ~ 6 membered in O, N and S, the aryl groups of $C_6 \sim C_{10}$ replaced by one or more R^{Y1-1-1} , or the heteroaryl groups of 1 ~ 2 heteroatoms replaced by one

or more R^{Y1-1-1} , and the heteroaryl atoms are selected from one or more heteroaryl groups of 5 ~ 10 membered in O, N and S;

R^{Y1-1-1} is independently halogen, hydroxyl, nitro, amino, alkyl from C_1 to C_4 , or alkoxy from C_1 to C_4 ;

R^{Y1-3} and R^{Y1-4} are independently H, alkyl groups of $C_1 \sim C_4$, alkyl groups of $C_2 \sim C_4$, alkynyl groups of $C_2 \sim C_4$, naphthyl groups of $C_3 \sim C_4$, "containing 1 ~ 2 heteroatoms, heteroatoms selected from one or more, 3 ~ 6 membered" heteroalkyl groups in O, N and S, aryl groups of $C_6 \sim C_{10}$, "containing 1 ~ 2 heteroatoms, heteroatoms selected from one or more, 5 ~ 10 membered" heteroaryl groups in O, N and S, alkyl groups of $C_1 \sim C_4$ replaced by one or more R^{Y1-3-1} , alkene groups of $C_2 \sim C_4$ replaced by one or more R^{Y1-3-1} , alkynyl groups of $C_2 \sim C_4$ replaced by one or more R^{Y1-3-1} , naphthyl groups of $C_3 \sim C_4$ replaced by one or more R^{Y1-3-1} , and "containing 1 ~ 2 heteroatoms replaced by one or more R^{Y1-3-1} . The heteroatoms are selected from one or more heterocyclic alkyl groups in O, N and S, 3-6 membered" heterocyclic alkyl groups, $C_6 \sim C_{10}$ aryl groups substituted by one or more R^{Y1-3-1} , or "1-2 heteroatoms substituted by one or more R^{Y1-3-1} , and heteroatoms are selected from one or more heteroaryl groups in O, N and S, 5-10 membered" heteroaryl groups.

R^{Y1-3-1} is independently halogen, hydroxyl, nitro, amino, alkyl of $C_1 \sim C_4$ or alkoxy of $C_1 \sim C_4$;

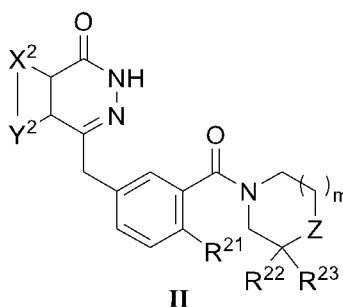
R^{12} is an alkyl group of H or $C_1 \sim C_4$;

X^1 is O or S;

R^{14} is an alkyl group of H, halogen (e.g., fluorine, chlorine, or bromine), or C_1 to C_4 ;

R^{13} is an alkyl group of H or C_1 to C_4 .

In a protocol, the PARP inhibitors described in CN1788000A are compounds shown in Equation II;



Among them, X^2 、 Y^2 and the carbon atom connected with them form the aryl group of $C_6 \sim C_{10}$ (such as phenyl group), or the aryl group of $C_6 \sim C_{10}$ replaced by one or more R^{X2-1} ;

R^{X2-1} is independently halogen, nitro, hydroxyl, thiol, amino, alkyl of $C_1 \sim C_7$, aryl of $C_6 \sim C_{20}$, "contains 1 ~ 6 heteroatoms, which are selected from one or more of O, N and S, 3 ~ 20 membered" heterocyclic groups, $-OR^{X2-1-1}$ or $-SR^{X2-1-2}$;

R^{X2-1-1} and R^{X2-1-2} are independently alkyl groups of $C_1 \sim C_7$, aryl groups of $C_6 \sim C_{20}$, or, "containing 1 ~ 6 heteroatoms, which are selected from one or more of O, N and S, and 3 ~ 20 membered" heterocyclic groups;

R^{Z1} is an H or halogen (e.g., fluorine, chlorine, or bromine);

Z is $-NR^{Z-1}$ - or $-CR^{Z-2}R^{Z-3}$ -;

When Z is $-NR^{Z-1}$ -, m is 1 or 2; when Z is $-CR^{Z-2}R^{Z-3}$ -, m is 1;

R^{Z-1} and R^{Z-2} are independently alkyl groups of $C_1 \sim C_{20}$, aryl groups of $C_6 \sim C_{20}$, "containing 1 ~ 6 heteroatoms, which are selected from one or more heterocyclic groups in O, N and S, 3 ~ 20 membered" heterocyclic groups, $-C(=O)NR^{Z-1-1}R^{Z-1-2}$, $-C(=O)R^{Z-1-3}$ (e.g.), $-C(=O)OR^{Z-1-4}$, $-C(=S)NR^{Z-1-5}R^{Z-1-6}$, $-S(=O)2R^{Z-1-7}$, alkyl groups of $C_1 \sim C_{20}$ substituted by one or more R^{Z-1-8} , aryl groups of $C_6 \sim C_{20}$ substituted by one or more R^{Z-1-9} , or "containing 1 ~ 6 heteroatoms replaced by one or more R^{Z-1-10} . The heteroatoms are selected from one or more heterocyclic bases of 3 ~ 20 elements in O, N and S.

R^{Z-1-1} , R^{Z-1-2} , R^{Z-1-3} , R^{Z-1-4} , R^{Z-1-5} , R^{Z-1-6} and R^{Z-1-7} are independently hydrogen, hydrocarbon group of $C_1 \sim C_7$, aryl group of $C_6 \sim C_{20}$, or, "containing 1 ~ 6 heteroatoms, which are selected from one or more of O, N and S, and heteroring groups of 3 ~ 20 elements";

Or, R^{Z-1-1} , R^{Z-1-2} and the carbon atoms connected with them form a "heterocyclic ring base containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

Or, R^{Z-1-5} , R^{Z-1-6} and the carbon atoms connected with them form a "heterocyclic ring base containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

R^{Z-1-8} , R^{Z-1-9} and R^{Z-1-10} are independently alkyl groups of $C_1 \sim C_7$, aryl groups of $C_6 \sim C_{20}$, "containing 1 ~ 6 heteroatoms, Heteroatoms were selected from one or more of O, N, and S, 3 to 20 membered" heterocyclic groups, halogens, hydroxyl, nitro, cyanogen, carboxyl, thiol, ureido, $-C(=O)NR^{Z-1-8-1}R^{Z-1-8-2}$, $-C(=O)R^{Z-1-8-3}$, $-C(=O)OR^{Z-1-8-4}$, $-C(=S)NR^{Z-1-8-5}R^{Z-1-8-6}$,

$-S(=O)2R^{Z-1-8-7}$, $-OR^{Z-1-8-8}$, $-SR^{Z-1-8-9}$, $-S(=O)2NR^{Z-1-8-10}R^{Z-1-8-11}$, $-OC(=O)R^{Z-1-8-12}$, $-S(=O)NR^{Z-1-8-13}R^{Z-1-8-14}$, or $-C(=O)-NH-C(=O)R^{Z-1-8-15}$;

$R^{Z-1-8-1}$, $R^{Z-1-8-2}$, $R^{Z-1-8-3}$, $R^{Z-1-8-4}$, $R^{Z-1-8-5}$, $R^{Z-1-8-6}$, $R^{Z-1-8-7}$, $R^{Z-1-8-8}$, $R^{Z-1-8-9}$, $R^{Z-1-8-10}$, $R^{Z-1-8-11}$, $R^{Z-1-8-12}$, $R^{Z-1-8-13}$, $R^{Z-1-8-14}$, and $R^{Z-1-8-15}$ are independently hydrocarbon groups of hydrogen, C1 ~ C7, aryl groups of C6 ~ C20, or, "containing 1 ~ 6 heteroatoms, and heteroatoms are selected from one or more of the O, N, and S, and 3 ~ 20 membered" heterocyclic groups;

Or, $R^{Z-1-8-1}$, $R^{Z-1-8-2}$ and the carbon atoms connected with them form a "heterocyclic ring group containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

Or, $R^{Z-1-8-5}$, $R^{Z-1-8-6}$ and the carbon atoms connected with them form a "heterocyclic ring group containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

Or, $R^{Z-1-8-10}$, $R^{Z-1-8-11}$ and the carbon atoms connected with them form a "heterocyclic ring group containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

Or, $R^{Z-1-8-13}$, $R^{Z-1-8-14}$ and the carbon atoms connected with them form a "heterocyclic ring group containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

R^{Z-3} is H, hydroxyl or amino;

Or, R^{Z-2} , R^{Z-3} and the carbon atom connected with them form spironecylalkyl groups of C3 ~ C7, or, "containing 1 ~ 3 heteroatoms, heteroatoms are selected from one or more of O, N and S, and 3 ~ 7 element" heteronecylalkyl groups;

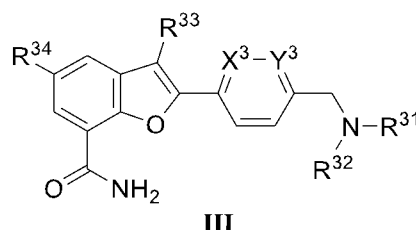
Both R^{22} and R^{23} are hydrogen, or, when Z is $-CR^{Z-2}R^{Z-3}-$, R^{22} , R^{23} , R^{Z-2} , R^{Z-3} , and the carbon atoms connected to them form aryl groups of C6 ~ C10 (e.g., phenyl groups), or aryl groups of C6 ~ C10 substituted by one or more R^{22-1} ;

R^{22-1} is independently the alkyl group of C1 ~ C7, the aryl group of C6 ~ C20, "contains 1 ~ 6 heteroatoms, which are selected from one or more of O, N and S, and 3 ~ 20 membered" heterocyclic group, hydroxyl group, thiol group, amino group, $-OR^{22-1-1}$, $-SR^{22-1-2}$ or $-O-(CH_2)_p-O-$; p is 1, 2 or 3;

R^{22-1-1} and R^{22-1-2} are independently alkyl groups of C1 ~ C7, aryl groups of C6 ~ C20, or, "containing 1 ~ 6 heteroatoms, which are selected from one or more of O, N, and S, and 3 ~ 20

membered" heterocyclic groups.

In a protocol, the PARP inhibitors described in CN103242273A are compounds shown in Equation III;



R^{31} and R^{32} are independently hydrogen, alkyl groups of C1 ~ C4 (e.g. methyl), naphthyl groups of C3 ~ C4, or "containing 1 ~ 3 heteroatoms, which are selected from one or more of O and N, 5-membered or 6-membered" heteroalkyl groups;

Or, R^{31} , R^{32} and N atoms connected with them form "containing 1-3 heteroatoms, which are selected from one or more heterocyclic alkyl groups in O, N and S, 5-6 element" heterocyclic alkyl groups, or "containing 1-3 heteroatoms replaced by one or more R^{31-1} , which are selected from one or more heterocyclic alkyl groups in O, N and S, 5-6 element" heterocyclic alkyl groups;

R^{31-1} is the alkyl group (e.g. methyl) of C1 ~ C4 on N;

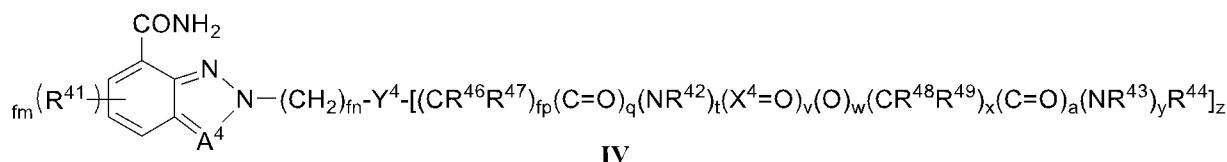
X^3 is CH, CF or N;

Y^3 is CH, CF or N;

R^{33} is H or Cl;

R^{34} is H or F.

In a protocol, the PARP inhibitors described as described in CN101415686A are compounds shown in Equation IV; 4 are H or F.



f_m is 0, 1, 2 or 3;

R^{41} is independently hydroxyl, halogen (e.g., fluorine), cyano, C1-6 alkyl, halogenated C1-6 alkyl, C1-6 alkoxy, or halogenated C1-6 alkoxy;

A^4 is CH or N;

fn is 0, 1, 2, 3, 4, 5, or 6;

Y⁴ is a single bond, C₃₋₅ cycloalkyl, a 4-membered saturated heterocyclic ring containing one N atom, a 5-, 6-, or 7-membered saturated or partially saturated heterocyclic ring containing one, 2-, 3-, or 4-membered heterocyclic ring containing one, N, and S heterocyclic atom independently selected from heteroatoms of N, O, or S but no more than one 5-membered unsaturated heterocyclic ring containing O or S, a 6-membered unsaturated heterocyclic ring containing one, two, or three nitrogen atoms, a 6-13-membered saturated, partially saturated, or unsaturated hydrocarbon ring "(e.g., an aryl group of C₆ to C₁₀, and also a phenyl group), or" an 8-13-membered or partially saturated heterocyclic ring containing one, two, three, or four heteroatoms independently selected from heteroatoms of N, O, and S";

Z of 1, 2 or 3

Fp is 0, 1, 2, 3, 4, 5, or 6;

R⁴⁶ and R⁴⁷ are independently hydrogen or C1-6 alkyl;

Q is 0 or 1;

T is 0 or 1;

R⁴² is hydrogen, C1-6 alkyl or C3-10 cycloalkyl;

V is 0 or 1;

X₄ is C or S = O;

W is 0 or 1;

X is 0, 1, 2, 3, 4, 5 or 6;

R⁴⁸ and R⁴⁹ are independently hydrogen, C1-6 alkyl, hydroxyl, halogenated C1-6 alkyl, hydroxyl C1-6 alkyl, amino, C1-6 alkyl amino, or bis (C1-6 alkyl) amino;

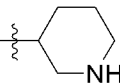
A is 0 or 1;

Y is 0 or 1;

R⁴³ is hydrogen or C1-6 alkyl;

R⁴⁴ is R₄₄₋₃ substituted by hydrogen, hydroxyl, cyanide, halogen (e.g. fluorine, chlorine or bromine), C1-6 alkyl, C2-10 dienyl, halogenated C1-6 alkyl, hydroxyl C1-6 alkyl, C1-6 alkyl carbonyl, C1-6 alkoxy, halogenated C1-6 alkoxy, C1-6 alkoxycarbonyl, carboxyl, nitro, R⁴⁴⁻¹, or one or more - (CH₂) bR⁴⁴⁻²;

R⁴⁴⁻¹ and R⁴⁴⁻³ are independently C6-10 aryl, C6-10 aryloxy, C6-10 aryl carbonyl, C3-10 cycloalkyl, 4-membered saturated heterocyclic ring containing one N atom, "5- or 6-membered

saturated or partially saturated heterocyclic rings (such as )、containing 1, 2, or 3 independently selected atoms from N, O, and S" (e.g.), "5-membered heterocyclic rings containing 1, 2, 3, or 4 independently selected heteroatoms from N, O, and S, of which no more than one heteroatom is O or S", "6-membered heteroaromatic ring containing 1, 2, or 3 nitrogen atoms", or "7-15 membered, partially saturated, or saturated heterorings containing 1, 2, 3, or 4 independently selected heteroatoms from N, O, and S";

b Independently 0, 1, 2, 3, 4, 5 or 6;

R^{44-2} is independently R^{44-2-3} of hydroxyl, oxo, cyano, halogen, C1-6 alkyl, C2-10 streptoenyl, halogenated C1-6 alkyl, C1-6 alkyl carbonyl, C1-6 alkoxy, halogenated C1-6 alkyl, hydroxy C1-6 alkyl, C1-6 alkoxy carbonyl, carboxyl, -NRaRb, -C(=O)NRaRb, S(=O)frRe, R^{44-2-1} , or, substituted by one or more R^{44-2-2} ;

R^a and R^b are independently hydrogen, C1-6 alkyl, C1-6 alkyl carbonyl, halogenated C1-6 alkyl, hydroxy C1-6 alkyl, S(O)srRc or S(O)trN(Rd)2;

Sr and tr are independently 0, 1 or 2;

R^c is C1-6 alkyl, Rc-1 or Rc-3 substituted by one or more Rc-2;

R^{c-1} and R^{c-3} are independently C6-10 aryl groups, "5-membered heterocyclic aromatic rings containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S, of which no more than one heteroatom is O or S", "6-membered heterocyclic aromatic rings containing 1, 2, or 3 nitrogen atoms", or, "7-10-membered unsaturated or partially saturated heterocycles containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S";

R^{c-2} is independently hydroxyl, cyanide, halogen, C1-6 alkyl, C2-10 streptoenyl, or halogenated C1-6 alkyl;

R^d is independently hydrogen or C1-6 alkyl;

Alternatively, R^a , R^b , and the N atom associated with them form R^{a-3} that R^{a-1} or is replaced by one or more R^{a-2} ;

R^{a-1} and R^{a-3} are independently "4-membered saturated heterocycles containing one N atom", or, "5-, 6-, or 7-membered saturated or partially saturated heterocycles containing 1, 2, or 3 N atoms and 0 or 1 O atoms";

R^{a-2} is independently hydroxy, cyanide, halogen, C1-6 alkyl, C1-6 alkoxy, C2-10 streptenyl, or halogenated C1-6 alkyl;

Fr is 0, 1 or 2;

R^e is C1-6 alkyl, Re-1 or Re-3 substituted by one or more R^{e-2};

R^{e-1} and R^{e-3} are independently C6-10 aryl groups, "5-membered heterocyclic aromatic rings containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S, of which no more than one heteroatom is O or S", "6-membered heterocyclic aromatic rings containing 1, 2, or 3 nitrogen atoms", or, "7-10-membered unsaturated or partially saturated heterocycles containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S";

R^{e-2} is independently hydroxyl, cyano, halogen, C1-6 alkyl, C2-10 streptoenyl, or halogenated C1-6 alkyl;

R⁴⁴⁻²⁻¹ and R⁴⁴⁻²⁻³ are independently C6-10 aryl, C6-10 aryl C1-6 alkyl, "4-membered saturated heterocyclic ring containing one N atom", "5-, 6-, or 7-membered saturated or partially saturated heterocyclic rings containing 1, 2, or 3 atoms independently selected from N, O, and S", "5-membered heterocyclic aromatic rings containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S, of which no more than one heteroatom is O or S", "6-membered heteroaromatic ring containing 1, 2, or 3 nitrogen atoms", or "7-10 membered or partially saturated heterorings containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S";

R⁴⁴⁻²⁻² is independently hydroxyl, cyano, halogen, C1-6 alkyl, C1-6 alkoxy, C2-10 streptoenyl, halogenated C1-6 alkyl, amino, C1-6 alkyl amino, and bis (C1-6 alkyl) amino groups.

In a scheme, a compound described as shown in Equation I has the following definitions:

Where R¹¹ is the aryl group of C6 ~ C10 substituted by one or more R¹¹⁻¹ (the "aryl group of C6 ~ C10" is described as phenyl group; the "aryl group of C6 ~ C10 substituted by one R¹¹⁻¹" is described as);

R¹¹⁻¹ is independently halogen, hydroxyl, carboxyl, nitro, amino, alkyl of C1 ~ C4 or alkyl of C1 ~ C4 substituted by one or more NR¹¹⁻¹⁻¹R¹¹⁻¹⁻² (described as "alkyl of C1 ~ C4" e.g. methyl);

R¹¹⁻¹⁻¹ and R¹¹⁻¹⁻² are independently alkyl groups of hydrogen or C1 to C4 (e.g. methyl);

Y¹ is - (CR^{Y1-1}R^{Y1-2}) (CR^{Y1-3}R^{Y1-4}) n-;

N is 0 or 1;

R^{Y1-1} and R^{Y1-2} are independently alkyl groups of H or C1 ~ C4;

R^{Y1-3} and R^{Y1-4} are independently alkyl groups of H or C1 ~ C4;

R^{12} is an alkyl group of H or C1 ~ C4;

X^1 is O or S;

R^{14} is a H or halogen (e.g., fluorine, chlorine, or bromine);

R^{13} is an alkyl group of H or C1 to C4.

In a scheme, a compound described as shown in Equation II has the following definitions:

X^2 , Y^2 and the carbon atom connected to them form an aryl group of C6 ~ C10 (e.g., phenyl group), or an aryl group of C6 ~ C10 substituted by one or more R^{X2-1} ;

R^{X2-1} is independently halogen, nitro, hydroxyl, thiol, amino, alkyl of C1 ~ C7, aryl of C6 ~ C20, "contains 1 ~ 6 heteroatoms, which are selected from one or more of O, N and S, 3 ~ 20 membered" heterocyclic groups, $-OR^{X2-1-1}$ or $-SR^{X2-1-2}$;

R^{X2-1-1} and R^{X2-1-2} are independently alkyl groups of C1 ~ C7, aryl groups of C6 ~ C20, or, "containing 1 ~ 6 heteroatoms, which are selected from one or more of O, N and S, and 3 ~ 20 membered" heterocyclic groups;

R^{21} is an H or halogen (e.g., fluorine, chlorine, or bromine);

Z is $-NR^{Z-1-}$; m is 1 or 2;

R^{Z-1} is independently $-C(=O)NR^{Z-1-1}R^{Z-1-2}$, $-C(=O)R^{Z-1-3}$ (e.g.,), $-C(=O)OR^{Z-1-4}$, $-C(=S)NR^{Z-1-5}R^{Z-1-6}$, or $-S(=O)2R^{Z-1-7}$;

R^{Z-1-1} , R^{Z-1-2} , R^{Z-1-3} , R^{Z-1-4} , R^{Z-1-5} , R^{Z-1-6} and R^{Z-1-7} are independently hydrogen, hydrocarbon group of C1 ~ C7, aryl group of C6 ~ C20, or, "containing 1 ~ 6 heteroatoms, which are selected from one or more of O, N and S, and heteroring groups of 3 ~ 20 elements";

Or, R^{Z-1-1} , R^{Z-1-2} and the carbon atoms connected with them form a "heterocyclic ring base containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

Or, R^{Z-1-5} , R^{Z-1-6} and the carbon atoms connected with them form a "heterocyclic ring base containing 1 ~ 2 heteroatoms, which are selected from one or more of O, N and S and 4 ~ 8 elements";

Both R^{22} and R^{23} are hydrogen.

In a scheme, a compound described as shown in Equation III has the following definitions:

R^{31} is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, piperidin-4-yl, or (R) - tetrahydrofuran-3-yl;

R^{32} is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, piperidin-4-yl, or (R) -

tetrahydrofuran-3-yl;

Alternatively, R³¹, R³² and the N atom connected to them form an unsubstituted or substituted morpholine, piperazine, homopiperazine, thiomorpholine, piperidine, or tetrahydropyrrole group, where the substitution refers to the substitution of N by a methyl group;

X³ is CH, CF or N;

Y³ is CH, CF or N;

R³³ is H;

R³⁴ is F.

In a certain scheme, the compound as shown in formula III has the following definition:

R³¹ is hydrogen or methyl;

R³² is methyl, isopropyl, cyclopropyl, piperidine-4-yl or (R)-tetrahydrofuran-3-yl;

Alternatively, R³¹, R³² and the N atoms connected thereto form an unsubstituted or substituted morpholine group, piperazinyl, piperazine group, thiomorpholine group, piperidinyl or tetrahydropyrrolyl group, wherein said substitution means that N is substituted by a methyl group;

X³ is CH, CF or N;

Y³ is CH, CF or N;

R³³ is H;

R³⁴ is F.

In one embodiment, the compound as shown in formula IV has the following definition:

fm is 0, 1, 2 or 3;

R⁴¹ is independently hydroxyl, halogen, cyano, C1-6 alkyl, halogen C1-6 alkyl, C1-6 alkoxy or halogen C1-6 alkoxy;

A⁴ is CH or N;

fn is 0;

Y⁴ is a 5,6 or 7-membered saturated or partially saturated heterocyclic ring comprising 1, 2, or 3 heteroatoms independently selected from N, O and S, comprising 1, 2, 3 or 4 heteroatoms independently selected from O, N and S but no more than one 5-unsaturated heterocyclic ring of O or S, 6 unsaturated heterocyclic ring comprising 1, 2 or 3 nitrogen atoms, "6-13 member saturated, partially saturated or unsaturated hydrocarbon ring" (e.g., aryl groups of C6 to C10,

such as phenyl), or, "comprising 1,2, 3 or 4 heterocycles of 8-13 unsaturated or partially saturated heterocycles independently selected from the heteroatoms of N, O and S";

z is 1 or 2;

fp is 0;

q is 0;

t is 0;

v is 0;

w is 0;

x is 0;

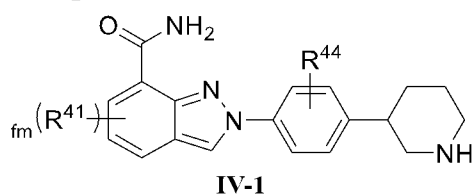
a is 0;

y is 0;

R⁴⁴ is halogen or R⁴⁴⁻¹;

R⁴⁴⁻¹ is C3-10 cycloalkyl, a 4-membered saturated heterocyclic ring comprising an N atom, "a 5 or 6-member saturated or partially saturated heterocyclic ring comprising 1, 2, or 3 atoms independently selected from N, O and S" (e.g.), or, "7-15 unsaturated, partially saturated or saturated heterocyclic ring comprising 1, 2, 3 or 4 heteroatoms independently selected from N, O and S".

In one embodiment, the compound as shown in formula IV has the following definition:

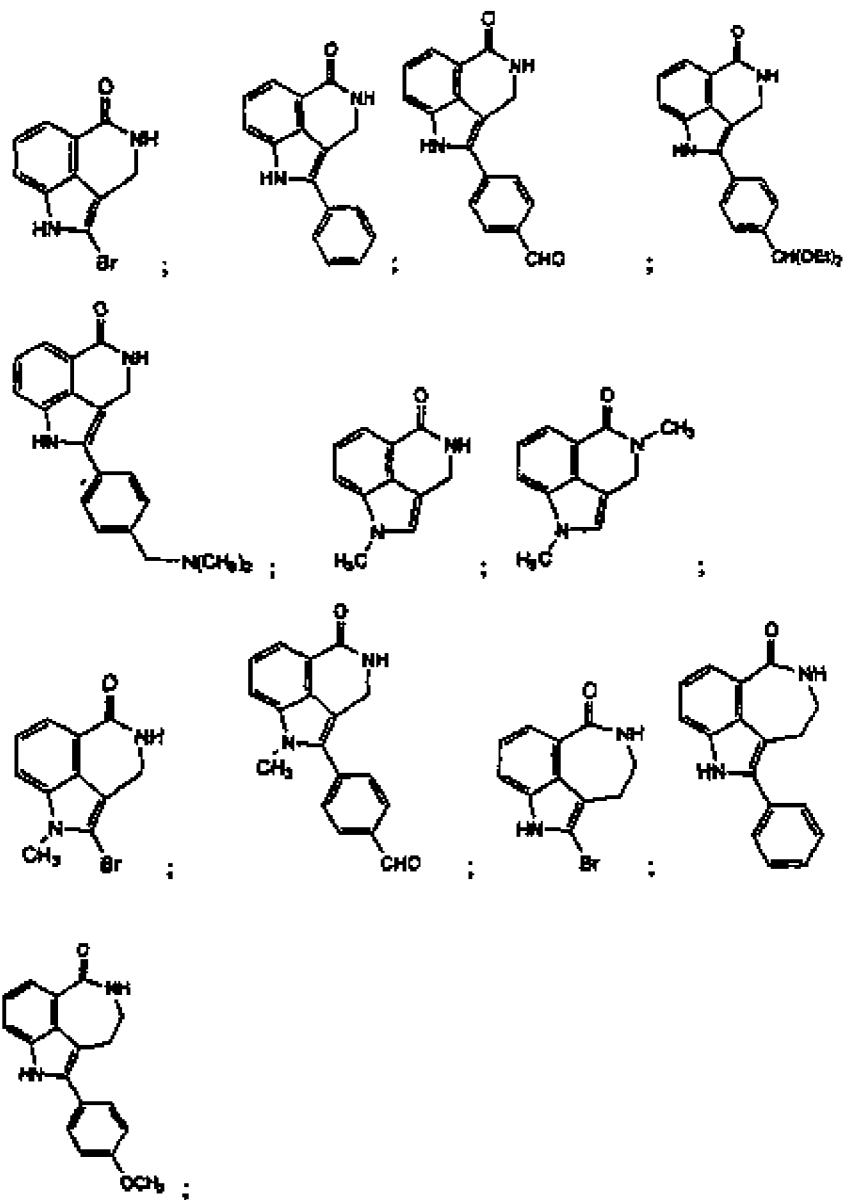


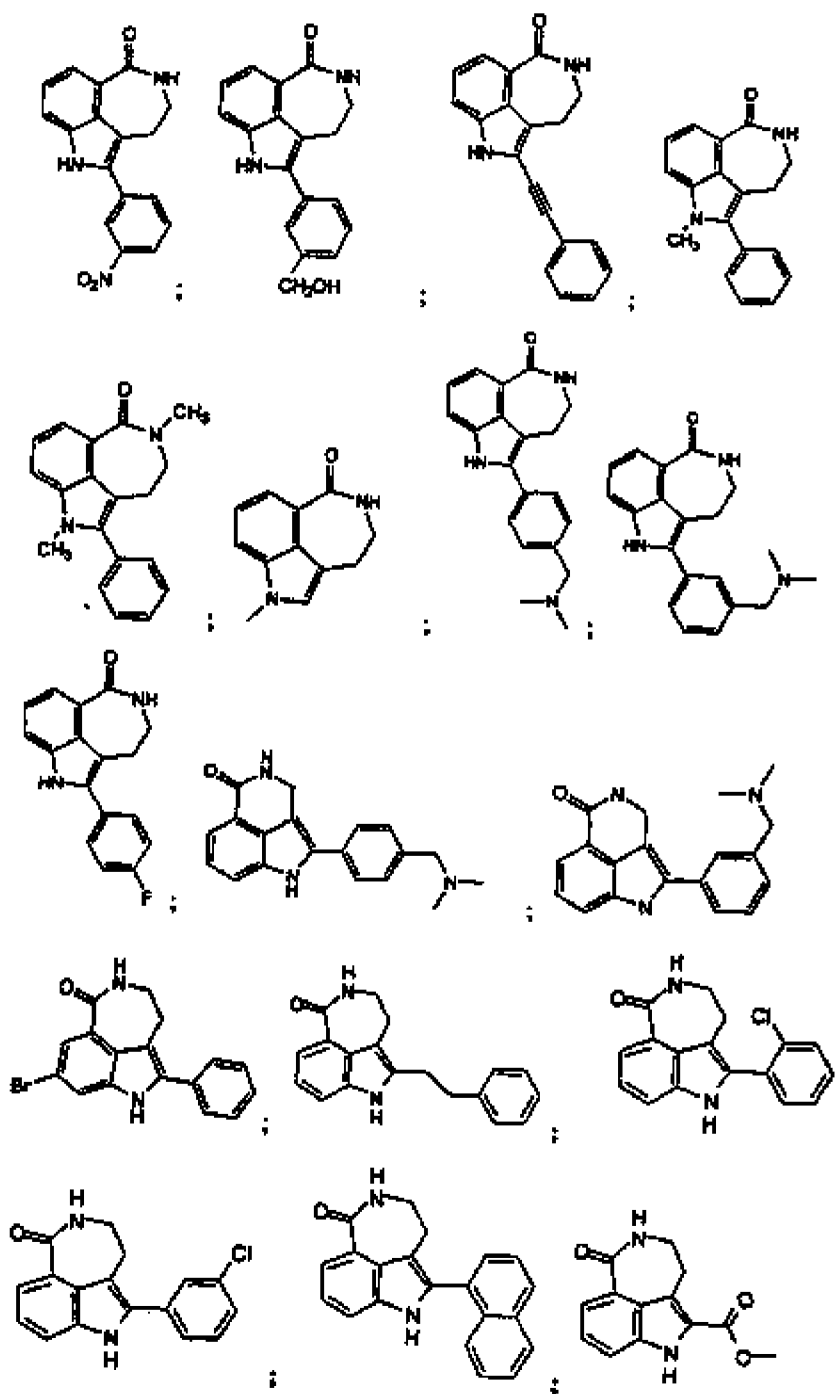
fm is 0 or 1;

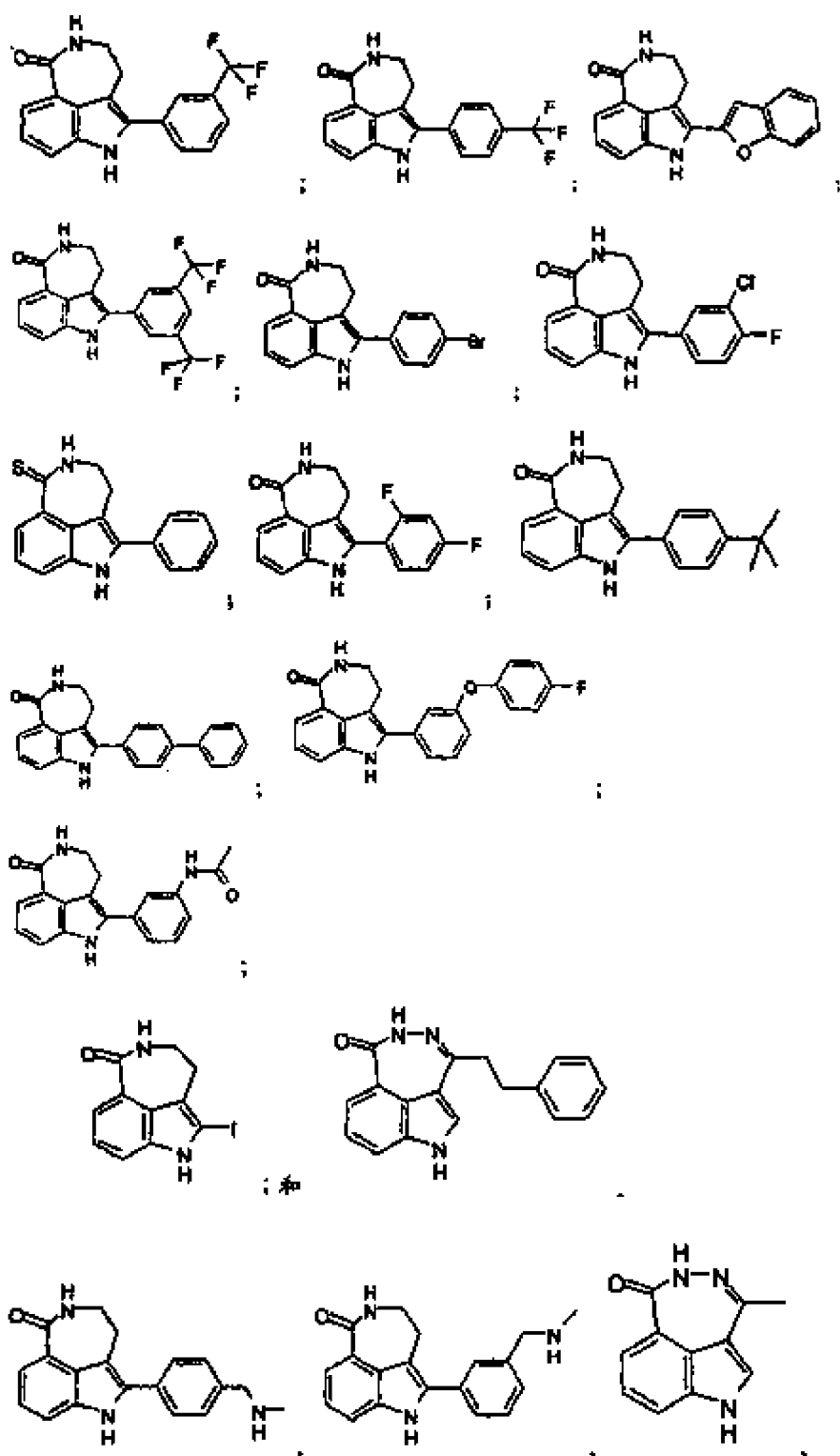
R⁴¹ is a halogen (e.g. fluorine);

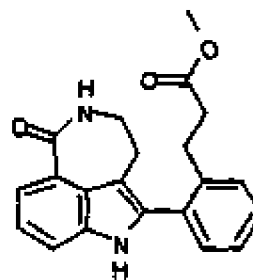
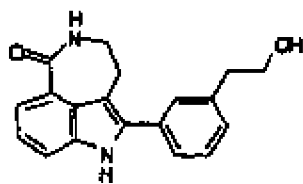
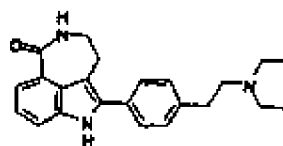
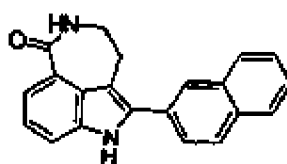
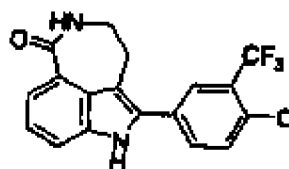
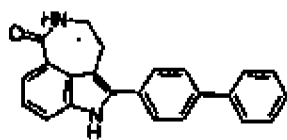
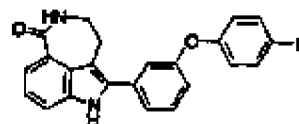
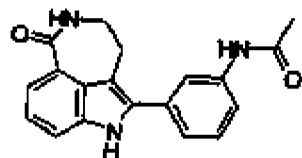
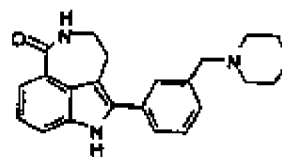
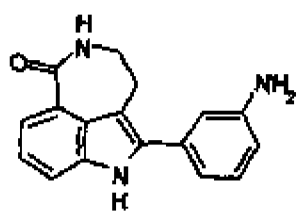
R⁴⁴ is hydrogen or halogen (e.g. fluorine).

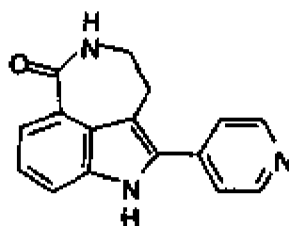
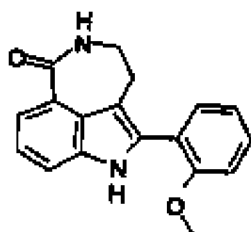
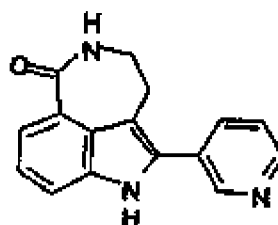
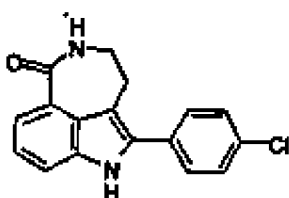
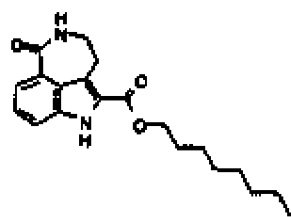
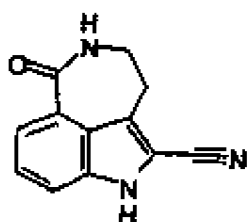
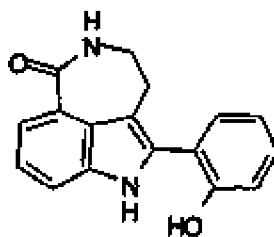
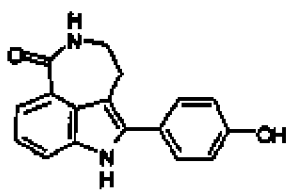
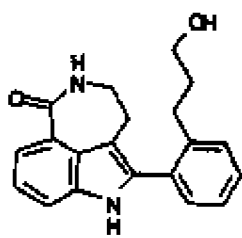
In a certain embodiment, the compound shown in formula I is any of the following compounds:

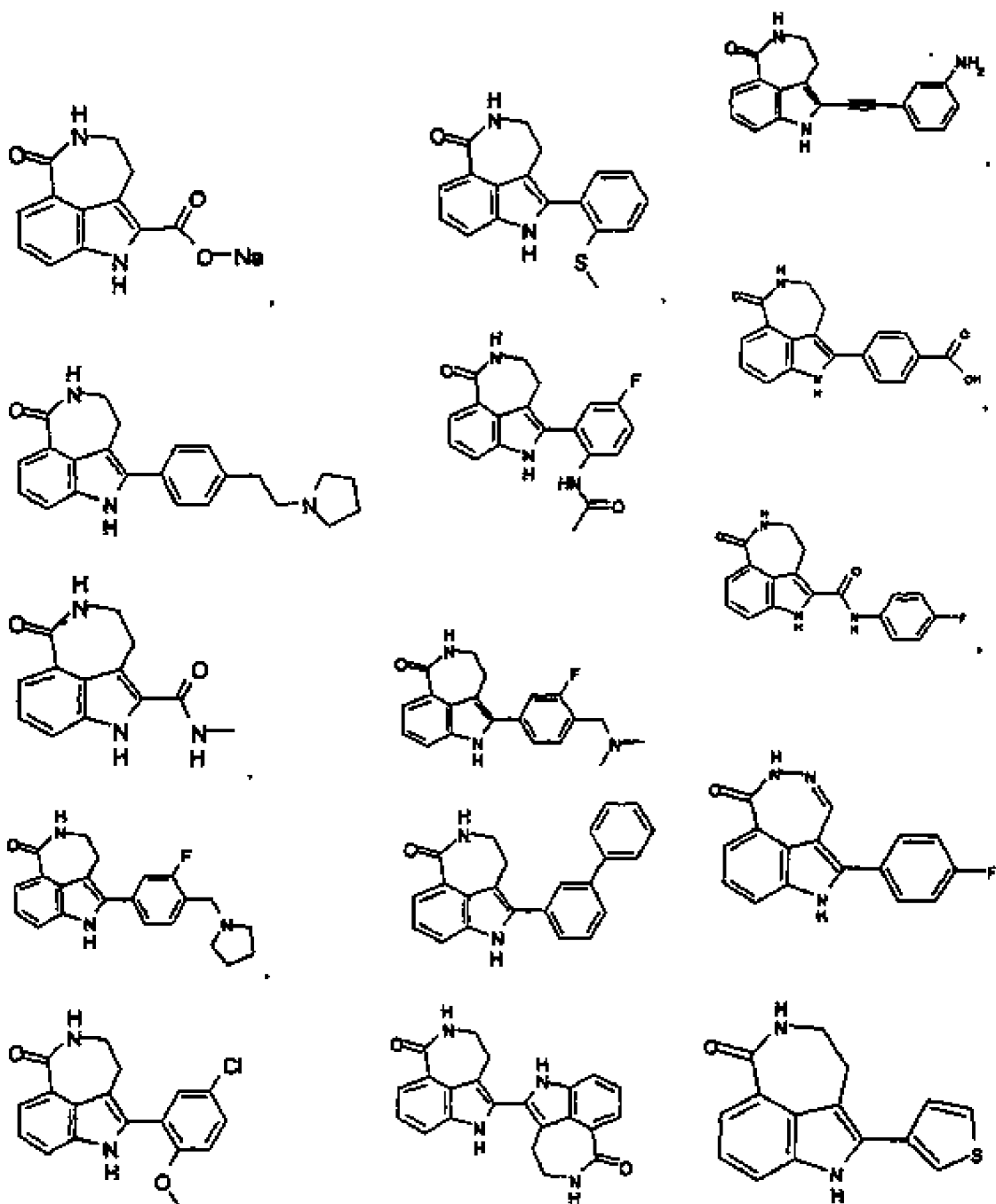


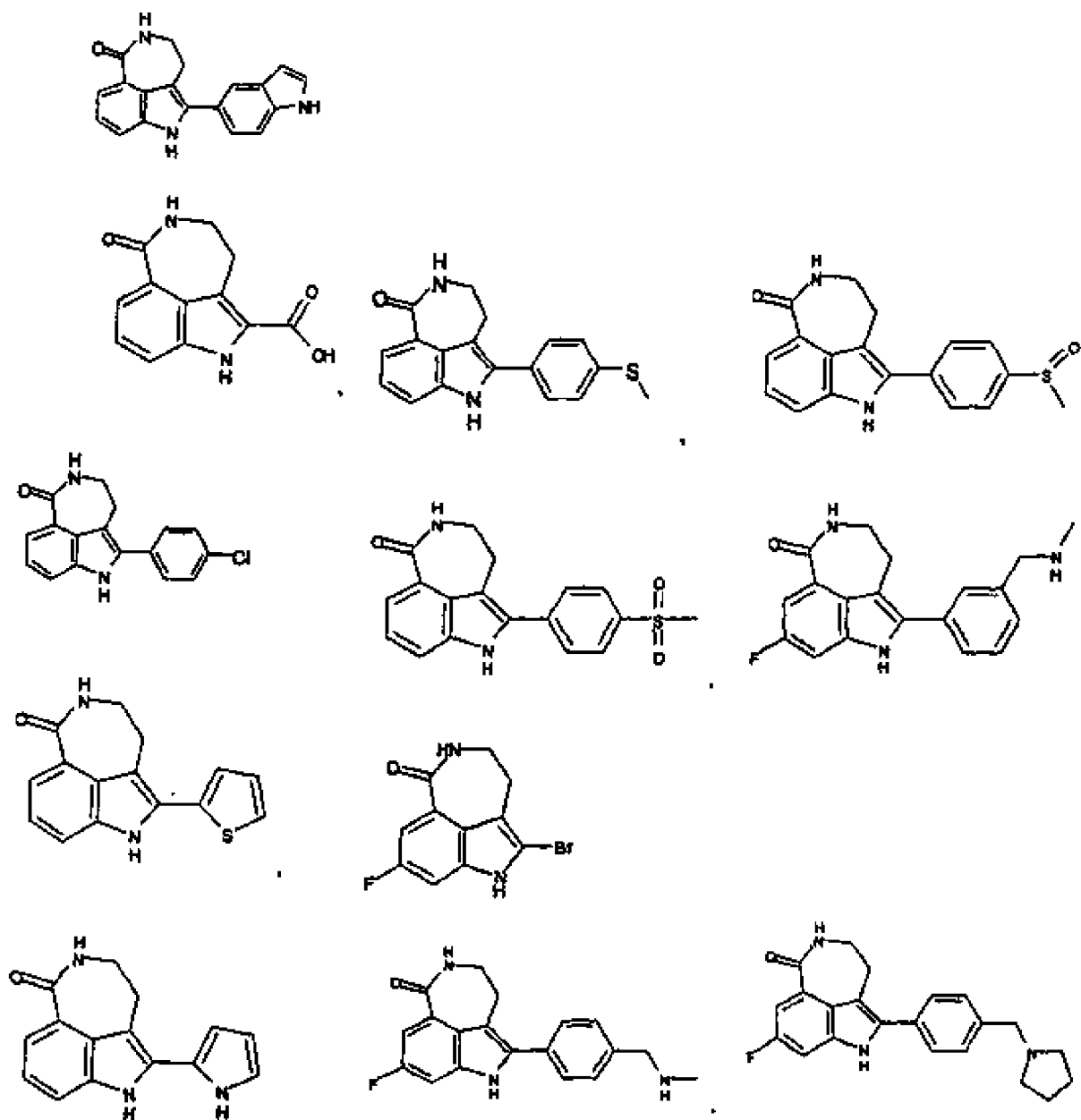


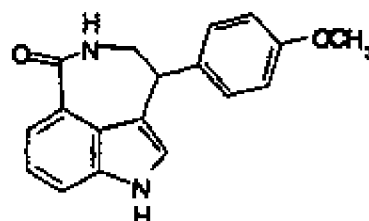
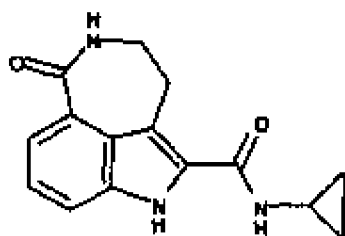
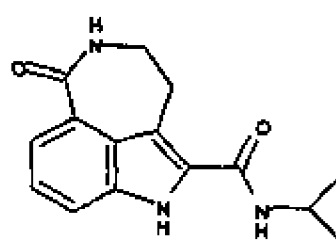
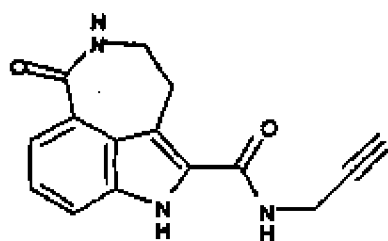
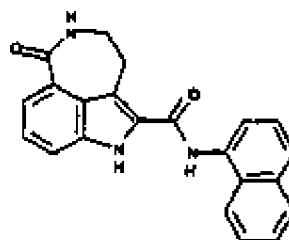
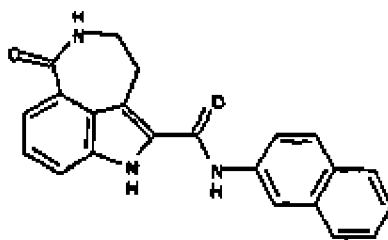
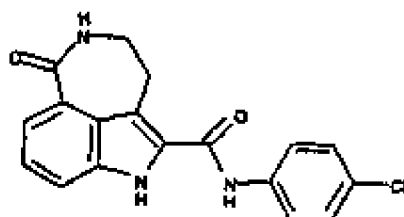
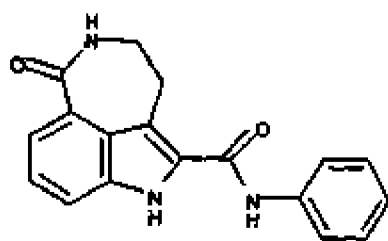


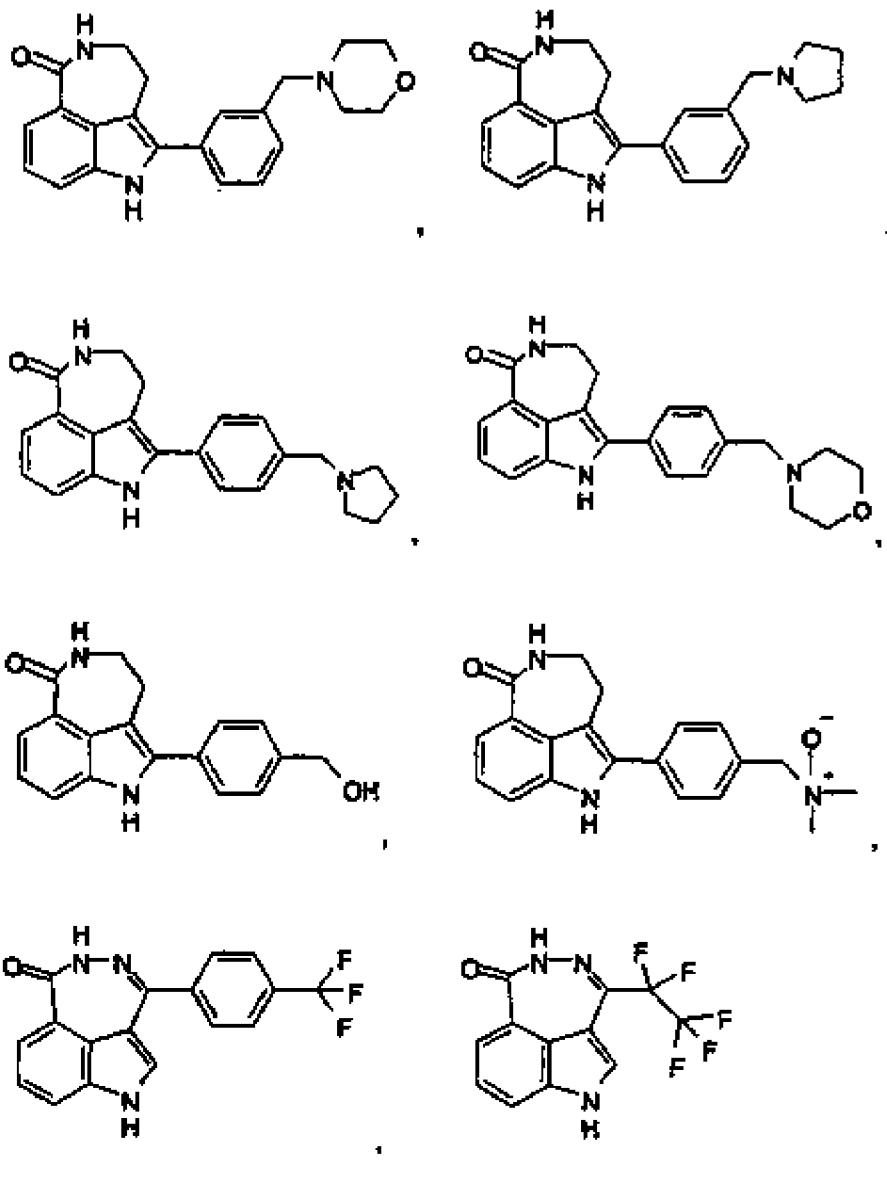




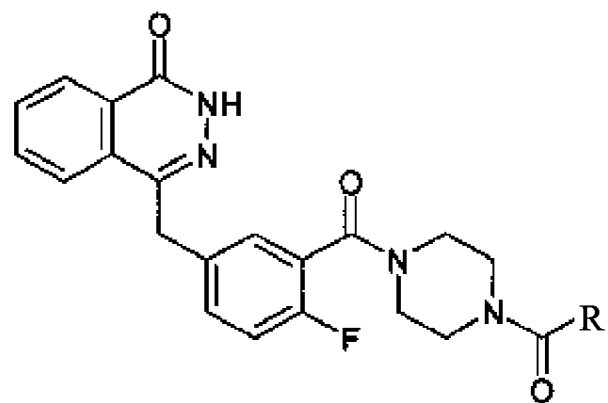






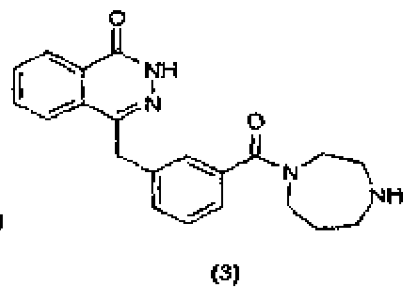
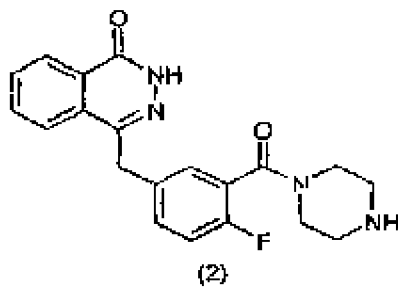
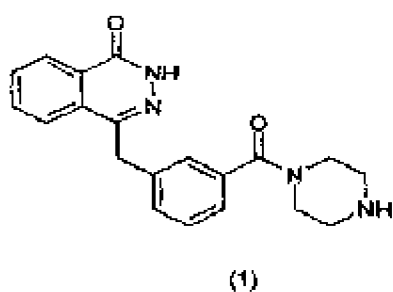


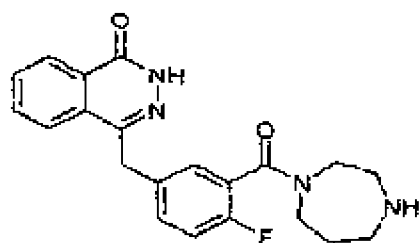
In a certain embodiment, the compound shown in formula II is any of the following compounds:



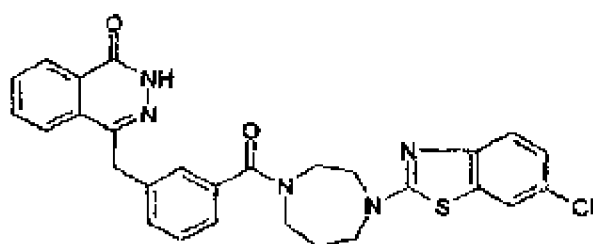
其中 R 选自

- a) $-\text{CH}_2\text{CH}_3$;
- b) $-\text{C}_6\text{H}_{11}\text{N}-$;
- c) $-\text{C}_3\text{H}_5$;
- d) $-\text{C}_4\text{H}_8\text{NO}-$;
- e) $-\text{CH}_2\text{CH}_2\text{N}(\text{C}_4\text{H}_8\text{NO})-$;
- f) $-\text{CH}_2\text{CH}_2\text{N}(\text{C}_7\text{H}_{13}\text{NH})-$;
- g) $-\text{CH}_2\text{CH}_2\text{N}(\text{C}_6\text{H}_{11}\text{NMe})-$; 和
- h) $-\text{C}_6\text{H}_{11}\text{NH}-$.

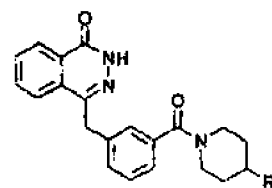
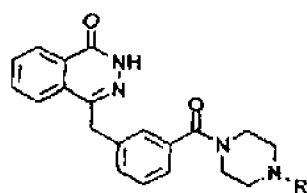
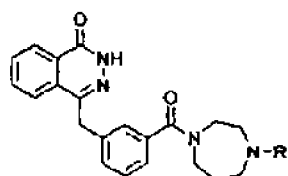




(4)



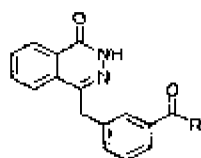
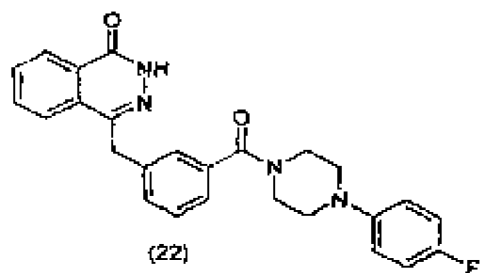
(5)



化合物	R
6	
7	
8	
9	
10	
11	
12	

化合物	R
13	
14	
15	
16	
17	

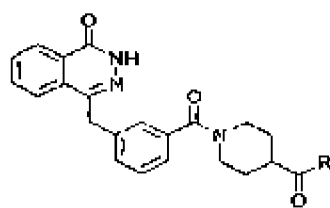
化合物	R
18	
19	
20	
21	



化合物	R
23	
24	

化合物	R
25	
26	
27	
28	
29	
30	
31	

化合物	R
32	
33	
34	
35	
36 (注 2)	

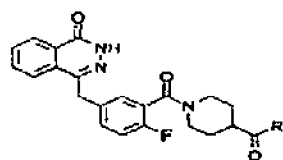


化合物	R
37	
38	
39	
40	
41	
42	

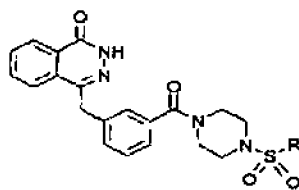
化合物	R
43	
44	
45	
46	
47	
48	
49	
50	

化合物	R
51	
52	
53	
54	
55	
56	
57	
58	

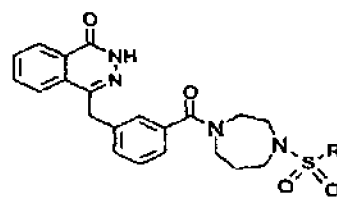
化合物	R	化合物	R
59		68	
60		69	
61		70	
62		71	
63			
64			
65			
66			
67			



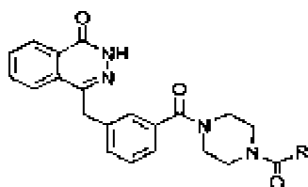
化合物	R
72	



化合物	R
73	
74	
75	
76	
77	
78	
79	
80	



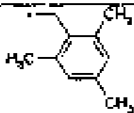
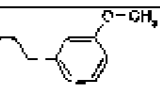
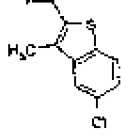
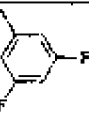
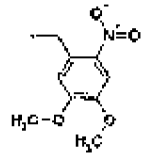
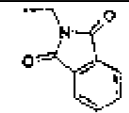
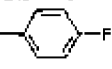
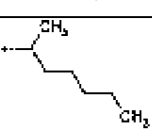
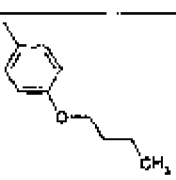
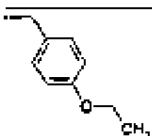
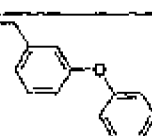
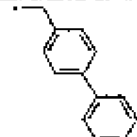
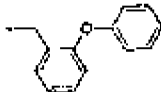
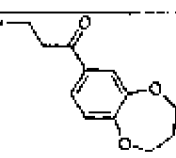
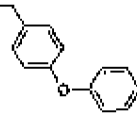
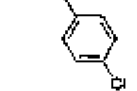
化合物	R
81	
82	

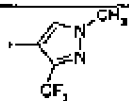
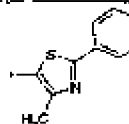
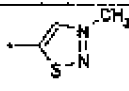
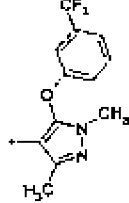
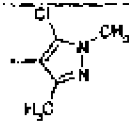
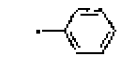
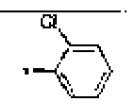
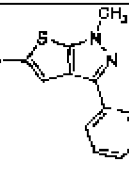
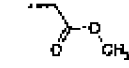
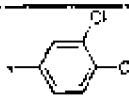
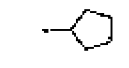
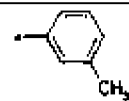
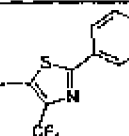
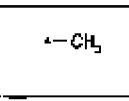
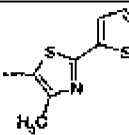
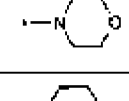
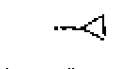
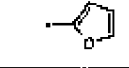
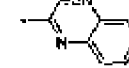
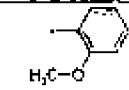
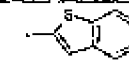
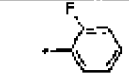


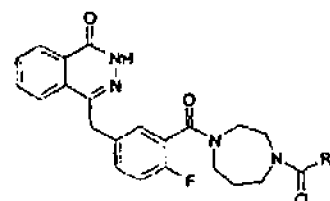
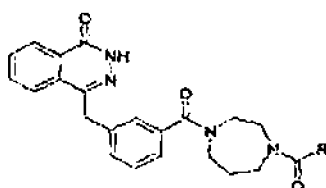
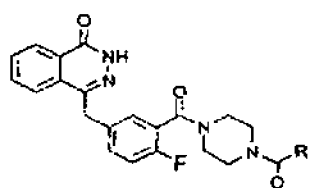
化合物	R
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109		119		129	
110		120		129	
111		121		130	
112		122		131	
113		123		132	
114		124		133	
115		125		134	
116		126		135	
117		127		136	
118				137	

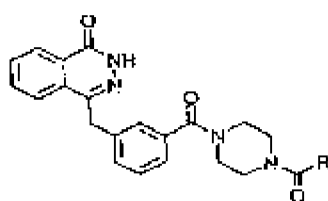
138		145		158	
139		146		159	
140		147		160	
141		148		161	
142		149		162	
143		150		163	
144		151		164	
		152		165	
		153			
		154			
		155			
		156			
		157			



化合物	R
166	
167	
168	
169	
170	
171	
172	
173	

化合物	R
174	
175	
176	
177	
178	
179	
180	
181	
182	

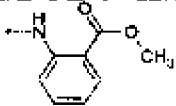
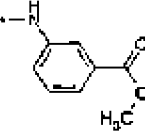
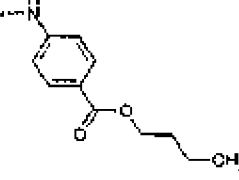
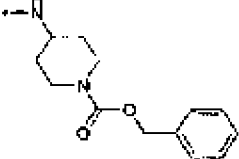
化合物	R
183	
184	

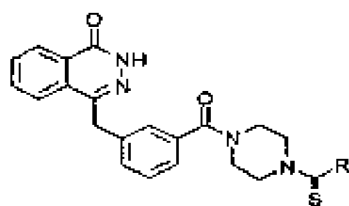


化合物	R
185	
186	
187	
188	
189	
190	
191	
192	

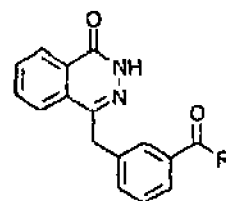
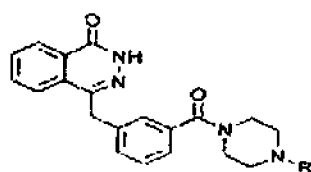
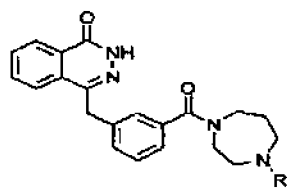
193	
194	
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217	



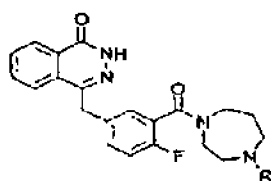
化合物	R
218	
219	
220	
221	
222	
223	
224	
225	
226	
227	
228	
229	
230	



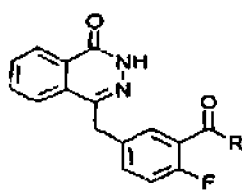
化合物	R
231	CH_3

化合物	R
232	
233	
234	
235	
236	
237	
238	
239	
240	
241	
242	

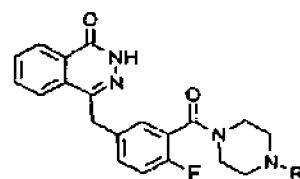
化合物	R
243	
244	
245	



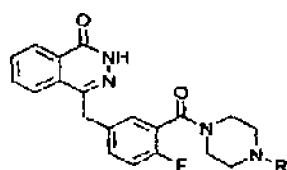
化合物	R
246	
247	



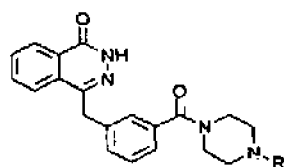
化合物	R
256	
257	



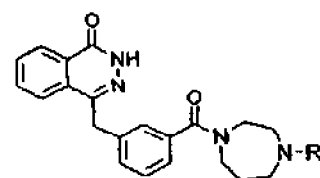
化合物	R
263	
264	



化合物	R
248	
249	
250	
251	
252	
253	
254	
255	



化合物	R
258	
259	
260	
261	
262	



化合物	R
265	
266	

o

In a certain embodiment, the compound shown in formula III is any of the following compounds:

5e	
5f	
5g	
5h	
5i	
5j	
5k	
5l	
5m	
5n	

编 号	结 构 式
5a	
5b	
7a	
5c	
5d	

5o	
5p	

o

In a certain embodiment, the compound as shown in formula IV is any of the following compounds:

Phenyl-2H-indazole-7-carboxamide; 2-(3-Chlorophenyl)-2H-indazole-7-carboxamide; and 2-{4-[(Dimethylamino)methyl]phenyl}-2H-indazole-7-carboxamide; 2-{4-[(N,N-Dimethylglyl)amino]phenyl}-2H-indazole-7-carboxamide; 2-Benzyl-2H-indazole-7-carboxamide; 2-(4-Chlorophenyl)-2H-indazole-7-carboxamide; 2-(2-Chlorophenyl)-2H-indazole-7-carboxamide; 2-{4-[(4-Methylpiperazine-1-yl)methyl]phenyl}-2H-indazole-7-

carboxamide; 2-[4-(Morpholine-4-methyl)phenyl]-2H-indazole-7-formamide; 2-{4-[(Methylamino)methyl]phenyl}-2H-indazole-7-carboxamide; 2-[4-(Pyrrolidin-1-ylmethyl)phenyl]-2H-indazole-7-carboxamide; 2-[4-(Piperidine-1-methyl)phenyl]-2H-indazole-7-carboxamide; {4-[7-(Aminocarbonyl)-2H-indazole-2-yl]phenyl}-N,N-dimethylmethane ammonium chloride; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl)-2H-indazole-2-yl]benzoyl)amino)methyl]pyridonium; 2-{4-[1-(Methylamino)ethyl]phenyl}-2H-indazole-7-carboxamide; N-{4-[7-(Aminocarbonyl)-2H-indazole-2-yl]benzyl}cyclohexane ammonium trifluoroacetate; {4-[7-(Aminocarbonyl)-4-chloro-2H-indazole-2-yl]phenyl}-N-methylmethanetrifluoroacetate; 2-Phenyl-2H-1,2,3-Benzotriazole-4-carboxamide; 2-Benzyl-2H-1,2,3-benzotriazole-4-carboxamide; 2-{3-[(methylamino)methyl]phenyl}-2H-indazole-7-formamide; Trifluoroacetic acid 4-[(3-[7-(aminocarbonyl)-2H-indazole-2-yl]benzoyl)amino]piperidine; {4-[7-(aminocarbonyl)-2H-indazole-2-yl]phenyl}-N-methylmethane ammonium chloride; 2-{3-chloro-4-[(dimethylamino)methyl]phenyl}-2H-indazole-7-formamide; Trifluoroacetic acid 1-[2-[(4-[7-(aminocarbonyl)-2H-indazole-2-base]phenyl)amino]ethyl]-2-oxygen generation-4-methyl-Weng piperazine-1; 2-(4-{[(4-pyrrolidine-1-yl)piperidine-1-yl]acetyl}amino)phenyl)-2H-indazole-7-formamide; 2-{4-[(pyrrolidine-1-yl)acetyl]amino}phenyl)-2H-indazole-7-formamide; 2-{4-[(piperidine-1-yl)acetyl]amino}phenyl)-2H-indazole-7-formamide; 2-{4-[(morpholine-4-yl)acetyl]amino}phenyl)-2H-indazole-7-formamide; Chloride 4-[2-[(4-[7-(aminocarbonyl)-2H-indazole-2-base]phenyl)amino]ethyl]-2-oxygen generation-4-Weng morpholine; 2-{4-[(ethylamino)methyl]phenyl}-2H-indazole-7-formamide; 2-{4-[(isopropylamino)methyl]phenyl}-2H-indazole-7-formamide; N-{4-[7-(aminocarbonyl)-2H-indazole-2-yl]benzyl}propane-2-ammonium chloride; 2-(4-{[(2-fluoroethyl)amino]methyl}phenyl)-2H-indazole-7-formamide; 2-(4-{[(2,2-difluoroethyl)amino]methyl}phenyl)-2H-indazole-7-formamide; 2-{4-[(cyclopropylamino)methyl]phenyl}-2H-indazole-7-formamide; Trifluoroacetic acid and 4-{4-[7-(aminocarbonyl)-2H-indazole-2-base]benzene formyl}-1,4,2-nitrogen heterocyclic heptane-1-Weng; 4-[2-[(7-(aminocarbonyl)-2H-indazole-2-base]benzene formyl)amino]-N,N-dimethylethane trifluoroacetic acid ammonium; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl)-2H-indazole-2-yl]benzoyl)amino)methyl]piperidonium; N-{4-[7-(aminocarbonyl)-2H-indazole-2-base]benzyl}-N,N'-3,1,2-methylethane ammonium chloride (2); Trifluoroacetic acid 4-

{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benformyl} -1-methylpiperazine-1-onium;
 Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl]
 azacyclobutanium; Trifluoroacetic acid (2 s) - 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole -
 2 - base] phenyl} amino) carbonyl] 1 - methyl - pyrrolidine Weng; Trifluoroacetic acid 3-
 [(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-methylpiperidine;
 Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -
 1-methylpiperidine; Trifluoroacetic acid 4-({4-[7-(aminocarbonyl) -2H-indazole-2-yl]
 benzoyl} amino) -1-benzyl piperidinium; 2-{4-[(pyridine-4-amino) carbonyl] phenyl} -2H-
 indazole-7-formamide; 2-{4-[(4-phenyl)piperazine-1-yl] carbonyl] phenyl} -2H-indazole-7-
 formamide; 2-(4-{[methyl (quinoxaline - 6-yl methyl) amino] carbonyl} phenyl) -2H-
 indazole-7-formamide; 2-(4-formylphenyl) -2H-indazole-7-formamide; Trifluoroacetic acid
 1-[2-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) ethyl] pyrrolidonium;
 Trifluoroacetic acid 1-[2-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) ethyl]
 piperidine onium; Trifluoroacetic acid and 4 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole -
 2 - base] benzene formyl} amino) ethyl] - 4 - Weng morpholine; Trifluoroacetic acid 4-({4-
 [7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) -1-methylpiperidine; 2-[4-[(4-
 methylpiperazine-1-yl) methyl]-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 2-[4-
 [(methylamino) methyl]-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 1-{4-[7-
 (aminocarbonyl) -2H-indazole-2-yl] phenyl} -n-methyl ethane ammonium chloride; 2-[4-
 (pyrrolidine - 1-methyl)-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 2-[4-
 (piperidine-1-methyl)-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 2-[4-
 [(ethylamino) methyl]-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; Trifluoroacetic
 acid 4-{4-[7-(aminocarbonyl) -4-chloro-2h-indazole-2-yl] benzyl} -1-methylpiperazine-1-ium;
 Bis (trifluoroacetic acid)1-[2-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium)
 ethyl] piperidine onium; Double (trifluoroacetic acid) 4 - [2 - ({4 - [7 - (amino carbonyl) - 2 h
 - indazole - 2 - base] benzyl} ammonium) ethyl] - 4 - Weng morpholine; Double
 (trifluoroacetic acid) 1 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl}
 ammonium) ethyl] pyrrolidine Weng; Bis (trifluoroacetic acid)4-({4-[7-(aminocarbonyl) -2H-
 indazole-2-yl] benzyl} ammonium) -1-methylpiperidine; Bis (trifluoroacetic acid)4-({4-[7-
 (aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) -1-benzyl piperidinium; Bis
 (trifluoroacetic acid)1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -4-phenylpiperazine

diphenyl; N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2 - (dimethyl amino) - 2 - oxygen generation ethane trifluoroacetic acid ammonium; Bis (trifluoroacetic acid)2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) methyl] pyridonium; Bis (trifluoroacetic acid)4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) methyl] pyridonium; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-methyl propane-2-trifluoroacetate ammonium; Double (trifluoroacetic acid) N' - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - N, N - dimethyl ethane - 1, 2 - diammonium; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - (1, 3 - oxazole - 2 - methyl) methane trifluoroacetic acid ammonium. 7-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline sulfonium chloride; 6-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline sulfonium chloride; Trifluoroacetic acid 5-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline; Trifluoroacetic acid 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] nitrogen heterocyclic butane Weng; 2-(4-{[(azacyclic butane-3-yl carbonyl)(methyl) amino] methyl} phenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} amino) carbonyl] azacyclobutanium; 2-(4-bromophenyl) -5-fluoro-2h-indazole-7-formamide; 5-fluoro-2 -(4-pyridine-3-phenyl) -2H-indazole-7-formamide; 2-(4-pyridine-3-phenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 4-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -1-methylpiperazine-1-onium; Trifluoroacetic acid 4-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} piperidine; 2-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -n-methyl ethane trifluoroacetate ammonium; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] azacyclobutanium; 2-{5-[(methylamino) methyl] pyridine-2-yl} -2H-indazole-7-formamide; 5-fluoro-2 -{3-fluoro-4 -[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; 5-fluoro-2 -{4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -n-methyl propane-2-trifluoroacetate ammonium; 2-(6-phenylpyrazine-3-yl) -2h-indazole-7-formamide; {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl) cyclohexyl] methyl} methane trifluoroacetic acid ammonium; 5-chloro-2 -(4-formyl phenyl) -2H-indazole-7-formamide; 2-{3-methoxy-4 -[(4-methylpiperazine-1-yl) methyl] phenyl} -2h-indazole-7-formamide; 2-{3-methoxy-4 -[(methylamino) methyl] phenyl} -2H-indazole-7-formamide; 5-chloro-2 -{4-[(4-

methylpiperazine-1-yl) methyl] phenyl} -2h-indazole-7-formamide; 5-chloro-2 -{4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; {4-[7-(aminocarbonyl) -4-fluoro-2h-indazole-2-l] phenyl} -n-methylmethane ammonium chloride; {4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-l] phenyl} -n-methylmethane ammonium chloride; Chlorinated 1-{4-[7-(aminocarbonyl) -4-fluoro-2h-indazole-2-yl] benzyl} -4-methylpiperazine-1-onium; Chlorinated 1-{4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] benzyl} -4-methylpiperazine-1-onium; Bis (trifluoroacetic acid)1-{3-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -4-methylpiperazine diphenyl; 2-[4-(1-hydroxy-1-methylethyl) phenyl] -2H-indazole-7-formamide; 2-(4-acetylphenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 3 - { {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} (methyl) amino] carbonyl} - 1 - methyl piperidine Weng; 2-{4-[1-(formyl amino) -1-methylethyl] phenyl} -2H-indazole-7-formamide; 2-[3-(1, 4-diazacyclic heptane-1-yl carbonyl) phenyl] -2H-indazole-7-formamide; Trifluoroacetic acid 3-[({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} amino) carbonyl] -1-methylpiperidine; Trifluoroacetic acid (2 s) - 2 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] pyrrolidine Weng; Trifluoroacetic acid 3-[({4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] pyrrolidonium; Trifluoroacetic acid (2 r) - 2 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] pyrrolidine Weng; Trifluoroacetic acid 3-[({4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] piperidine; Trifluoroacetic acid 4-[({4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] pyridonium; Trifluoroacetic acid 4-[({4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] quinoline onium; Trifluoroacetic acid 4-[({4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] isoquinoline onium; Trifluoroacetic acid, 2 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - nitrogen heterocyclic heptane Weng; Trifluoroacetic acid 3 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 2 - methyl - 1, 2, 3, 4 - four hydrogen isoquinoline Weng; Trifluoroacetic acid, 2 - {4 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] piperidine - 1 - base} pyrimidine - 1 - Weng; Chlorinated 1-{4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] benzyl} -4-methylpiperazine-1-onium; 5 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - three - eight hydrogen oxygen generation Yin oxazine - 2 - trifluoroacetic acid ammonium; Trifluoroacetic acid, 2 - {3 - [({4 - [7 - (amino

carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] piperidine - 1 - base} pyridine Weng; Trifluoroacetic acid, 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 4 - methyl - 4 - Weng morpholine; (1 r, 4 r) - N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - 1' - (methyl sulfonyl) - 1', 2' - dihydro screw/cyclohexane 1, 3' - indole - 4 - formamide; Trifluoroacetic acid 1 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 8 h - 1 h - different indole Weng; Trifluoroacetic acid, 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 4 - benzyl - 4 - Weng morpholine; Trifluoroacetic acid (3 s, 4 r) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 4 - (methoxy carbonyl) pyrrolidine Weng; Double (trifluoroacetic acid) 4 - {(2 s) - 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] pyrrolidine Weng - 1 - base} piperidine Weng; (1 s, 3 s) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] cyclopentane trifluoroacetic acid ammonium. Trifluoroacetic acid 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - pyrrolidine Weng; Trifluoroacetic acid, 2 - {4 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] piperidine - 1 - base} pyrimidine - 1 - Weng; Double (trifluoroacetic acid) 2 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} pyrrolidine Weng - 3 - base) pyridine Weng; Double (trifluoroacetic acid) 3 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} pyrrolidine Weng - 3 - base) pyridine Weng; Trifluoroacetic acid (3 s, 4 s) - 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3, 4-2 fluorine pyrrolidine Weng; 3 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 6 - ammonium nitrogen - 3 - Weng mixed double loop [3.1.0] hexane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 7 - methyl - 2, 7 - dinitrogen Weng miscellaneous screw [4.4] nonane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3 - (4 - (dimethyl ammonium) phenyl] pyrrolidine Weng; Double (trifluoroacetic acid) 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl}, 2,4,5,6,6-1 - methyl - 1 a - six hydrogen pyrrole and [3, 4 - b] pyrrole Weng; Double (trifluoroacetic acid) 3 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} (methyl) ammonium] methyl} - 1 - methyl piperidine Weng; (1 r, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - miscellaneous - 5-2 - oxygen nitrogen Weng

mixed double loop [2.2.1] heptane trifluoroacetic acid salt; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-hydroxy-2-methyl propane-1-trifluoroacetate ammonium; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl}-3, 3-difluorocyclobutane trifluoroacetate ammonium; Trifluoroacetic acid and 4 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 6 - fluoro - 1, 4-2 - Weng nitrogen heterocyclic heptane - 1; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - Weng - 2-4 - pyrimidine - 1 - base - 1, 4-2 - Weng nitrogen heterocyclic heptane - 1; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) -1-benzyl pyrrolidonium; The (trifluoroacetic acid) 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl - pyrrolidine Weng; Double (trifluoroacetic acid) 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - benzyl - pyrrolidine Weng; 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 7 - benzyl - 2, 7 - dinitrogen Weng miscellaneous screw [4.4] nonane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 8 - benzyl - 2, 8 - dinitrogen Weng miscellaneous screw [5.5] undecane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 6 - dinitrogen Weng miscellaneous screw [3.3] heptane double (trifluoroacetic acid salt); 7 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 7 - dinitrogen Weng miscellaneous screw [3.5] nonane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 6 - dinitrogen Weng miscellaneous screw [3.5] nonane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 8 - dinitrogen Weng miscellaneous screw [5.5] undecane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 8 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 7 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); 8 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 8 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); 3 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3, 9 - dinitrogen Weng miscellaneous screw [5.5] undecane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} pyrrole and eight hydrogen [3, 4 - c] pyrrole Weng; Double (trifluoroacetic acid) 5 - {4 - [7 -

(amino carbonyl) - 2 h - indazole - 2 - base] benzyl} [3, 4 - b] pyrrole and eight hydrogen pyrrole Weng; Double (trifluoroacetic acid) 4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) eight hydrogen cyclopentadiene and [c] pyrrole Weng; N2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - N1 N1-2 - pyridine - 2 - methyl - 1-1, 2 - double base ethane (trifluoroacetic acid) diammonium; Double (trifluoroacetic acid) 7 - (amino carbonyl) - 2 - [4 - ({2 - (2, 3-2 h - 1 h - indole - 1 - base) ethyl} ammonium) methyl} phenyl] - 2 h - 1 - Weng indazole -; Double (trifluoroacetic acid) (3 s, 4 s) - 1 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) ethyl] - 3, 4-2 fluorine pyrrolidine Weng; Trifluoroacetic acid 5 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} amino) - 1, 3 - benzothiazole - 3 - Weng; 1 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 8 - nitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 4 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl piperidine Weng; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-hydroxy-ethane trifluoroacetate ammonium; Trifluoroacetic acid 7-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline; Trifluoroacetic acid 3 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) - 2 - ethyl] oxygen generation nitrogen heterocyclic butane Weng; Bis (trifluoroacetic acid)4-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) piperidine; Double (trifluoroacetic acid) (3 r, 4 r) - 4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 3 - fluorine piperidine Weng; Double (trifluoroacetic acid) (3 s, 4 r) - 4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 3 - benzyl - 1 - methyl piperidine Weng; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -1-isobutylpiperidine-4-trifluoroacetate ammonium; Double (trifluoroacetic acid) 2 - (4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) piperidine - 1 - base] - 3 - methyl pyridine Weng; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) piperidine; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) -1-benzyl piperidinium; 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 5 - nitrogen hetero - 2 - Weng mixed double loop (2.2.2) octane trifluoroacetic acid salt; (1 s, 4 s) - 2 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 5 - methyl - 2, 5 - dinitrogen Weng mixed double loop [2.2.1] heptane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h -

indazole - 2 - base] benzyl} - 4 - (pyridine - 2 - methyl) piperazine Weng; 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2 - benzyl - 5 - nitrogen hetero - 2 - Weng mixed double loop (2.2.2) octane trifluoroacetic acid salt; 8 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3 - benzyl - 8 - nitrogen hetero - 3 - Weng mixed double loop [3.2.1] octane trifluoroacetic acid salt; (1 s, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 2 - benzyl - 5 - nitrogen hetero - 2 - Weng mixed double loop [2.2.1] heptane trifluoroacetic acid salt; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) pyrrolidonium;6 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 3 - n Weng mixed double loop [3.1.0] hexane double (trifluoroacetic acid salt); Trifluoroacetic acid (3 s, 4 s) - N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - hydroxyl ammonium tetrahydrothiophene - 3-1, 1-2 oxide; Double (trifluoroacetic acid) 4 - [{4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl - 4 - hydroxy - piperidine Weng; N-{4-[7-(aminocarbonyl) - 2H-indazole-2-yl] benzyl} -1-cyclopropyl -2-hydroxy-ethane trifluoroacetate ammonium; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl) cyclopentyl] methyl} methane trifluoroacetic acid ammonium; Double (trifluoroacetic acid) 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} hydrogen - 1, 2, 3, 4-4-2, 7 - two nitrogen impurity naphthalene two Weng; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3 - [(dimethyl ammonium) methyl] piperidine Weng; Double (trifluoroacetic acid) 4 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} piperidine Weng - 4 - base) thio - 4 - Weng morpholine; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - [(methyl sulfonyl) amino] piperidine Weng; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - (1 h - imidazole - 3 - Weng - 1 - methyl) piperidine Weng; 7 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 1 - oxygen mixed - 7 - nitrogen Weng miscellaneous screw [4.5] decane trifluoroacetic acid salt; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - (1 - hydroxy - 1 - methyl ethyl) piperidine Weng; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) - 2H-indazole-2-yl] phenyl} amino) carbonyl] -1-benzyl piperidinium; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-ethyl piperidonium; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -

1-ethyl piperidonium; 2-[3-(1, 4-diazacyclic heptane-1-yl carbonyl) -4-fluorophenyl] -2H-indazole-7-formamide trifluoroacetate; {4-[7-(aminocarbonyl) -4-chloro-2H-indazole-2-yl] benzyl} tert-butyl methyl carbamate; Trifluoroacetic acid 6-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline; Trifluoroacetic acid 2-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} pyrrolidonium; 6-fluoro-2-{4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; 5-fluoro-2-{2-fluoro-4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; 2-{3-hydroxy-4-[(methylamino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2-(4-{[formyl (methyl) amino] methyl} -3-hydroxyphenyl) -2H-indazole-7-formamide; 2-{2-chloro-4-[(methyl amino) methyl] phenyl} -5-fluoro-2h-indazole-7-formamide; 5-fluoro-2-{3-fluoro-4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2-{2, 5-difluoro-4-[(methyl amino) methyl] phenyl} -5-fluoro-2h-indazole-7-formamide trifluoroacetate; 2-(4-bromophenyl) -2H-indazole-7-formamide; Chloride (3 r) - 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 1 - methyl piperidine Weng; Trifluoroacetic acid (3 r) - 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 1 - methyl piperidine Weng; 2-(1, 2, 3, 4-tetrahydroisoquinoline-7-yl) -2H-indazole-7-formamide; (R) - 2 - (4 - ({3 - [(dimethyl amine) methyl] piperidine - 1 - base} methyl) phenyl) - 2 h - indazole - 7 - formamide; (S) - 2 - (4 - ({3 - [(dimethyl amine) methyl] piperidine - 1 - base} methyl) phenyl) - 2 h - indazole - 7 - formamide; 4 - [3 - ({7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) - 2 - (methyl chloride) - 3 - oxygen generation - trifluoroacetic acid ammonium propane - 1; 5-fluoro-2-{3-fluoro-4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide hydrochloride; 2-{4-[(dimethylamino) methyl] -3-fluorophenyl} -5-fluorophenyl - 2H-indazole-7-formamide trifluoroacetate; 2-{4-[(azacyclic butane-3-yl carbonyl) amino] phenyl} -5-fluoro-2h-indazole-7-formamide; 2-[4-(2, 7-diazania [4.5] decan-2-yl methyl) phenyl] -2H-indazole-7-formamide; (1 s, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 2 - (4 - benzyl chloride) - 5 - nitrogen hetero - 2 - Weng mixed double loop [2.2.1] heptane trifluoroacetic acid salt; (1 s, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 2 - (3 - benzyl chloride) - 5 - nitrogen hetero - 2 - Weng mixed double loop [2.2.1] heptane trifluoroacetic acid salt; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - [(methyl amino) carbonyl] piperazine - 1 - Weng; N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base]

benzyl} - 2 - hydroxy - 2 - pyridine - 3 - base ethane trifluoroacetic acid ammonium; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-cyclohexyl-2-hydroxy-ethane trifluoroacetate ammonium; Trifluoroacetic acid and 4 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 6 - (hydroxy methyl) - 1, 4 - oxygen mixed nitrogen heterocyclic heptane - 4 - Weng; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl) ring butyl] methyl} methane trifluoroacetic acid ammonium; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl) cyclohexyl] methyl} methane trifluoroacetic acid ammonium; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - (5 - methyl - 1 h - benzene and imidazole - 2 -) piperidine Weng; Double (trifluoroacetic acid) 2 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - hydroxy piperidine Weng - 4 - base) pyridine Weng; Trifluoroacetic acid 1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl}-3, 3-difluoropyrrolidonium; 2-(4-{[(2R)-2-(fluoromethyl) pyrrolidine 1-yl] methyl} phenyl) -2H-indazole-7-formamide; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-oxo pyrrolidine 3-trifluoroacetate ammonium; 5-fluoro-2 -(4-formyl phenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 3 - [({4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - nitrogen heterocyclic butane Weng; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] benzyl} - 3 - [(dimethyl ammonium) methyl] piperidine Weng; Trifluoroacetic acid 3 - [({4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} - 2 - fluorine amino) carbonyl] nitrogen heterocyclic butane Weng; 2 - {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] benzyl} - 2, 7 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); 4, 5-difluoro-2 -{4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2 - (3-5 - fluoro - fluoro - 4 - {[1 - methyl nitrogen heterocyclic butane - 3 - base) carbonyl] amino} phenyl) - 2 h - indazole - 7 - formamide trifluoroacetic acid salt; 5-fluoro-2 -(3-fluoro-4-formylphenyl) - 2H-indazole-7-formamide; 5-fluoro-2 -(5-fluoro-2-formylphenyl) -2H-indazole-7-formamide; {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} - 2 - fluorine - N - {[1 - (hydroxy methyl) cyclopentyl] methyl} methane trifluoroacetic acid ammonium; 5 - fluoro - 2 - [3 - fluoro - 4 - ({[(3 r) - 1 - methyl piperidine - 3 - base] carbonyl} amino) phenyl] - 2 h - indazole - 7 - formamide trifluoroacetic acid salt; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] - 2 - fluorine benzyl} - 4 - methyl

piperazine Weng; Double (trifluoroacetic acid) 4 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl piperidine Weng; Double (trifluoroacetic acid) 4 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] - 2 - fluorine benzyl} ammonium) methyl] 1 - methyl piperidine Weng;

And their pharmaceutically acceptable salts or tautomers.

Other special compounds within the scope of the invention are:

Trifluoroacetic acid 7-[7-(aminocarbonyl) -2H-indazole-2-yl] -1-methyl-1, 2, 3, 4-tetrahydroisoquinoline; Trifluoroacetic acid 3-{4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] phenyl} -1-ethylpiperidine; 2-(4-cyanophenyl) -5-fluoro-2h-indazole-7-formamide; 5-fluoro-2 - [4-(1H-tetrazole-5-yl) phenyl] -2H-indazole-7-formamide; 2-(4-aminophenyl) -5-fluoro-2h-indazole-7-formamide hydrochloride; 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] pyrrolidine-1-tert-butyl formate; Trifluoroacetic acid 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] pyrrolidonium; Trifluoroacetic acid 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] -1-methylpyrrolidonium; Trifluoroacetic acid 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] -1-ethyl pyrrolidonium; Trifluoroacetic acid 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] -1-propylpyrrolidonium; Trifluoroacetic acid 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] -1-isopropylpyrrolidonium; Trifluoroacetic acid 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] -1-cyclohexyl pyrrolidonium; Trifluoroacetic acid 3-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] -1-cyclobutyl pyrrolidonium; 4-[7-(aminocarbonyl) -2H-indazole-2-yl] -4-methylpiperidine-1-tert-butyl formate; Trifluoroacetic acid 4-[7-(aminocarbonyl) -2H-indazole-2-yl] -4-methylpiperidine; Trifluoroacetic acid 2-{4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] phenyl} pyrrolidonium; 2-[4-(4, 5-dihydro-1H-imidazole-2-yl) phenyl] -5-fluoro-2H-indazole-7-formamide trifluoroacetate; Chlorinated 6-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline onium; 2-{4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] phenyl} piperidine chloride; 5-fluoro-2 -[4-(1H-pyrazole-1-yl) phenyl] -2H-indazole-7-formamide; 5-fluoro-2 -(3-piperidine-3-phenyl) -2H-indazole-7-formamide; 2-[4-(aminosulfonyl) phenyl] -5-fluoro-2h-indazole-7-formamide; 5-fluoro-2 -(5, 6, 7, 8-tetrahydro-1, 7-diazanthothalene-3-yl) -2H-indazole-7-formamide; 5-fluoro-2 -(4-piperazine-2-phenyl) -2h-indazole-7-formamide; Methyl 4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] benzoate; 5-fluoro-2 -(1-methylpiperidine - 3-yl) -2H-indazole-7-formamide; 5-fluoro-2 -(1-ethylpiperidine-3-yl) -2H-indazole-7-formamide; 5-fluoro-2 -(1-propyl piperidine - 3-yl) -2H-

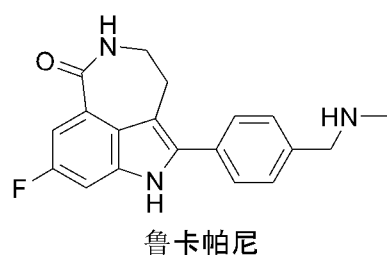
indazole-7-formamide; 5-fluoro-2-(1-isopropyl piperidine-3-yl)-2H-indazole-7-formamide; 2-(1-cyclohexyl piperidine-3-yl)-5-fluoro-2H-indazole-7-formamide; 5-fluoro-2-(1-methylpiperidine-4-yl)-2H-indazole-7-formamide; 5-fluoro-2-(1-ethylpiperidine-4-yl)-2H-indazole-7-formamide; 5-fluoro-2-(1-propyl piperidine-4-yl)-2H-indazole-7-formamide; 5-fluoro-2-(1-isopropyl piperidine-4-yl)-2H-indazole-7-formamide; 2-(1-cyclohexyl piperidine-4-yl)-5-fluoro-2H-indazole-7-formamide; 2-(1-cyclobutyl piperidine-4-yl)-5-fluoro-2H-indazole-7-formamide; 2-(1-cyclobutyl piperidine-3-yl)-2H-indazole-7-formamide; 2-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl]-N,N-dimethyl ethane trifluoroacetate ammonium; 2-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl]-N,N-diethyl ethane trifluoroacetate ammonium; N-{2-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] ethyl} propane-2-trifluoroacetate ammonium; N-{2-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] ethyl} cyclohexane trifluoroacetate ammonium; 2-[2-(dicyclobutyl amino) ethyl]-5-fluoro-2H-indazole-7-formamide; 3-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] piperidine-1-tert-butyl formate; 4-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] piperidine-1-tert-butyl formate; Trifluoroacetic acid 3-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] piperidine; Trifluoroacetic acid 4-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] piperidine; 3-[7-(aminocarbonyl)-2H-indazole-2-yl] piperidine-1-tert-butyl formate; {2-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] ethyl} tert-butyl carbamate; 2-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] ethane ammonium trifluoroacetate; Trifluoroacetic acid 3-[7-(aminocarbonyl)-2H-indazole-2-yl] piperidine; Trifluoroacetic acid 3-[7-(aminocarbonyl)-2H-indazole-2-yl]-1-methylpiperidine; Trifluoroacetic acid 3-[7-(aminocarbonyl)-2H-indazole-2-yl]-1-ethylpiperidine; Trifluoroacetic acid 3-[7-(aminocarbonyl)-2H-indazole-2-yl]-1-propyl piperidine; Trifluoroacetic acid 3-[7-(aminocarbonyl)-2H-indazole-2-yl]-1-isopropyl piperidine; Trifluoroacetic acid 3-[7-(aminocarbonyl)-2H-indazole-2-yl]-1-cyclohexyl piperidine; Trifluoroacetic acid 3-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl]-1-cyclobutyl piperidine; N-{2-[7-(aminocarbonyl)-5-fluoro-2H-indazole-2-yl] ethyl}-N-propyl propane-1-ammonium trifluoroacetate;

2-(4-哌啶-3-基苯基)-2H-吡唑-7-甲酰胺;
 2-{4-[(3R)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;
 2-{4-[(3S)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;
 5-氟-2-(4-哌啶-3-基苯基)-2H-吡唑-7-甲酰胺;
 5-氟-2-{4-[(3S)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;
 5-氟-2-{4-[(3R)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;
 5-氟-2-(3-氟-4-哌啶-3-基苯基)-2H-吡唑-7-甲酰胺;
 5-氟-2-{3-氟-4-[(3R)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;
 5-氟-2-{3-氟-4-[(3S)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;

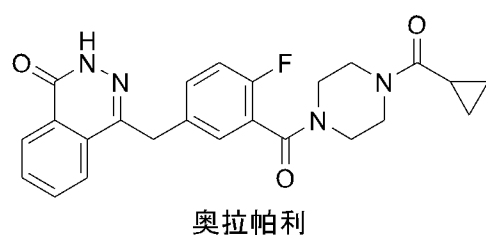
 2-{4-[(3R)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;
 2-{4-[(3S)-哌啶-3-基]苯基}-2H-吡唑-7-甲酰胺;

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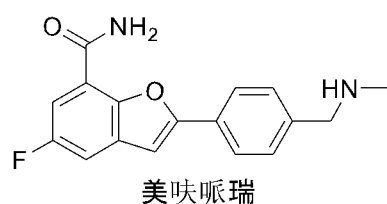
In a given scheme, the compound shown in Equation I is



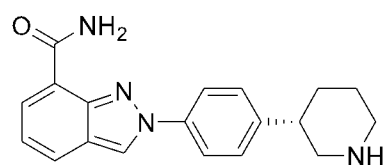
In a given scheme, the compound shown in Equation II is



In a given scheme, the compound shown in Equation III is

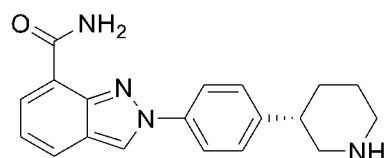


In a given scheme, the compound shown in Equation IV is

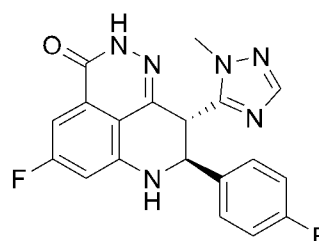


尼拉帕利

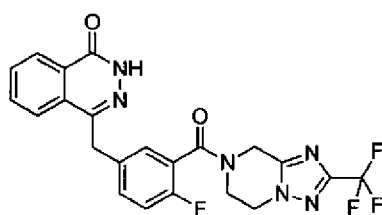
In A protocol, the substance A is selected from one or more of nitaparib, tarazoparib, fluzoparib, simpiperide, IMP4297, BGB-290, ABT-888, lucaparib, olaparib and melfupiperide;



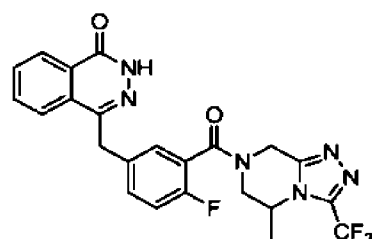
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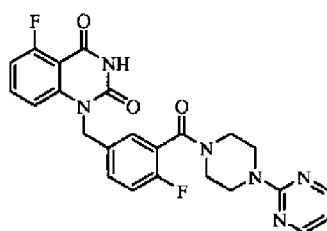
他拉唑帕利



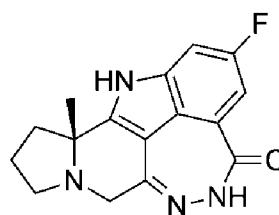
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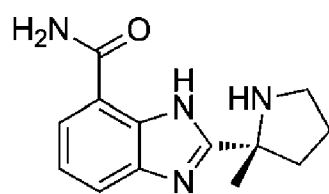
希明哌瑞



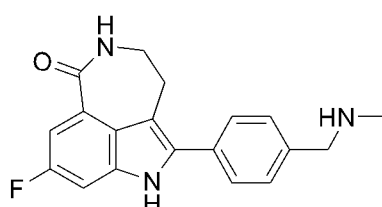
IMP4297



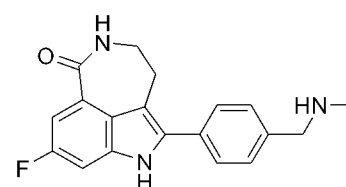
BGB-290



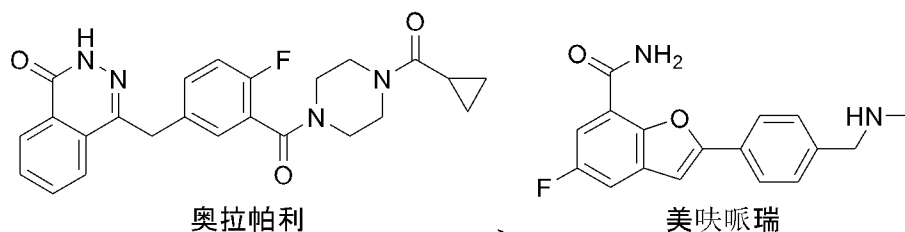
ABT-888



鲁卡帕尼

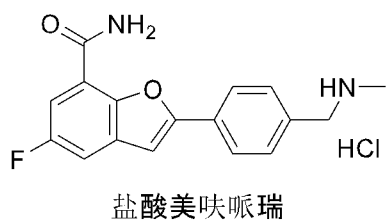


卢卡帕利(Rucaparib)



In a protocol, the pharmaceutically acceptable salt is hydrochloride.

In a protocol, the pharmaceutically acceptable salt of substance A is



In a protocol, the poly ADP ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof is in the form of a pharmaceutical composition containing it. Preferably, the drug composition has the poly ADP-ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof as the sole active ingredient of the drug composition; And/or, the drug composition also contains a pharmaceutically acceptable vehicle, such as a pharmaceutically acceptable pharmaceutical excipient.

In a protocol, the poly ADP-ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof is in the form of a kit containing it, which also includes drugs for the treatment of coronavirus-related diseases and/or drugs for the treatment of diseases caused by other viruses.

In order to solve the technical problems mentioned above, the second aspect of the invention provides an application of the compound shown in Equation III and/or the compound shown in Equation IV or a pharmaceutically acceptable salt thereof as described in the first aspect of the invention in the preparation of antiviral agents or in the preparation of drugs for the treatment of diseases caused by viruses. The viruses are viruses of the family HIV, HPV, EBV, IFV, and/or preferably the family orthocoronavirus subfamily.

In a protocol, the pharmaceutically acceptable salt is hydrochloride. In one of the better embodiments of the invention, the preferred pharmaceutically acceptable salt is mefuurperyl hydrochloride.

In a scheme, the compound shown in Equation III and/or the compound shown in Equation IV or a pharmaceutically acceptable salt thereof is present in the form of a pharmaceutical

composition containing it; Preferably, the drug composition has the compound shown in Equation III and/or the compound shown in Equation IV or a pharmaceutically acceptable salt thereof as the sole active ingredient of the drug composition; And/or, the drug composition also contains a pharmaceutically acceptable vehicle, such as a pharmaceutically acceptable pharmaceutical excipient.

In a protocol, the compounds shown in Equation III and/or the compounds shown in Equation IV or their pharmaceutically acceptable salts are in the form of a kit containing them, which also includes other drugs against diseases caused by coronaviruses.

In one scenario, described are coronavirus subfamily of the virus to alpha coronavirus genus, gamma, beta coronavirus coronavirus and/or delta virus of the genus coronavirus, optimization of upper respiratory tract infection cause acute respiratory syndrome coronavirus, virus such as SARS associated coronavirus and/or the Middle East respiratory syndrome coronavirus (MERS - CoV).

Preferably, the coronaviruses that cause upper respiratory tract infections are human coronavirus 229E, human coronavirus HKU1 (HCOV-HKU1), human coronavirus OC43 (HCOV-OC43), human coronavirus NL63 (HCOV-NL63) and/or mouse hepatitis virus A59 (MHV-A59).

Preferably, the SARS-associated coronavirus is SARS-CoV (Severe acute respiratory syndrome coronavirus) or SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2).

In a better embodiment of the invention, the coronaviruses include severe acute respiratory syndrome coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In a better embodiment of the invention, the coronavirus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In addition, in order to solve the technical problems mentioned above, the present invention also provides a polyADP ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof for the preparation of drugs for virus-related diseases.

Preferably, the poly ADP ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof is described in the first aspect of the invention.

Preferably, the medicine for the virus-related disease is as described in the second aspect of the invention.

In order to solve the technical problems mentioned above, the invention also provides a drug for the treatment of virus-related diseases as described in the second aspect of the invention, which includes a polyADP ribose polymerase inhibitor as described in the first aspect of the invention or a pharmaceutical acceptable salt thereof.

In order to solve the technical problems mentioned above, the invention also provides a virus inhibitor, which includes a polyADP ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof as described in the first aspect of the invention. The virus is the virus described in the second aspect of the invention.

In order to solve the above technical problems, the invention also provides an application of a polyADP-ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof as described in the first aspect of the invention in the treatment of virus-related diseases as described in the second aspect of the invention.

The term "pharmaceutically acceptable" means that salts, solvents, excipients, etc. are generally non-toxic, safe, and appropriate for patient use. The "patient" is preferably a mammal and preferably a human being.

The term "pharmaceutically acceptable salt" means a salt prepared from a compound of the invention with a relatively non-toxic, pharmaceutically acceptable acid or base. When a compound of the present invention contains a relatively acidic functional group, a base addition salt may be obtained by contacting the neutral form of such compound with a sufficient amount of a pharmaceutically acceptable base in a pure solution or in a suitable inert solvent. Pharmaceutically acceptable alkali addition salts include but are not limited to: lithium, sodium, potassium, calcium, aluminum, magnesium, zinc, bismuth, ammonium and diethanolamine salts. When a compound of the present invention contains a relatively basic functional group, an acid addition salt may be obtained by contacting the neutral form of such compound with a sufficient amount of a pharmaceutically acceptable acid in a pure solution or in a suitable inert solvent. The pharmaceutically acceptable acids include inorganic acids, which include but are not limited to: hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, carbonic acid, phosphoric acid, phosphite, sulfuric acid, etc. The pharmaceutically acceptable acids include organic acids, which include but are not limited to: Acetic acid, propionic acid, oxalic acid, isobutyric acid, maleic acid and malonic acid, benzoic acid, succinic acid, adipic acid, fumaric acid, lactic acid and mandelic acid, phthalic acid, benzene sulfonic acid, p-toluene sulfonic acid, citric acid, salicylic

acid, tartaric acid and methyl sulfonic acid, isonicotinic acid, citric acid, oleic acid, tannic acid type acid, pantothenic acid, tartaric acid, ascorbic acid, hydrogen gentisic acid, fumaric acid, gluconic acid, Glycolic acid, formic acid, ethanesulfonic acid, dihydroxynaphthalinic acid (i.e. 4, 4'-methylene - bis (3-hydroxy-2-naphthalamic acid)), amino acids (e.g., glutamic acid, arginine), etc. When the compounds of the present invention contain relatively acidic and relatively basic functional groups, they can be converted into base addition salts or acid addition salts. For details, see Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977) or Handbook of Pharmaceutical Salts: Properties, Selection, and Use (P. Heinrich Stahl and Camille G. Wermuth, ed., Wiley-VCH, 2002).

The term "solvent complex" means a substance formed by the combination of a compound of the invention with a stoichiometric or non-stoichiometric solvent. The solvent molecules in a solvent complex may exist in an ordered or nonordered arrangement. The solvent includes but is not limited to: water, methanol, ethanol, etc.

The terms "pharmaceutically acceptable salt" and "solvent compound" in "pharmaceutically acceptable salt solvent complex" refer, as described above, to substances formed by combination of the compound of the invention with 1, prepared from a relatively non-toxic, pharmaceutically acceptable acid or base, 2, and stoichiometric or non-stoichiometric solvent. The "solvent complex of pharmaceutically acceptable salts" includes, but is not limited to, the hydrochloric acid monohydrate of the compound of the invention.

The term "multiple" means two, three, four, or five.

When any variable (such as R^{11-1}) appears several times in the definition of a compound, the definition of each position of the variable has nothing to do with the definition of the other positions, and their meanings are independent and do not affect each other. Therefore, if a group is replaced by one, two, or three R^{11-1} groups, that is, the group may be replaced by up to three R^{11-1} groups, and the definition of R^{11-1} at this position is independent of the definition of R^{11-1} at the other positions. In addition, combinations of substituents and/or variables are allowed only if the combination yields a stable compound.

The term "halogen" refers to fluorine, chlorine, bromine, or iodine.

The term "hydrocarbon group" means the monovalent fraction obtained by the removal of hydrogen atoms from the carbon atoms of a hydrocarbon compound having between 1 and 20 carbon atoms (unless otherwise specified), which may be aliphatic or aliphatic and may be

saturated or unsaturated (e.g., partially unsaturated, completely unsaturated). Thus, THE term "hydrocarbon group" includes small alkyl groups, alkenyl groups, alkyne groups, cycloalkyl groups, cycloalkenyl groups, cycloalkyne groups, etc.

The term "alkyl" refers to a straight or branched alkyl group with a specified number of carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl and similar alkyl groups.

The term "alkenyl" refers to a straight-chain or branched alkenyl group with a specified number of carbon atoms.

The term "alkyne group" refers to a straight or branched alkyne group with a specified number of carbon atoms.

The term "alkoxy group" refers to the group $-O-R^X$, where R^X is the alkyl group as defined above.

THE TERM "CYCLOALKYL" REFERS TO UNIVALENT SATURATED CYCLIC ALKYL GROUPS, PREFERABLY WITH 3 to 7 cyclic carbon atoms, or preferably with 3 to 6 CARBON ATOMS, SUCH AS cycloPROPYL, cyclobutyl, CYCLOpentyl, or CYCLOhexyl.

The term "heterocyclic group" or "heterocyclic" refers to the univalent fraction of a heterocyclic compound, obtained by the removal of hydrogen atoms from the ring atom, having 3 to 20 ring atoms (unless otherwise specified), of which 1 to 10 are ring heterocyclic atoms and may be aromatic or nonaromatic. Preferably, each ring has three to seven ring atoms, of which one to four are ring heteroatoms.

The term "heterocyclic alkyl" refers to a saturated monocyclic group with heteroatoms, preferably a 3-to 7-member-saturated monocyclic group containing one, two, or three ring heteroatoms independently selected from N, O, and S. Heterocyclic alkyl example is: pyrrole alkyl, tetrahydrofuran, four hydrogen pyran, tetrahydrothiophene base, four hydrogen pyridine, pyrrole four hydrogen, nitrogen heterocyclic butyl alkyl, thiazole alkyl, alkyl, piperidine, morpholine, sulfur, generation of morpholine, piperazine, alkyl, two nitrogen heterocyclic nitrogen heterocyclic g heptyl alkyl, oxygen and nitrogen heterocyclic heptyl alkyl, etc. The preferred heterocyclic groups are morpholine 4-group, piperidine-1-group, pyrrolidine 1-group, thio-morpholine 4-group and 1, 1-dioxy-thio-morpholine 4-group.

The term "hetero-aryl group" or "hetero-aromatic ring" refers to an aromatic group containing hetero-atoms, preferably one, two, or three aromatic 5-6 membered rings or 9-10-

membered double rings independently selected from nitrogen, oxygen, and sulfur. Such as furan base, pyridyl, pyridazine, pyrimidine base, pyrazine, thiophene, different imidazolyl, pbo base, two imidazolyl, imidazole, pyrrole, pyrazole, triazole,, thiazolyl tetrazolium group and different thiazolyl, thiamethoxam imidazolyl, benzene and imidazole, indole, indazole, benzothiazole base, benzene and different thiazolyl, benzene and imidazolyl, benzene and different imidazolyl, quinoline, isoquinoline, etc.

The pharmaceutical compositions mentioned in the invention, which use the compound as the active ingredient, can be prepared according to a method known in the field. The compound of the invention may be made into any dosage form suitable for human or animal use. The weight content of the compound of the invention is usually 0.1 to 99.0% in its pharmaceutical composition.

The pharmaceutically acceptable carrier may be a conventional carrier in this field, and the carrier may be any appropriate physiologically or pharmaceutically acceptable pharmaceutical excipient. The pharmaceutical excipients mentioned above are conventional pharmaceutical excipients in this field, preferably including pharmaceutically acceptable excipients, fillers or diluents, etc. Better, the drug composition includes 0.01 to 99.99% of the protein and/or the antibody-drug conjugate, and 0.01 to 99.99% of the pharmaceutical carrier, the percentage being the mass percentage of the drug composition.

The compound of the invention or the pharmaceutical composition containing it can be administered in the form of unit dose, and the route of administration can be intestinal or parenteral, such as oral, intravenous, intramuscular, subcutaneous, nasal, oral mucosa, eye, lung and respiratory tract, skin, vagina, rectum, etc.

The dosage form may be liquid, solid, or semi-solid. Liquid dosage forms can be solution (including real solution and colloid solution), emulsion (including O/W type, W/O type and compound emulsion), suspension, injection (including water injection, powder injection and infusion), eye drops, nose drops, lotion and liniment, etc.; Solid dosage forms can be tablets (including ordinary tablets, enteric-coated tablets, lozenges, dispersible tablets, chewing tablets, effervescent tablets, oral disintegrating tablets), capsules (including hard capsules, soft capsules, enteric-soluble capsules), granules, dispersions, pellets, drops, suppositories, film agents, patches, gas (powder) fog, sprays, etc.; Semi-solid dosage form can be ointment, gel, paste, etc.

The compound of the invention can be prepared into ordinary preparations, sustained

release preparations, controlled release preparations, targeted preparations and various particle delivery systems.

On the basis of conforming to the common knowledge in this field, the above optimal conditions can be arbitrarily combined to obtain the better examples of the invention.

The reagents and raw materials used in the invention are commercially available.

The positive progressive effect of the present invention is that the present invention has proved for the first time that the poly ADP ribose polymerase inhibitor can inhibit the infection of coronavirus to host cells and the replication of coronavirus in a dose-dependent manner and has no obvious cytopathic effect, which can be used for the treatment of anti-coronavirus infection. The polyADP ribose polymerase inhibitor or its pharmaceutically acceptable salt, and the pharmaceutical composition containing it, and the drug box set of the invention have a lower effective concentration and a higher antiviral activity when they are used in the human body, ensuring that they are less toxic and safer. Therefore, it can play an effective role in suppressing the virus when it is applied to the clinical treatment of diseases caused by coronavirus. In one of the better embodiments of the invention, the inhibition rate of the polyADP-ribose polymerase inhibitor against the virus is up to 35% (the inhibition rate of Arbidol against the virus is only 21% under the same conditions).

Figures and figure legends

Figure 1 shows the results of the inhibitory activities of mefururidine hydrochloride (CVL218) and Olaparib against SARS-CoV-2.

Figure 2 shows the viral activity and cell activity of mefuurperide hydrochloride (CVL218) against SARS-CoV-2, where A and B are different batches of experiments.

Figure 3 shows the cytotoxicity of Olaparib in Vero-E6 cells.

Figure 4 shows the in vitro anti-SARS-CoV-2 activity of the test drug. (A) The expression of viral nucleoprotein (NP) in Vero cells treated with CVL218 14 hours after SARS-CoV-2 infection (NP denotes nuclear protein staining, DAPI denotes nuclear DNA staining, where DAPI is staining agent 4', 6-diaminidine-2-phenylindole) was observed by fluorescence microscopy. (B) The inhibitory effects of CVL218 and remdesivir on SARS-CoV-2 in vitro and their relationship with different time of action. The viral inhibitory activities of CVL218 and remdesivir were measured at the "whole process", "during virus entry" and "after virus entry" stages, respectively. (C) The expression of viral NP in cells infected with CVL218 and remdesivir

was analyzed by Western blot

Figure 5 shows that CVL218 attenuated CpG-induced IL-6 production in a time-and dose-dependent manner.

Figure 6 shows the effects of CVL218 on body weight in rats (A) and monkeys (B). CVL218 was orally administered to rats and monkeys at doses of 20/60/160 mg/kg and 5/20/80 mg/kg for 28 days and then discontinued for 28 days, demonstrating a good safety profile of CVL218.

Figure 7 shows the interaction model structure of the N-terminal nucleocapsid protein (N-NTD) of SARS-CoV-2 in complex with PARP1 inhibitor. (A). Simulated structure of SARS-CoV-2-N-NTD complex bound to CVL218 and OLapariB (both modeled by AutoDock4.2). (B). Interaction patterns of viral N-NTD and PARP1 inhibitors CVL218 and Olaparib. Key residues are shown as sticks. Hydrogen bonds are shown as dashed lines.

Figure 8 shows the tissue distribution characteristics of CVL218 in rats, with the highest concentration in the lungs. After oral administration of 20 mg/kg, the concentration of CVL218 in different tissues was measured at the time point of 3/6/8 h.

Specific mode of implementation

The invention is further described below by means of embodiments without thereby limiting the invention to the scope of the embodiments. Experimental methods not specified in the following embodiments are usually performed in accordance with conventional conditions such as those described in the Guidelines for Molecular Cloning Experiments (Third edition, Science Press, 2005) and other commonly used reference books in this field, or as recommended by the reagent manufacturer.

(1) Main instruments (name and number) are shown in Table 1 below.

Table 1

Instrument Name	Manufacturer	instrument number
Quantitative PCR QuantStudio Dx	ABI	04-620
MagNA Pure LC2.0 automatic nucleic acid extractor	Roche	-
Carbon Dioxide Incubator (GALAXYS)	RsBiotech	04-0303
Inverted microscope	NiKon	0393

(2) Experimental reagents and virus strains

1) The reagents are shown in Table 2.

Table 2

Name article	manufacturer	number	validity
DMSO	Biyuntian Biotechnology	ST-1276-500ml	-
DMEM	Gibco	12430-054	2020-10-30
CCK-8	Biyuntian Biotechnology	C0039	-
Nucleic acid Extraction Kit	Roche	03038505001	2021-06
Novel Coronavirus 2019 nucleic Acid Test Kit	Shanghai Berger	SJ-HX-226-2	2021-01-16

2) SARS-CoV-2 virus strain

① Obtained from BSL-3 Laboratory of Jiangsu Center for Disease Control and Prevention. The internal number of this strain is 2019-NCOV-1.

② The virus was obtained from Wuhan Institute of Virology (IVCAS 6.7512), Wuhan Institute of Virology, Chinese Academy of Sciences, National Virus Repository.

After identification, the genomes of the above two virus strains were completely identical, so they were both SARS-CoV-2 virus strains, and 2019-NCOV-1 was the main virus strain used in the subsequent experiment.

(3) Drugs

Zanamivir, oseltamivir, Remdesivir, baricitinib, Olaparib and Arbidol, all supplied by MCE (Medchem Express, China). The PARP1 inhibitor mefurperil hydrochloride (CVL218, also see patent application 201210028895.0) has a purity of more than 99.0% and is provided by Fukang (Shanghai) Health Technology Co., LTD.

Example 1. In vitro anti-SARS-CoV-2 activity detection of mefururidine hydrochloride (CVL218)

1.1 Experimental groups:

- 1) Arbidol 3 μ m group and 30 μ m group
- 2) Mefurperide hydrochloride (CVL218) 3 μ m group
- 3) Mefurperide hydrochloride (CVL218) 30 μ m group
- 4) Zanamivir group
- 5) Oseltamivir group
- 6) Olaparib 3.2 μ m group
- 7) Baricitinib 3.2 μ m group
- 8) DMSO control group

9) Virus control group: only virus was added, and no drug was added

10) Cell control group: containing only cells, without adding virus and drugs

1.2 Drug dilution:

For each group of drugs, 15 μ l of 1mM mother liquor was added with 4985 μ l of cell maintenance solution (i.e. DMEM medium) to obtain 3 μ m application solution. 30 μ m application solution was obtained by taking 3 μ l 20mM mother solution and adding 1997 μ l cell maintenance solution for CVL218. DMSO was diluted according to the dilution ratio of the corresponding drug.

1.3 Experimental procedure:

1.3.1 Cell preparation and Drug pretreatment (Cell culture chamber)

Vero-e6 cells (purchased from ATCC cell bank) were seeded in 96-well culture plates according to 1×10^4 cells/well, and cultured in DMEM containing 10% (v/v) fetal bovine serum for 16 hours until 80% slices were formed. After that, the cell culture medium of each well was absorbed and washed once with sterile PBS. According to the experimental groups, different drugs diluted in cell maintenance solution (50 μ L/well) in 1.2 were added to each well, and 4 multiple Wells were set up in each group, and the cells were pretreated in 5% CO₂ incubator at 37°C for 1h. Only 50 μ L cell maintenance solution was added to virus control group and cell control group.

1.3.2 Virus infection and culture (BSL-3 Laboratory) :

After 1 hour of drug pretreatment, in addition to the cell control group, 2 μ l SARS-CoV-2 strain was added to each well to make the Multiplicity of infection (MOI = 0.05). The virus was placed at 37°C and absorbed in 5% CO₂ incubator for 2 hours. After adsorption, the medium with virus was discarded, and a new drug-containing medium was added according to the experimental group, and the culture was incubated for 48h at 37°C in 5% CO₂ incubator. At the end of culture, the cytopathic conditions of each experimental group were observed and recorded under the microscope. 120 μ l of culture supernatant from each well was absorbed and placed at 56°C for 30min. After inactivation, 100 μ l of each well was added to the reagent tank lysate of nucleic acid extraction reagent. The external surface of the reagent tank was disinfected and then transferred to BSL-2 laboratory for viral nucleic acid extraction and genetic testing.

1.3.3 Nucleic acid extraction:

Virus nucleic acid RNA extraction was carried out according to the operation instructions

of automatic nucleic acid extraction instrument and extraction kit.

1.3.4 Fluorescence quantitative PCR detection

The PCR reaction system was configured according to the Shanghai Berger Novel Coronavirus 2019 nucleic acid testing Kit instructions. The specific reaction system was as follows: qRT-PCR reaction solution 6 μ L, qRT-PCR enzyme mixture 2 μ L, primer probe 2 μ L, and 2.5 μ L of viral nucleic acid RNA template extracted above; The reaction parameters were as follows: 50°C for 10min, 95°C for 5min, 40 cycles of 95°C for 10s, 55°C for 40s (FAM channel and VIC channel fluorescence signals were collected at this step). The transcription levels of SARS-CoV-2 genes (ORF1ab and N) were measured to reflect the level of viral replication. The $2^{-\Delta CT}$ value was calculated according to the CT value given by the PCR instrument to represent the relative virus content of the experimental group compared with the control group. The viral replication inhibition rate (%) = $(1 - 2^{-\Delta CT}) \times 100\%$.

1.4 Experimental Results

Mefururidine hydrochloride (CVL218), Olaparib and other compounds and their inhibitory effects on SARS-CoV-2 coronavirus are shown in Figure 1, Figure 2 and Table 3. No inhibitory activity was detected in the control group. It can be seen from Figure 1 and Table 3 that CVL218 can effectively inhibit the replication of SARS-CoV-2 in Vero-E6 cells. The inhibition rate of CVL218 at 3 μ M concentration to the virus was 35%, which was higher than 21% of the control drug Arbidol. The anti-influenza drugs Zanamivir and Oseltamivir showed no activity against SARS-CoV-2. When the concentration of CVL218 reached 30 μ M, the inhibition rate of CVL218 against the virus was more than 99%. Figure 2 shows that the EC₅₀ of CVL218 against SARS-CoV-2 was 7.67 μ M and 5.12 μ M in different batches, respectively, in a dose-dependent manner (experimental procedure as shown in Example 2). Figure 1 and Table 3 also show that the PARP-1 inhibitor Olaparib also showed mild anti-SARS-CoV-2 activity, with an inhibition rate of about 12% or 15.8% against the virus at 3.2 μ M, while the inhibition rate of the JAK-1 inhibitor Baricitinib virus was almost 0%.

In conclusion, both PARP1 inhibitors Olaparib and CVL218 showed inhibitory effects on SARS-CoV-2 replication. Moreover, the inhibition rate of CVL218 was higher than olaparib. Notably, the antiviral efficacy of CVL218 exceeds that of Arbidol, which is one of the standard treatment methods for COVID-19 in the Novel Coronavirus Diagnosis and Treatment Protocol for Pneumonia (6th Edition) issued by the Chinese government.

Table 3

drugs	Arbidor 3μM	CVL21 8 3μM	zanamivir 3μM	Oseltamivir 3μM	CVL21 8 30μM	olaparib	Baritinib	Abidor 30μM
Inhibition %	21.73	35.16	No inhibitory activity (-10.69)	No inhibitory activity (-13.47)	99.68	12% (15.48 inhibition in another batch when different batches were tested)	No inhibitory activity (-10%) (for different batches, the inhibition rate of another batch was -7.52)	98.93

Embodiment 2: The cytotoxicity of mefururidine hydrochloride (CVL218) on Vero-E6 cells

2.1 Experimental grouping:

- 1) Mefuroperide hydrochloride (CVL218) group
- 2) DMSO control group
- 3) Olaparib group
- 4) Cell control group: only containing cells, no drugs added

5) Blank control group (only containing medium without cells)

2.2 Drug dilution:

Mifupiril hydrochloride was obtained from Fukang (Shanghai) Health Technology Co., LTD. The purity was > 99.0%. After solubilization with DMSO, mifupiril was diluted in gradient according to Table 4 (maintenance solution was DMEM medium). DMSO was serially diluted according to the same dilution gradient.表 4

Diluent	combined	concentration
Dilution1	0.05mlmefuorperil hydrochloride stock solution (20 mM) +2.45ml maintenance solution	400 μ M
Dilution2	1ml Dilution1 +1ml maintenance solution	200 μ M
Dilution3	1ml Dilution2 +1ml maintenance solution	100 μ M
Dilution4	1ml Dilution3 +1ml maintenance solution	50 μ M
Dilution5	1ml Dilution4 +1ml maintenance solution	25 μ M
Dilution6	1ml Dilution5 +1ml maintenance solution	12.5 μ M
Dilution7	1ml Dilution6 +1ml maintenance solution	6.25 μ M
Dilution8	1ml Dilution7 +1ml maintenance solution	3.125 μ M

2.3 Experimental procedure:

2.3.1 Cell preparation and drug culture

Vero-e6 cells were seeded in a 96-well culture plate at a rate of 1×10^4 cells/well, and cultured with DMEM containing 10% fetal bovine serum for 16 hours until 80% slices were formed. After that, the cell culture medium of each well was aspirated, and the cells were washed once with sterile PBS. According to the experimental groups, different concentrations of drugs diluted in cell maintenance solution (200 μ L/well) were added to each well, and three multiple Wells were set up in each group and incubated at 37°C in 5% CO₂ incubator for 48h. DMSO control group was diluted with cell maintenance solution, and 200 μ L cell maintenance solution was added to cell control group. The blank control group contained only cells and no cells in the maintenance solution.

2.3.2 Toxicity test of mefupiperi hydrochloride and Olaparib on Vero-E6

The cell status was observed and recorded under an inverted microscope, and the toxicity of the drug to Vero-E6 cells was detected according to the operating instructions of CCK-8 kit: 20 μ L CCK-8 solution was added to all experimental Wells and control Wells, and the cell culture plates were incubated in 5% CO₂ incubator at 37°C for 1 hour. The absorbance value was measured at 450nm wavelength using a multifunctional microplate reader. According to the formula, the inhibition rate of cell activity (%) = $[1-(\text{drug group} - \text{blank control group})/(\text{cell control group} - \text{blank control group})] \times 100\%$.

The concentrations of mefuuridine hydrochloride and Olaparib were plotted on the abscissa, and the inhibition rate of cell proliferation was plotted on the ordinate. The result is shown in FIG. 3 as a circular solid point. As can be seen from the figure, the CC50 (50% cytotoxic concentration, the drug concentration at the time of 50% cell death) of mefuruperil hydrochloride in Vero-E6 cells was around 92 μm . There was no cytotoxicity at 30 μm mefuurperil hydrochloride. The results show that the safety of mefurupril hydrochloride (CVL218) is higher. The CC50 of Olaparib in Vero-E6 cells (50% cytotoxic concentration, the drug concentration at 50% cell death) was around 100-300 μm .

Example 3:

3.1 Indirect immunofluorescence assay

Vero E6 cells were treated with CVL218 at 5 μM , 15 μM and 25 μM , respectively, following the "whole process" treatment procedure. Infected cells were fixed with 80% acetone in PBS, permeated with 0.5% Triton X-100, and blocked with 5% BSA in PBS buffer containing 0.05% Tween 20 for 30 min at room temperature. Rabbit polyclonal antibody to SARS-CoV nucleocapsid protein (Cambridgebio, USA) was further incubated at a dilution of 1:200 for 2 h, followed by Alexa 488-labeled goat anti-rabbit antibody (Beyotime, China) at a dilution of 1:500 as a secondary antibody. Nuclei were stained with DAPI (Beyotime, China). The immunofluorescence was observed by fluorescence microscope.

Immunofluorescence microscopy showed that at 14 h after SARS-CoV-2 infection, the expression of viral nuclear protein (NP) in cells treated with CVL218 showed A dose-response relationship with the concentration of treated drugs, and the expression of NP in cells treated with CVL218 was significantly lower than that in cells treated with DMSO (A in Figure 4). No significant cytopathic effect was observed in infected cells treated with 25 μM CVL218.

3.2 Study on action time

To systematically evaluate the inhibitory activity of the compounds against SARS-CoV-2, we also performed addition time assays (methods) to determine at which stage the compounds inhibited viral infection. A relatively high dose of CVL218 (20 μm) and remdesivir (10 μm) was used for the determination of action time. Vero E6 cells with a density of 5×10^4 cells per well were treated with the test drug at different stages of virus infection, or DMSO as a control. The MOI of cells infected with virus was 0.05." The "whole process" treatment was performed to evaluate the maximum antiviral effect, and throughout the experiment, the test drug in the cell

medium was consistent with the description in the viral infection assay. In the "virus at entry" treatment, the test drug is added to the cells 1 hour before virus infection, and then the cells are maintained in the drug-virus mixture for 2 hours during virus infection. After that, the medium containing the virus and the test drug was replaced with fresh medium until the end of the experiment. In the "after virus entry" experiment, virus was first added to the cells and infected for 2 hours, and then the supernatant containing virus was replaced with medium containing drug until the end of the experiment. At 14 h after infection, the inhibition effect of the drug on the virus in the cell supernatant was quantified by qRT-PCR, and the DMSO group was used as the reference calculation.

The results showed that both CVL218 and remdesivir showed stronger antiviral activity throughout SARS-CoV-2 infection of Vero E6 cells compared with DMSO controls (B of Figure 4). The results of action time assay showed that CVL218 could partially counter virus entry and significantly inhibit replication after entry, whereas remdesivir was only effective at the post-entry stage (B and C of Figure 4). In conclusion, CVL218 may be a more advantageous potential therapeutic agent for COVID-19.

Embodiment 4: CVL218 inhibits CpG-ODN 1826-induced IL-6 production in PBMCs

Recently, interleukin-6 (IL-6) has been found to be one of The most important cytokines in The process of viral infection (L. Velazquez-Salinas, A. Verdugo-Rodriguez, L. L. Rodriguez, M. V. Borca, The Role Of interleukin 6 during Viral infections, *Frontiers in Microbiology* 10 (2019) 1057), Emerging clinical studies in humans and animals showed that Oversynthesis of IL-6 has been linked to the persistence of many viruses, Such as human immunodeficiency virus (HIV) (M. M. McFarland-mancini, H. M. Funk, A. M. Paluch, M. Zhou,P. V. Giridhar, C. A. Mercer, S. C. Kozma, A. F. Drew, Differences in wound healing in mice with deficiency of IL-6 versus IL-6 receptor,*The Journal of Immunology* 184 (12) (2010) 7219 -- 7228), foot-and-mouth disease virus (G. A. Palumbo, c. Scisciani, n. Pediconi, l. Lupacchini, da Ifalate, f. Guerrieri, Calvo, d. l. Salerno, s. Di Levrero Cocco, m., et al., IL6 inhibits HBV transcription by targeting the epigenetic control of the nuclear cccdna Minichromosome, *PLoS ONE* 10 (11)) and vesicular stomatitis virus (VSV) (L. Velazques-Salinas, S. J. Pauszek, C. Stenfeldt, E. S. O'Hearn, J. M. Pacheco, M. V. Borca, A. Verdugo-Rodriguez, J. Arzt, L. L. Rodriguez, Increased virulence of an Epidemic strain of Vesicular stomatitis virus is associated with interference of the innate response

in pigs, *Frontiers in Microbiology* 9 (2018) 1891. In addition, in vivo studies in a Friend retrovirus (FV) mouse model showed that IL-6 blockade reduced viral load, Enhancing virus-specific CD8+T cell immunity (W. Wu, K. K. Dietze, K. Gibbert, K. S. Lang, m. Trilling, h. Yan, Wu, J., Yang, m. d., m. Lu Roggendorf, et al., TLR ligand induced IL - 6 counter - regulates the Anti-viral CD8+ T cell Response during an Acute Retrovirus Infection, *Scientific Reports* 5 (2015) 10501). These findings support the hypothesis that That is, the rapid production of IL-6 may be a possible mechanism leading to harmful clinical manifestations in virus onset (J. Zheng, Y. Shi, L. Xiong, W. Zhang, Y. Li, P. G. Gibson, J.). L.S impson, c. j. Zhang, Lu, j. Sai, et al., The expression of IL - 6, tNF alpha, McP-1 in respiratory viral infection in acute Exacerbations of Chronic obstructive pulmonary disease, *Journal of Immunology Research* 2017). Recently published studies on the clinical features of severely ill patients with SARS-CoV-2 infection show that IL-6 is significantly elevated, especially in those in the ICU, Causes hyperactivated immune responses (Y. Zhou, B. Fu, X. Zheng, D. Wang, C. Zhao, Y. Qi, R. Sun, Z. Tian, X. Xu, H. Wei, Y. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+ CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus, *bioRxiv*; J.-J. Zhang, X. Dong, Y.-Y. Cao, Y.-d. Yuan, Y.-b. Yang, Y.-q. Yan, C. A. Akdis, Y.-d. Gao, Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China, *Allergy*; B. Diao, C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, L. Chen, M. Li, Y. Liu, G. Wang, et al., Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19), *medRxiv*; X. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, Gu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *The Lancet* 395 (10223) (2020) 497 -- 506; Immunoglobulin G/M and cytokines detections in continuous sera from patients with novel coronaviruses (2019-nCoV) Infection, Available at SSRN 3543609). The pathologic role of IL-6 in SARS-CoV-2 infection suggests that IL-6 blockade may provide a viable therapy for the treatment of COVID-19. In addition, in vivo studies in a Friend retrovirus (FV) mouse model showed that IL-6 blockade reduced viral load, Enhancing virus-specific CD8+T cell immunity (W. Wu, K. K. Dietze, K. Gibbert, K. S. Lang, m. Trilling, h. Yan, Wu, J., Yang, m. d., m. Lu Roggendorf, et al., TLR ligand induced IL - 6 counter - regulates the Anti-viral CD8+ T cell Response during an Acute Retrovirus Infection, *Scientific Reports* 5 (2015) 10501). These findings support the hypothesis that That is, the rapid production of IL-6 may be a possible mechanism leading to harmful clinical manifestations in virus onset (J. Zheng, Y. Shi,

L. Xiong, W. Zhang, Y. Li, P. G. Gibson, J.). L.S impson, c. j. Zhang, Lu, j. Sai, et al., The expression of IL - 6, tNF alpha, McP-1 in respiratory viral infection in acute Exacerbations of Chronic obstructive pulmonary disease, *Journal of Immunology Research* 2017).

Recently published studies on the clinical features of critically ill patients with SARS-CoV-2 infection have shown that significantly elevated IL-6, especially in those in the ICU, elicits an overactivated immune response (Y. Zhou, B. Fu, X. Zheng, D. Wang, C. Zhao, Y. Qi, R. Sun, Z. Tian, X. Xu, H. Wei, Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+ CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus, *bioRxiv*; J.-J. Zhang, X. Dong, Y.-Y. Cao, Y.-d. Yuan, Y.-b. Yang, Y.-q. Yan, C. A. Akdis, Y.-d. Gao, Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China, *Allergy*; B. Diao, C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, L. Chen, M. Li, Y. Liu, G. Wang, et al., Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19), *medRxiv*; X. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, Gu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *The lancet* 395 (10223) (2020) 497–506; Y. B. Li, F. Feng, G. Yang, A. Liu, N. Yang, Q. Jiang, H. Zhang, T. Wang, P. Li, Mao, et al., Immunoglobulin G/M and cytokines detections in continuous sera from patients with novel coronaviruses (2019-nCoV) infection, Available at SSRN 3543609) . The pathologic role of IL-6 in SARS-CoV-2 infection suggests that IL-6 blockade may provide a viable therapy for the treatment of COVID-19.

To test whether CVL218 could modulate IL-6 production in vitro, we stimulated IL-6 production in peripheral blood mononuclear cells (PMBCs) with CpG-ODN 1826, a potent stimulator of cytokines and chemokines. Incubation of PBMCs with 1 μ M CpG-ODN 1826 for 6 h (Methods) induced 40% of IL-6 production compared with untreated cells (FIG. 5). In the presence of CVL218, the stimulatory effect of CPG-ODN 1826 was cancelled. Further studies showed that CVL218 inhibited CpG-induced IL-6 upregulation in a time-and dose-dependent manner (FIG. 5). More specifically, exposure to CVL218 for 12 h at 1 μ M and 3 μ M concentrations attenuated CpG-induced IL-6 production by 50% and 72.65%, respectively. These results provide in vitro evidence for CVL218 as a potential therapeutic agent for the treatment of the proinflammatory response caused by SARS-CoV-2 infection.

The experimental procedures of IL-6 production induced by CPG-PDN1826 in PBMCs were as follows: Peripheral blood mononuclear cells (Beijing Yokang) were cultured in 96-well

plates of RPMI1640 cell growth medium (Corning, CAT.10-040-CVR) at 37°C and 5% CO₂ atmosphere. For stimulation, PBMC cells were incubated with 1 μM CpG-ODN1826(InvivoGen, cat.TLRL-1826). To test whether CVL218 could inhibit IL-6 production, 1 μM and 3 μM concentrations of CVL218 were added to the cell medium for 6 and 12 hours, respectively. IL-6 concentrations were determined by ELISA using a commercial kit (Dakewe Biotech, Cat.1110602).

Embodiment 5: Metabolism and safety characteristics of CVL218 in animals

(1) Experimental steps

5.1. Pharmacokinetic studies

Sprague-dawley rats were purchased from Shanghai Laboratory Animal Center, China. The experimental animals were divided into groups and housed in wire cages with no more than 6 animals in each cage. The experimental conditions were good (temperature $25 \pm 2^{\circ}\text{C}$; Relative humidity $50 \pm 20\%$), light/dark cycle (12 hours /12 hours). One hundred and forty-four Sprague-Dawley rats were randomly divided into 4 groups ($n = 18$ / sex/group). CVL218 was administered at doses of 20, 40, 60 and 160 mg/kg. For all groups, 20 randomly selected rats (10 rats/sex/group) were euthanized on day 28, and sections of their various tissues and organs were obtained and frozen. Ten animals (5 animals/sex/group) were euthanized after a 28-day drug-free period, and their tissues and organs were sectioned and frozen. Six animals (3 animals/sex/group) were euthanized after obtaining blood samples. For pharmacokinetic and safety evaluation, blood concentrations, clinical symptoms, mortality and body weight were measured

5.2. Tissue distribution studies

Thirty Sprague-Dawley rats were randomly divided into 3 time point groups (3 rats/sex/group). At 3, 6 and 8h after CVL218 administration, the animals were sacrificed and the brain, heart, lung, liver, spleen, stomach and kidney tissues were collected. Tissue samples were washed with ice-cold saline, blotted with paper towels to remove excess fluid, and weighed. The tissue sample solution, after weighing, was stored at $-20 \pm 2^{\circ}\text{C}$ until the drug concentration was determined by LC-MS-MS.

5.3. Safety studies of cynomolgus monkeys.

Healthy male and female monkeys, aged 3-4 years, were purchased from Landau Biotechnology, Guangdong, China. Animals were maintained in accordance with the Guide for

the Care and Use of Laboratory Animals. Randomized groups (5 animals/sex/group) were fed CVL218 through nasogastric feeding at dose levels of 0 (control), 5, 20, and 80mg/kg. The monkeys were observed twice daily for any changes in viability/mortality and behaviour, response to treatment, or health status.

5.4. Statistical analysis

All data represent the mean $\pm$ standard deviation (SDs) of N values, where N corresponds to the number of data points used. Figures were compiled using GraphPad Prism (GraphPad Software, USA). Statistical significance was calculated using SPSS(VER.12). If P value <0.05, the two values were considered to be significantly different.

(2) Experimental results and conclusions

5.5. CVL218 has the largest distribution in rat lung tissue

The concentrations of CVL218 in different tissues at different times after different oral doses in rats are shown in Figure 8 and Table 5. Among the seven tissues (namely lung, spleen, liver, kidney, stomach, heart, and brain), we observed the highest CVL218 concentration in lung, which was 188-fold higher than in plasma (Table 6). The highest concentration of CVL218 was observed in the lungs, which is consistent with the fact that SARS-CoV-2 virus has the greatest pathological impact in the lungs and has a high viral load, suggesting that CVL218 may be used as an indication for lung lesions caused by SARS-CoV-2 infection.

In addition, the results showed that the pharmacokinetic parameters of CVL218 and Arbidol were comparable, with similar plasma concentrations and drug exposures (Table 7). After administration of arbidol to rats, it was mainly distributed in the stomach and plasma. In contrast, the higher distribution of CVL218 in tissues, especially in lungs but not in plasma, compared with arbidol, indicates that CVL218 has better pharmacokinetic characteristics, which may make it a potential antiviral agent for pulmonary SARS-CoV-2 infection.

Table 5 Comparison of tissue distribution of CVL218 and Arbidol after 20 mg/kg and 54 mg/kg oral administration in rats

药物	剂量 (mg/kg)	时间 (min)	肺	脾	肝	肾	胃	心脏	脑
CVL218	20	180	69318±10476	20202±2300	17215±1919	15201±1984	8145±2624	6077±496	3580±416
		360	18858±2365	6358±1058	2187±859	3903±594	1871±813	1390±292	998±220
		480	4183±847	1475±324	213±88	993±327	569±293	275±80	317±55
阿比多尔	54	5	933±837	48±35	104±82	79±54	8210±5410	72±47	101±67
		15	2603±1848	519±281	963±290	259±190	23180±10170	132±69	50±10
		360	833±937	143±51	262±175	58±21	52750±3059	41±28	31±21

Table 6 Comparison of tissue to plasma concentration ratios of CVL218 and Arbidol in rats. Arbidol's data came from X. Liu, K. Pei, X.-h. Chen, K.-s. Bi, Distribution and excretion of arbidol hydrochloride in rats, Chinese journal of new drugs 22 (7) (2013) 829–833。

组织	组织/血清 中药物浓度比	
	CVL218	阿比多尔
肺	188.364±28.467	0.553±0.392
脾	54.897±6.250	0.110±0.060
肝	46.780±5.215	0.204±0.062
肾	41.307±5.391	0.055±0.040
胃	22.133±7.130	4.920±2.159
心脏	16.514±1.348	0.028±0.015
脑	9.728±1.130	0.011±0.002

Table 7 Comparison of pharmacokinetic parameters of CVL218 and Arbidol after oral administration of 20/40 mg/kg and 18/54 mg/kg, respectively. Arbidol's data came from Liu, Q.-g. Zhou, H. Li, B.-c. Cai, X.-h. Chen, K.-s. Bi, Pharmacokinetics of arbidol hydrochloride in rats, Chinese pharmacological bulletin 28 (12) (2012) 1747–1750.

药物	剂量 (mg/kg)	性别	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-t} (ng·h/mL)	AUC _{0-∞} (ng·h/mL)	MRT _{0-∞} (h)	t _{1/2} (h)
CVL218	20	雄性	4.0	234 ± 35	1070 ± 176	1111 ± 192	3.91 ± 0.19	1.19 ± 0.09
		雌性	3.0	502 ± 80	2196 ± 228	2222 ± 241	3.16 ± 0.41	1.1 ± 0.16
		总数	3.5	368 ± 157	1633 ± 643	1666 ± 639	3.54 ± 0.50	1.15 ± 0.13
	40	雄性	3.0	510 ± 259	2802 ± 967	2830 ± 983	4.51 ± 0.18	1.3 ± 0.33
		雌性	2.0	940 ± 117	5220 ± 1113	5242 ± 1115	4.05 ± 0.43	1.29 ± 0.21
		总数	2.5	725 ± 296	4011 ± 1620	4036 ± 1620	4.28 ± 0.39	1.3 ± 0.24
阿比多尔	18	雄性	0.28 ± 0.11	1002 ± 298	1956 ± 895	2224 ± 1058	-	3.6 ± 1.2
	54	雄性	0.18 ± 0.06	4711 ± 2361	6790 ± 2749	7558 ± 2877	-	3.3 ± 0.7

5.6. CVL218 has a good safety profile in animals

After oral administration of 20/60/160 mg/kg CVL218 to rats for 28 days and no administration of CVL218 for another 28 days (Methods), we observed no significant differences in body weight between rats and cynomolgus monkeys with different doses and controls (FIG. 6).

These in vivo data indicate that CVL218 has good pharmacokinetic and safety characteristics in rats and monkeys, and its high level distribution in the therapeutic target tissues (namely lungs) will be beneficial for the treatment of SARS-CoV-2 infection.

Embodiment 6: Molecular docking demonstrates the interaction between PARP1 inhibitors and the N-terminal domain of the coronavirus nuclear cap protein

Molecular docking was performed in this embodiment to investigate the potential interaction mode between two drugs, olaparib and CVL218, and the N-NTD of SARS-CoV-2.

To establish the molecular interaction model of PARP1 inhibitor CVL218 and olaparib with the N-terminal domain of SARS-CoV-2 protein (SARS-CoV-2-N-NTD), the docking program AutoDock4.2 was used to generate the model. The structure of SARS-CoV-2-N-NTD used for molecular docking was established by homology modeling. The AutoGrid program was used to generate grid plots with 60 × 60 × 60 points spaced equally at 0.375 Å to evaluate binding energies between proteins and ligands.

The results showed (Figure 7) that both CVL218 and olaparib could bind to the N-NTD of

SARS-CoV-2. In terms of hydrogen bond formation, CVL218 shows stronger binding capacity than olaparib. Meanwhile, the key residues involved in drug binding on SARS-CoV-2-N-NTD (namely, S51, Y109 and Y111) are also highly conserved in other viruses such as SARS-CoV, HCOV-OC43, murine hepatitis virus (MHV) and infectious bronchitis virus (IBV). These results indicate that N-NTD of different viruses may exhibit similar binding behavior to PARP inhibitors, thereby inhibiting viral replication.

In conclusion, it is known that PARP1 inhibitors may have therapeutic potential for the treatment of diseases caused by viruses, such as COVID-19. First, PARP1 inhibitors may inhibit viral growth during the coronavirus life cycle by inhibiting viral replication and hindering the binding of nuclear cap proteins to viral RNA, which can also be supported by our molecular docking results. Second, PARP1 inhibitors play a key role in controlling inflammatory responses by modulating proinflammatory factors such as IL-6, thus providing clinical potential for attenuating cytokine storm and inflammatory response induced by SARS-COV-2 infection. Tosituzumab, a monoclonal antibody against IL-6, was recommended for the treatment of COVID-19 in the COVID-19 Diagnosis and Treatment Protocol (Trial version 7) issued by the Chinese government, which also highlights the important role of the anti-inflammatory response in the current treatment of SARS-CoV-2. CVL218 could effectively inhibit CpG-induced IL-6 production in PBMCs. This finding suggests that CVL218 may also have IL-6-specific anti-inflammatory effects in patients with severe SARS-CoV-2 infection.

Although the above describes specific embodiments of the invention, technicians in the field should understand that these are only examples and that many changes or modifications may be made to these embodiments without departing from the principle and substance of the invention. Therefore, the scope of protection of the invention is limited by the attached claims.

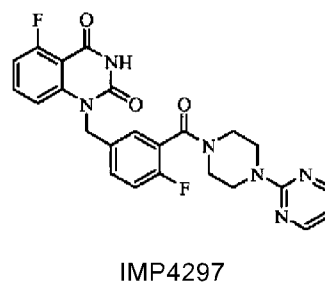
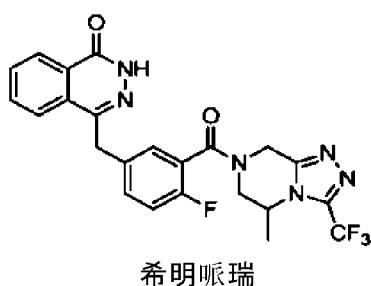
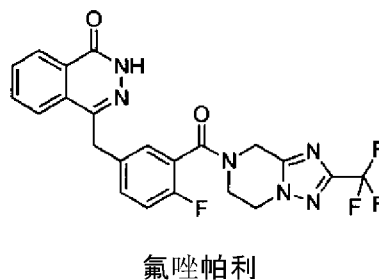
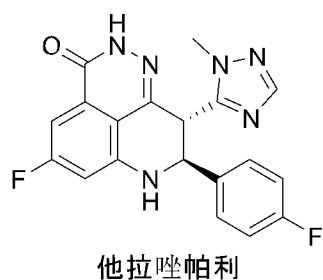
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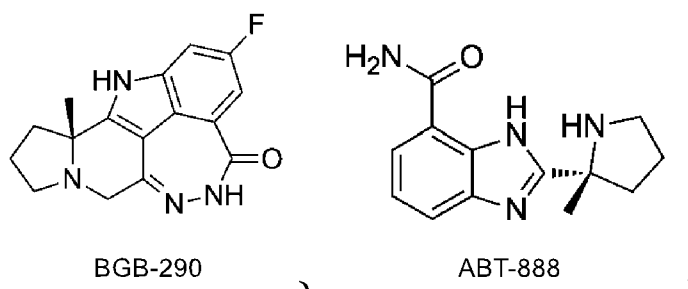
1. Application of poly ADP-ribose polymerase inhibitors or their pharmaceutically acceptable salts in the preparation of antiviral agents or in the preparation of drugs for the treatment of diseases caused by viruses, of which the viruses are viruses of the genus β - coronaviruses; Preferably a virus that causes acute respiratory syndrome such as SARS-associated coronavirus; Sars-cov and/or SARS-CoV-2 are preferred.

2. The application described in claim 1 is characterized in that the poly ADP-ribose polymerase inhibitor is an inhibitor of PARP L and/or PARP2.

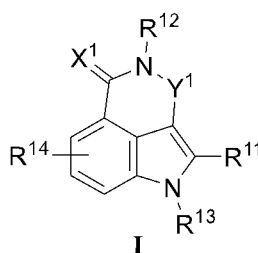
3. The application described in claim 1 is characterized in that the poly ADP-ribose polymerase inhibitor is substance A, A pharmaceutically acceptable salt thereof;

The substance A is selected from one or more of the compounds shown in Formula I, Formula II, Formula III and Formula IV, talazoparib, fluzoparib, ximperamide, IMP4297, BGB-290, ABT-888;





Where, the compound shown in Equation I is:



Among them, R11 is H, halogen, cyanogroup, C1-C4 alkyl group, C2-C4 alkenyl group, C2-C4 alkyne group, C3-C4 cycloalkyl group, "containing 1~2 heteroatoms, heteroatoms selected from one or more of O, N and S, 3~6 element" heterocyclic alkyl group, C6-C10 aryl group, "containing 1~2 heteroatoms, Heteroatoms are selected from one or more "hetero-aryl groups of 5 to 10 elements in O, N, and S, alkyl groups of C1 to C4 substituted by one or more R11-1, alkenes of C2 to C4 substituted by one or more R11-1, alkyne groups of C2 to C4 substituted by one or more R11-1, rings of C3 to C4 substituted by one or more R11-1 Alkyl, substituted by one or more R11-1, "containing one or two heteroatoms, Heteroatoms selected from one or more of O, N, and S, 3-to 6-membered "heterocyclic alkyl groups, aryl groups of C6 to C10 substituted by one or more R11-1 (" aryl groups of C6 to C10" such as phenyl groups; The "aryl group of C6 to C10 substituted by an R11-1", for example), the "containing 1 to 2 heteroatoms substituted by one or more R11-1", Heteroatoms from one or more of O, N and S, 5 to 10 elements of "hetero-aryl groups, -c (=O)-R11-2, -c (=O)-O-R11-3 or -c (=O)-NR11-4R11-5;

R11-1 is independently a halogen, hydroxyl, carboxyl, nitro, amino, C1-C4 alkyl group or a C1-C4 alkyl group substituted by one or more NR11-1-1R11-1-2 (the "C1-C4 alkyl group" e.g. methyl);

R11-1-1 and R11-1-2 are independently hydrogen or C1-C4 alkyl groups (e.g. methyl groups);

R11-2, R11-3, R11-4, and R11-5 are H, the alkyl group of C1 to C4, the alkenyl group of C2 to C4, the alkyl group of C2 to C4, the cycloalkyl group of C3 to C4, "containing one or two heteroatoms, Heteroatoms from one or more of O, N, and S, 3-to 6-membered "heterocyclic alkyl groups, aryl groups from C6 to C10," containing one or two heteroatoms, Heteroatoms are selected from one or more of the 5 to 10-membered "heteraryl groups of O, N, and S, alkyl groups of C1 to C4 substituted by one or more R11-2-1, alkenes of C2 to C4 substituted by one or more R11-2-1, alkyne groups of C2 to C4 substituted by one or more R11-2-1, or acetylene groups of C2 to C4 substituted by one or more R11-2-1, or substituted by one or more R11-2-1 The cycloalkyl group of C3 to C4, substituted by one or more r11-2-1, containing one or two heteroatoms, Heteroatoms selected from one or more of O, N and S, 3 to 6-membered "heterocyclic alkyl groups, C6 to C10 aryl groups substituted by one or more R11-2-1, or" 1 to 2 membered heterocyclic groups substituted by one or more R11-2-1, 5 to 10-membered "heterocyclic groups;

R11-2-1 is independently a halogen, hydroxyl, carboxyl, nitro, amino, or C1-C4 alkyl group;

Y1 is -(cry1-1ry1-2)(CRY1-3ry1-4) N - or -n = C(RY1-5)-;

N is 0 or 1;

RY1-1, RY1-2, and RY1-5 are independently H, alkyl groups of C1 to C4, alkenyl groups of C2 to C4, alkyl groups of C2 to C4, cycloalkyl groups of C3 to C4, heterocyclic alkyl groups of 3 to 6 elements, aryl groups of C6 to C10, heterocyclic alkyl groups of 1 to 2, heterocyclic alkyl groups of 3 to 6, heterocyclic alkyl groups of 3 to 6, heterocyclic alkyl groups of 3 to 4, heterocyclic alkyl groups of 3 to 4, heterocyclic alkyl groups of 3 to 4, heterocyclic alkyl groups of 3 to 4, heterocyclic alkyl groups of 3 to C10, and heterocyclic alkyl groups of 1 to 2. Heteroatoms are selected from one or more of the 5 to 10-membered "hetero-aryl groups of O, N, and S, alkyl groups of C1 to C4 substituted by one or more RY1-1-1, alkenes of C2 to C4 substituted by one or more RY1-1-1, acetylene groups of C2 to C4 substituted by one or more RY1-1-1, or substituted by one or more RY1-1-1 "Containing one or two heteroatoms," substituted by one or more RY1-1-1, Heteroatoms selected from one or more of O, N and S, 3 to 6-membered "heterocyclic alkyl groups, C6 to C10 aryl groups substituted by one or more RY1-1-1, or" 1 to 2 heteroatoms substituted by one or more RY1-1-1, 5 to 10-membered "heteroaryl groups;

Ry1-1-1 is independently a halogen, hydroxyl, nitro, amino, alkyl group of C1 to C4, or alkoxy group of C1 to C4;

Ry1-3 and Ry1-4 are independently H, an alkyl group of C1 to C4, an alkenyl group of C2 to C4, an alkyne group of C2 to C4, a cycloalkyl group of C3 to C4, a heterocyclic alkyl group of 3 to 6 elements, an aryl group of C6 to C10, a heterocyclic group of 1 to 2, and a heterocyclic group of 3 to 6. Heteroatoms are selected from one or more of the 5 to 10-member "heteraryl groups of O, N, and S, alkyl groups of C1 to C4 substituted by one or more RY1-3-1, alkenes of C2 to C4 substituted by one or more RY1-3-1, alkyne groups of C2 to C4 substituted by one or more RY1-3-1, and alkyne groups of C2 to C4 substituted by one or more RY1-3-1, or substituted by one or more RY1-3-1 The cycloalkyl group of C3 to C4, substituted by one or more ry1-3-1, containing one or two heteroatoms, Heteroatoms selected from one or more of O, N, and S heterocyclic alkyl groups of three to six elements, aryl groups of C6 to C10 substituted by one or more Ry1-3-1, or heteraryl groups of five to ten elements containing one or two heteroatoms substituted by one or more Ry1-3-1

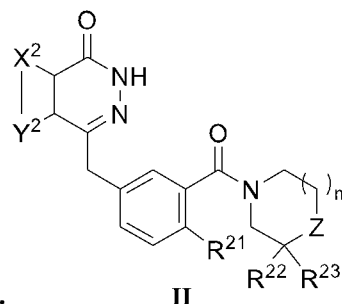
Ry1-3-1 is independently a halogen, hydroxyl, nitro, amino, alkyl group of C1 to C4, or alkoxy group of C1 to C4;

R12 is an alkyl group of H or C1 to C4;

X1 is either O or S;

R14 is an alkyl group of H, a halogen (such as fluorine, chlorine, or bromine), or C1 to C4;

R13 is an alkyl group of H or C1 to C4;



The compound shown in Equation II is:

Wherein, X₂, Y₂ and the carbon atom connected with them together form the aryl group (such as phenyl) of C₆~C₁₀, or the aryl group of C₆~C₁₀ replaced by one or more RX₂-1;

Rx₂-1 is independently a halogen, nitro, hydroxyl, sulfhydryl, amino group, hydrocarbon group of C₁ to C₇, aryl group of C₆ to C₂₀, heterocyclic group "containing 1 to 6 heteroatoms, heteroatoms selected from one or more of O, N and S, 3 to 20 elements", -OR_{x2}-1-1 or -SR_{x2}-1-2;

Rx₂-1-1 and rx₂-1-2 are independently heterocyclic groups of C₁~C₇, C₆~C₂₀, or 3~20 heterocyclic groups "containing 1~6 heteroatoms selected from one or more of O, N, and S;

R₂₁ is H or a halogen (e.g. fluorine, chlorine or bromine);

Z is -nr_z-1 - or -CR_Z-2R_Z-3-;

When Z is minus NR_Z minus 1 minus, m is 1 or 2; When Z is -CR_z-2R_z-3 -, m is 1;

R_z-1 and R_Z-2 are independently the hydrocarbon group of C₁~C₂₀, the aryl group of C₆~C₂₀, "containing 1~6 heteroatoms, Heteroatoms are selected from one or more of the "heterocyclic groups of 3 to 20 elements in O, N, and S, -c (= O)NR_Z-1-1R_Z-1-2, -c (= O)R_Z-1-3 (e.g.), -c (= O)OR_Z-1-4, -c (= S)NR_Z-1-5R_Z-1-6, -s (= O)2R_Z-1-7, being one or more R_z-1-8 substituted hydrocarbon groups of C₁~C₂₀, aryl groups of C₆~C₂₀ substituted by one or more R_Z-1-9, or heterocyclic groups of 3~20 elements substituted by one or more R_Z-1-10 containing 1~6 heteroatoms selected from one or more of O, N, and S;

R_z-1-1, R_Z-1-2, R_Z-1-3, R_Z-1-4, R_Z-1-5, R_Z-1-6 and R_Z-1-7 are independently heterocyclic groups of hydrogen, hydrocarbon groups of C₁ to C₇, aryl groups of C₆ to C₂₀, or "heterocyclic groups containing 1 to 6 heteroatoms selected from one or more of O, N, and S, 3 to 20 elements";

Alternatively, R_Z-1-1, R_Z-1-2, and their associated carbon atoms together form heterocyclic groups "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

Alternatively, RZ-1-5, RZ-1-6, and their associated carbon atoms together form heterocyclic groups "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

Rz-1-8, RZ-1-9, and RZ-1-10 are independently the hydrocarbon groups of C1 to C7, the aryl groups of C6 to C20, "containing 1 to 6 heteroatoms, Heteroatoms are selected from one or more of O, N and S heterocyclic groups, halogen, hydroxyl, nitro, cyano, carboxyl, thiol, urea-group, -c (= O)NRZ-1-8-1RZ-1-8-2, -C(= O)RZ-1-8-3, -C(= O)ORZ-1-8-4, -C(= S)NRZ-1-8-RZ -, 1-8-6-5 S (= O) 2 RZ, ORZ - 1-8-8, 1-8-7 - SRZ -, 1-8-9 - S (= O RZ NRZ - 1-8-10-2, 1-8-11 - OC (= O) RZ -, 1-8-12 - S (= O) NRZ, RZ - or 1-8-14-1-8-13 C (= O)-NH-C(= O)RZ-1-8-15;

RZ - 1-8-1, in fact - 1-8-1, the RZ - 1-8-3, in fact - 1-8-3, RZ - 1-8-5, in fact - 1-8-5, RZ - 1-8-7, in fact - 1-8-7, the RZ - 1-8-9, RZ - 1-8-10, RZ - 1-8-9, RZ - 1-8-12, in fact - 1-8-12 RZ-1-8-14 and RZ-1-8-15 are independently heterocyclic groups of hydrogen, hydrocarbon groups of C1 to C7, aryl groups of C6 to C20, or heterocyclic groups of 3 to 20 elements "containing 1 to 6 heteroatoms selected from one or more of O, N, and S";

Alternatively, RZ-1-8-1, RZ-1-8-2, and their associated carbon atoms together form heterocyclic groups "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

Alternatively, RZ-1-8-5, RZ-1-8-6, and their associated carbon atoms together form heterocyclic groups "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

Alternatively, RZ-1-8-10, RZ-1-8-11, and their associated carbon atoms together form heterocyclic groups "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

Or, RZ-1-8-13, RZ-1-8-14 and their associated carbon atoms together form a heterocyclic group "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

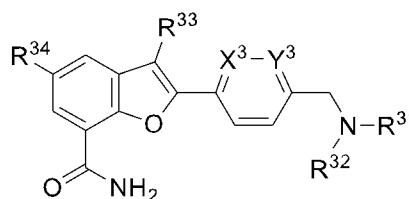
Rz-3 is H, hydroxyl or amino;

Alternatively, RZ-2, RZ-3 and their linked carbon atoms together to form a spirocycloalkyl from C3 to C7, or, "containing 1 to 3 heteroatoms, heteroatoms selected from one or more of O, N and S, 3 to 7 elements";

R22 and R23 are both hydrogen, or, when Z is -CRZ-2RZ-3-, R22, R23, RZ-2, RZ-3 and their associated carbon atoms together form an aryl group (e.g., phenyl) of C6 to C10, or an aryl group of C6 to C10 substituted by one or more R22-1;

R22-1 is independently a hydrocarbon group from C1 to C7, an aryl group from C6 to C20, a heterocyclic group "containing 1 to 6 heteroatoms from one or more of O, N, and S, 3 to 20 elements", a hydroxyl group, a sulfhydryl group, an amino group, -OR22-1-1, -SR22-1-2, or -O-(CH2)_p-O-; P is 1, 2 or 3;

R22-1-1 and R22-1-2 are independently heterocyclic groups of C1~C7, C6~C20, or 3~20 heterocyclic groups "containing 1~6 heteroatoms selected from one or more of O, N, and S";



III

The compound shown in Equation III is:

R31 and R32 are independently hydrogen, C1-C4 alkyl groups (e.g., methyl groups), C3-C4 cycloalkyl groups, or heterocyclic alkyl groups "containing one to three heteroatoms, with heteroatoms selected from one or more of O and N, of five or six elements";

Or, R31, R32 and linked to the N atoms together to form "with 1 ~ 3 heteroatoms, impurity atoms in O, N and S in one or more, 5 ~ 6 yuan" heterocyclic alkyl, or, be replaced by one or more of the R31 1 of "containing 1 ~ 3 heteroatoms, impurity atoms in O, N and S in one or more, 5 ~ 6 yuan" heterocyclic alkyl;

R31-1 is a C1-C4 alkyl group (e.g. methyl group) on N;

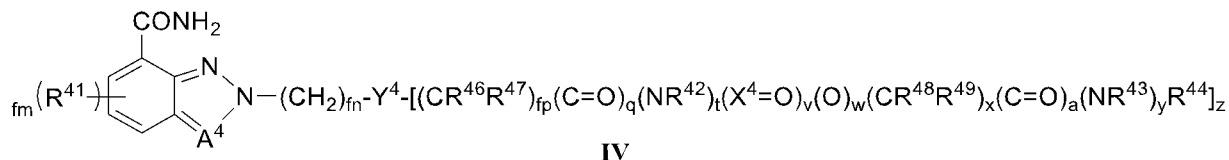
X3 is CH, CF, or N;

Y3 is CH, CF, or N.

R33 is H or Cl;

R34 is H or F;

The compounds described in Equation IV are:



FM is 0, 1, 2, or 3;

R41 is independently hydroxyl, halogen (e.g., fluorine), cyanogroup, C1-6-alkyl, halogenated C1-6-alkyl, C1-6-alkoxy or halogenated C1-6-alkoxy; A⁴ 为 CH 或 N;

F_n is 0, 1, 2, 3, 4, 5 or 6;

Y₄ for a single bond, C3-5 naphthenic base, contains a N atom of 4 yuan saturated heterocyclic, containing 1, 2, or 3 independently selected from N, O and S heteroatomic 5, 6 or 7 yuan saturated or partially saturated heterocyclic, containing 1, 2, 3 or 4 independently from the O, N and S heteroatoms but not more than a 5 yuan for O or S unsaturated heterocyclic, 1, 2, or contains A 6-membered unsaturated heterocyclic ring of three nitrogen atoms, "a 6-to 13-membered saturated, partially saturated, or unsaturated hydrocarbon ring" (e.g., aryl groups of C6 to C10, and also phenyl groups), or "an 8-to 13-membered unsaturated or partially saturated heterocyclic ring containing one, two, three, or four heteroatoms independently selected from N, O, and S"; z 为 1、2 或 3

F_p is 0, 1, 2, 3, 4, 5 or 6;

R₄₆ and R₄₇ are independently hydrogen or C1-6 alkyl groups;

Q is 0 or 1;

T is 0 or 1;

R₄₂ is hydrogen, C1-6 alkyl or C3-10 cycloalkyl;

V is 0 or 1;

X₄ is C or S=O;

W is 0 or 1;

X is 0, 1, 2, 3, 4, 5 or 6;

R₄₈ and R₄₉ are independently hydrogen, C1-6-alkyl, hydroxyl, halogenated C1-6-alkyl,

hydroxyl C1-6-alkyl, amino, C1-6-alkyl amino or dimethyl (C1-6-alkyl) amino;

A is 0 or 1;

Y is 0 or 1;

R43 is hydrogen or C1-6 alkyl;

R44 is hydrogen, hydroxyl, cyano, halogen (e.g., fluorine, chlorine, or bromine), C1-6 alkyl, C2-10 alkenyl, halogenated C1-6 alkyl, hydroxyl C1-6 alkyl, C1-6 alkyl carbonyl, C1-6 alkoxy, halogenated C1-6 alkoxy, C1-6 alkoxy carbonyl, carboxyl, nitro, R44-1, or, by one or more - (CH₂)) R44-3 replaced by BR44-2;

R44-1 and R44-3 are independently C6-10 aryl groups, C6-10 aryl oxygen groups, C6-10 aryl carbonyl groups, C3-10 cycloalkyl groups, 4-membered saturated heterocycles containing one N atom, "5-or 6-membered saturated or partially saturated heterocycles containing one, two, or three atoms independently selected from N, O, and S" (e.g.), "containing 1, 2, 3, or 4 Independently selected from N, O and S of the 5 yuan of mixed aromatic ring of the atom, which is not more than one heteroatom O or S ", "contains 1, 2, or 3 nitrogen atom 6 yuan miscellaneous aromatic ring", or "contains 1, 2, 3, or 4 independently selected from N, O and S heteroatomic 7 to 15 yuan of saturated or unsaturated, partially saturated heterocyclic";

B is 0, 1, 2, 3, 4, 5 or 6 independently;

R44-2 is independently hydroxyl, oxyl, cyanol, halogen, C1-6 alkyl, C2-10 chainenyl, halogenated C1-6 alkyl, C1-6 alkoxy, C1-6 alkoxy, halogenated C1-6 alkoxy, hydroxyl C1-6 alkyl, C1-6 alkoxy carbonyl, carboxyl, -NRARB, C(=O)NRaRb, S(=O) F RRe, R44-2-1, or R44-2-3 replaced by one or more R44-2-2;

Ra and Rb are independently hydrogen, C1-6 alkyl, C1-6 alkyl carbonyl, halogenated C1-6 alkyl, hydroxyl C1-6 alkyl, S(O)srRc or S(O)trN(Rd)₂;

Sr and TR are 0, 1, or 2 independently;

Rc is C1-6 alkyl, RC-1 or RC-3 substituted by one or more RC-2;

Rc-1 and RC-3 are independently C6-10 aryl groups, "5-membered hetero-aromatic rings containing one, two, three, or four heteroatoms independently selected from N, O, and S, Where not more than one heteroatom is O or S ", "a 6-membered hetero-aromatic ring containing 1, 2 or 3 nitrogen atoms", or "or a 7-10-membered unsaturated or partially saturated hetero-ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S";

Rc-2 is independently hydroxyl, cyanogenic, halogen, C1-6 alkyl, C2-10-linked alkenyl or

halogenated C1-6 alkyl;

Rd is independently hydrogen or C1-6 alkyl;

Alternatively, Ra, Rb and their connected N atoms together form RA-1 or RA-3 replaced by one or more RA-2;

Ra-1 and RA-3 are independently "4-membered saturated heterocycles containing one N atom", or "5-membered 6-membered or 7-membered saturated heterocycles containing one, two, or three N atoms and zero or one O atom";

Ra-2 independent hydroxyl, cyano, halogen, C1-6 alkyl, C1-6 alkoxy, C2-10 alkenyl or halogenated C1-6 alkyl;

Fr is 0, 1, or 2;

Re is C1-6 alkyl, RE-1, or re-3 substituted by one or more re-2;

Re-1 and re-3 are independently C6-10 aryl groups, "5-membered hetero-aromatic rings containing one, two, three, or four heteroatoms independently selected from N, O, and S, Where not more than one heteroatom is O or S ", "a 6-membered hetero-aromatic ring containing 1, 2 or 3 nitrogen atoms", or "or a 7-10-membered unsaturated or partially saturated hetero-ring containing 1, 2, 3 or 4 heteroatoms independently selected from N, O and S";

Re-2 is independently hydroxyl, cyanogenic, halogen, C1-6 alkyl, C2-10-linked alkenyl, or halogenated C1-6 alkyl;

R44-2-1 and R44-2-3 are independently C6-10 aryl groups, C6-10 aryl C1-6 alkyl groups, "4-membered saturated heterocycles containing one N atom", "5-membered, 6-membered or 7-membered saturated or partially saturated heterocycles containing one, two or three atoms independently selected from N, O and S", "1-membered, 2, 3 or 4 independently selected from N, O and S" A 5-membered hetero-aromatic ring of not more than one hetero-atom of O or S, a 6-membered hetero-aromatic ring containing one, two or three nitrogen atoms, or a 7-to 10-membered unsaturated or partially saturated hetero-ring containing one, two, three or four heteroatoms independently selected from N, O and S;

R44-2-2 are independently hydroxyl, cyano, halogen, C1-6 alkyl, C1-6 alkoxy, C2-10 alkenyl, halogenated C1-6 alkyl, amino, C1-6 alkyl amino, and di (C1-6 alkyl) amino groups.

4. An application, as described in claim 3, is characterized by the following definition of the said compound shown in Equation I:

Where R11 is the aryl group of C6 to C10 substituted by one or more R11-1 (the "aryl group

of C6 to C10" such as phenyl; The "aryl group of C6 to C10 substituted by an R11-1" for example);

R11-1 is independently a halogen, hydroxyl, carboxyl, nitro, amino, C1-C4 alkyl group or a C1-C4 alkyl group substituted by one or more NR11-1-1R11-1-2 (the "C1-C4 alkyl group" e.g. methyl);

R11-1-1 and R11-1-2 are independently hydrogen or C1-C4 alkyl groups (e.g. methyl groups);

Y1 for - (ry1 CRY1-1-2) ry1 (CRY1-3-4) n -;

N is 0 or 1;

Ry1-1 and Ry1-2 are independently alkyl groups of H or C1 to C4;

Ry1-3 and Ry1-4 are independently alkyl groups of H or C1 to C4;

R12 is an alkyl group of H or C1 to C4;

X1 is either O or S;

R14 is H or a halogen (such as fluorine, chlorine or bromine);

R13 is an alkyl group of H or C1 to C4;

The compounds described in Equation II have the following definitions:

X2, Y2 and their associated carbon atoms together form an aryl group (e.g., a phenyl group) of C6 to C10, or an aryl group of C6 to C10 substituted by one or more RX2-1;

Rx2-1 is independently a halogen, nitro, hydroxyl, sulfhydryl, amino group, hydrocarbon group of C1 to C7, aryl group of C6 to C20, heterocyclic group "containing 1 to 6 heteroatoms, heteroatoms selected from one or more of O, N and S, 3 to 20 elements", -ORx2-1-1 or -SRX2-1-2;

Rx2-1-1 and rx2-1-2 are independently heterocyclic groups of C1~C7, C6~C20, or 3~20 heterocyclic groups "containing 1~6 heteroatoms selected from one or more of O, N, and S;

R21 is H or a halogen (e.g. fluorine, chlorine or bromine);

Z - NRZ - 1 -; M is 1 or 2;

Independently for RZ - 1 - C = O RZ NRZ - 1-1-1 -, 2 - C = O RZ - 1-3 (for example), C (= O) ORZ - 1-4, - C (= S) NRZ 1-6-1-5 RZ - or - S (= O) 2 RZ - 1-7;

Rz-1-1, RZ-1-2, RZ-1-3, RZ-1-4, RZ-1-5, RZ-1-6 and RZ-1-7 are independently heterocyclic groups of hydrogen, hydrocarbon groups of C1 to C7, aryl groups of C6 to C20, or

"heterocyclic groups containing 1 to 6 heteroatoms selected from one or more of O, N, and S, 3 to 20 elements";

Alternatively, RZ-1-1, RZ-1-2, and their associated carbon atoms together form heterocyclic groups "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

Alternatively, RZ-1-5, RZ-1-6, and their associated carbon atoms together form heterocyclic groups "containing one or two heteroatoms selected from one or more of O, N, and S, of 4 to 8 elements";

R22 and R23 are hydrogen;

The compounds described in Equation III have the following definitions:

R31 is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, piperidine-4-group or (R) - tetrahydrofuran-3-group, preferably hydrogen or methyl;

R32 is hydrogen, methyl, ethyl, isopropyl, cyclopropyl, piperidine 4-yl or (R) - tetrahydrofuran 3-yl, preferably methyl, isopropyl, cyclopropyl, piperidine 4-yl or (R) - tetrahydrofuran 3-yl;

Alternatively, R31, R32 and their associated N atoms together form an unsubstituted or substituted morpholine group, piperazine group, hyperpiperazine group, thiomorpholine group, piperidine group or tetrahydropyrrole group, where the substitution means the substitution of N by a methyl group;

X3 is CH, CF, or N;

Y3 is CH, CF, or N.

R33 H;

R34 to F;

The compounds described in Equation IV have the following definitions:

FM is 0, 1, 2, or 3;

R41 is independently hydroxyl, halogen, cyano, C1-6-alkyl, halogenated C1-6-alkyl, C1-6-alkoxy or halogenated C1-6-alkoxy;

A4 is CH or N;

Fn to 0;

Y4 to include 1, 2, or 3 independently selected from N, O and S heteroatomic 5, 6 or 7 yuan saturated or partially saturated heterocyclic, containing 1, 2, 3 or 4 independently from the O, N

and S heteroatoms but not more than one for \$5 O or S unsaturated heterocyclic, containing 1, 2, or 3 unsaturated heterocyclic nitrogen atom of 6 yuan, "6-13 yuan of saturated and partially full "And or unsaturated hydrocarbon rings" (e.g., aryl groups of C6 to C10, also e.g., phenyl groups), or "unsaturated or partially saturated 8-13 membered heterocycles containing one, two, three, or four heteroatoms independently selected from N, O, and S";

Z is 1 or 2;

Fp is 0;

Q is zero;

T is 0;

V 0;

W to 0;

X is 0;

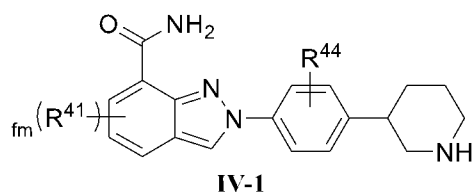
A, 0.

Y is 0;

R44 is halogen or R44-1;

For C3 R44-1-10 of naphthenic base, contains a N atom 4 yuan saturated heterocyclic, "contains 1, 2, or 3 independently selected from N, O and S atoms of 5 or 6 yuan fully or partially saturated heterocyclic" (for example), or, "containing 1, 2, 3 or 4 independently selected from N, O and S heteroatomic 7 to 15 yuan of saturated or unsaturated, partially saturated heterocyclic";

And/or, the compound described in Equation IV has the following definition: it is a compound described in Equation IV-1,

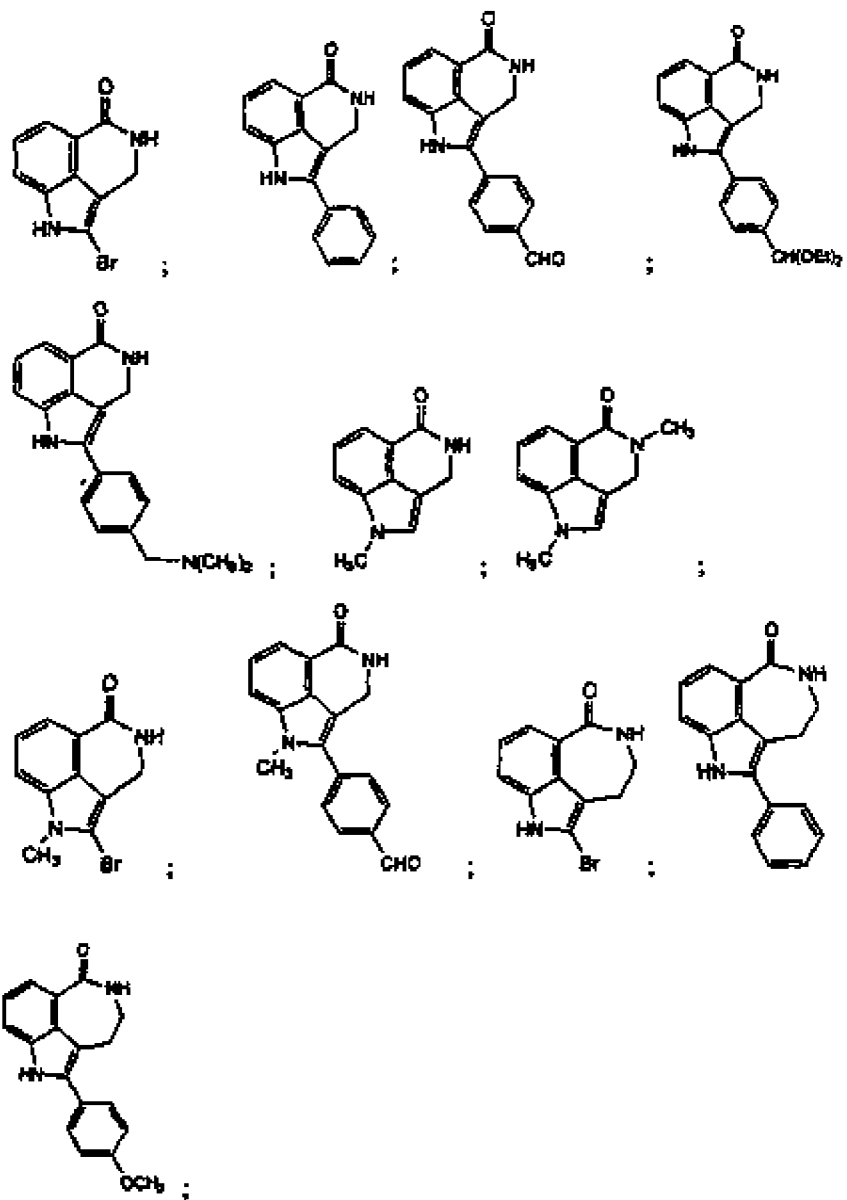


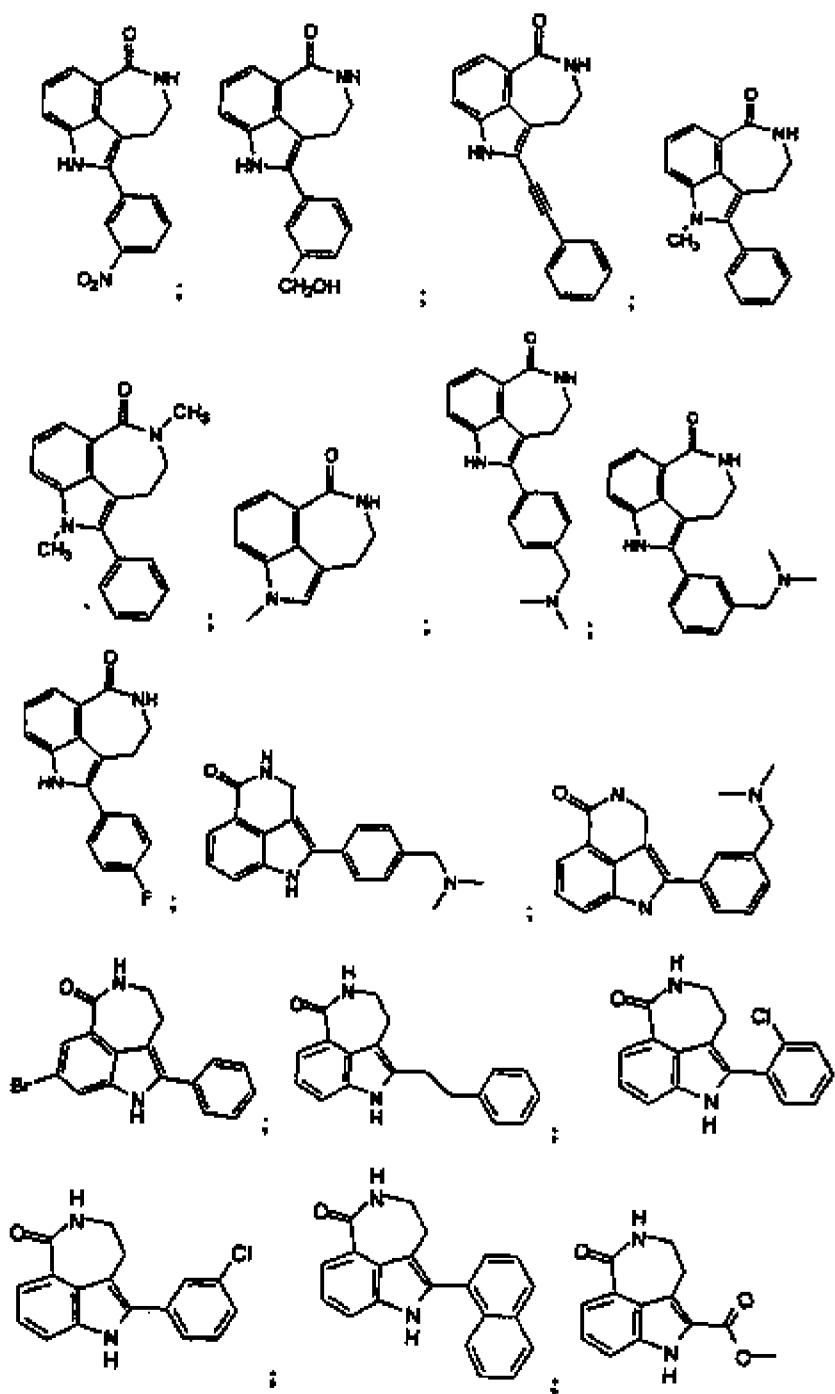
FM is 0 or 1;

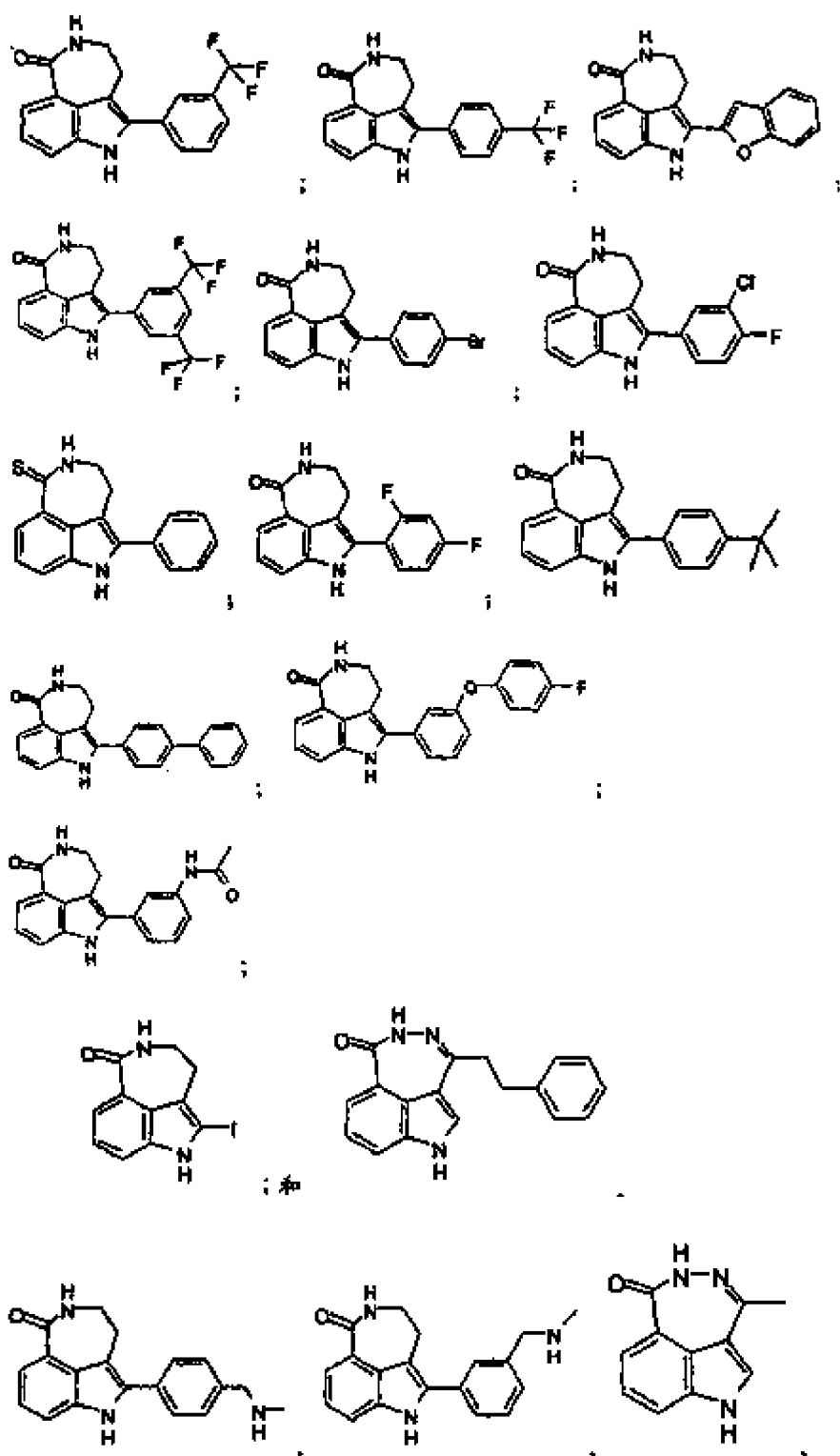
R41 is a halogen (e.g. fluorine);

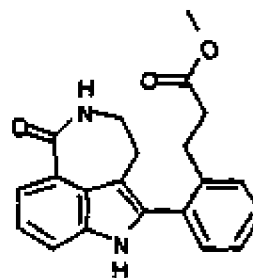
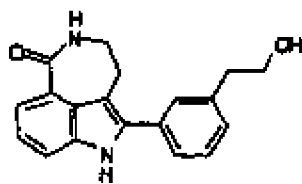
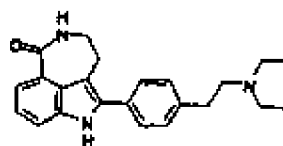
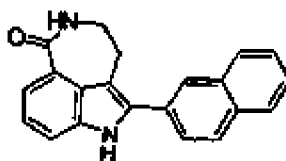
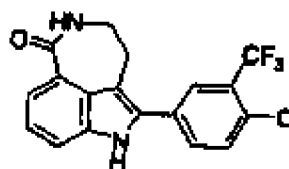
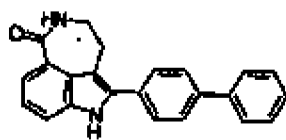
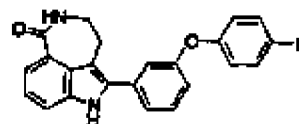
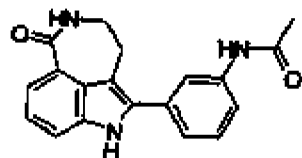
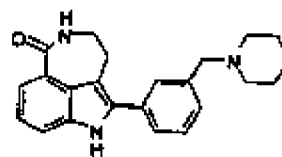
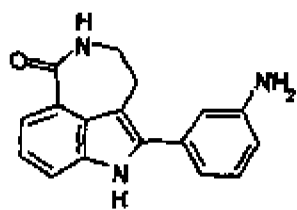
R44 is hydrogen or a halogen (e.g. fluorine).

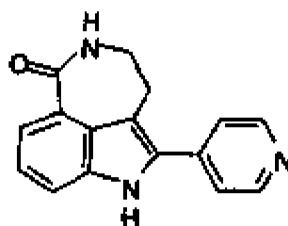
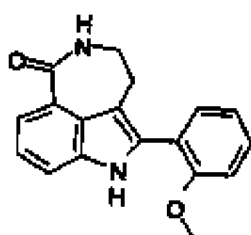
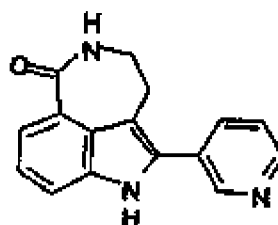
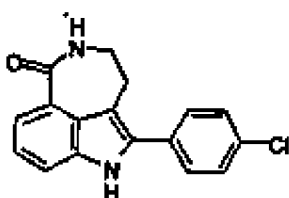
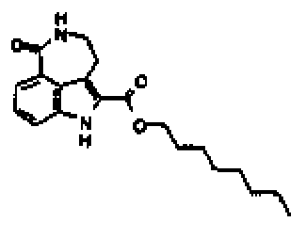
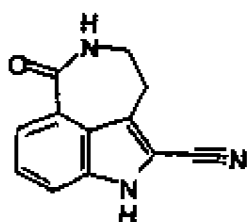
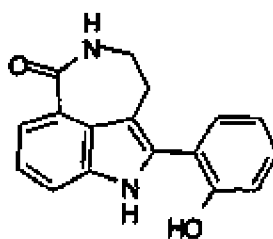
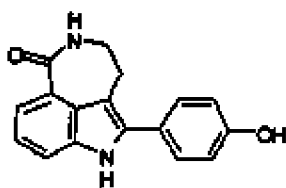
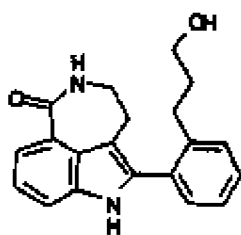
5. An application as described in claim 4 is characterized in that the said compound shown in Equation I is any of the following compounds:

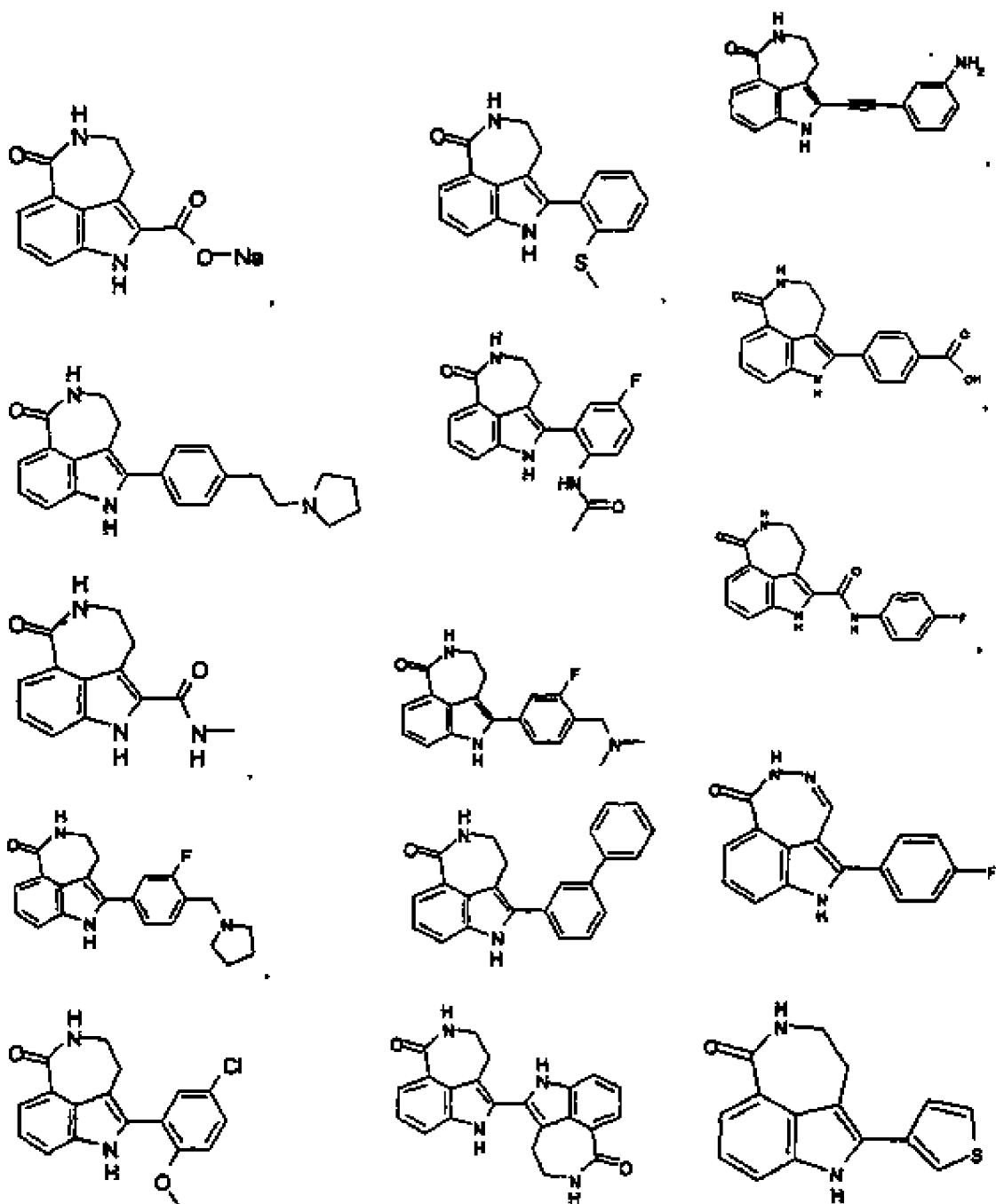


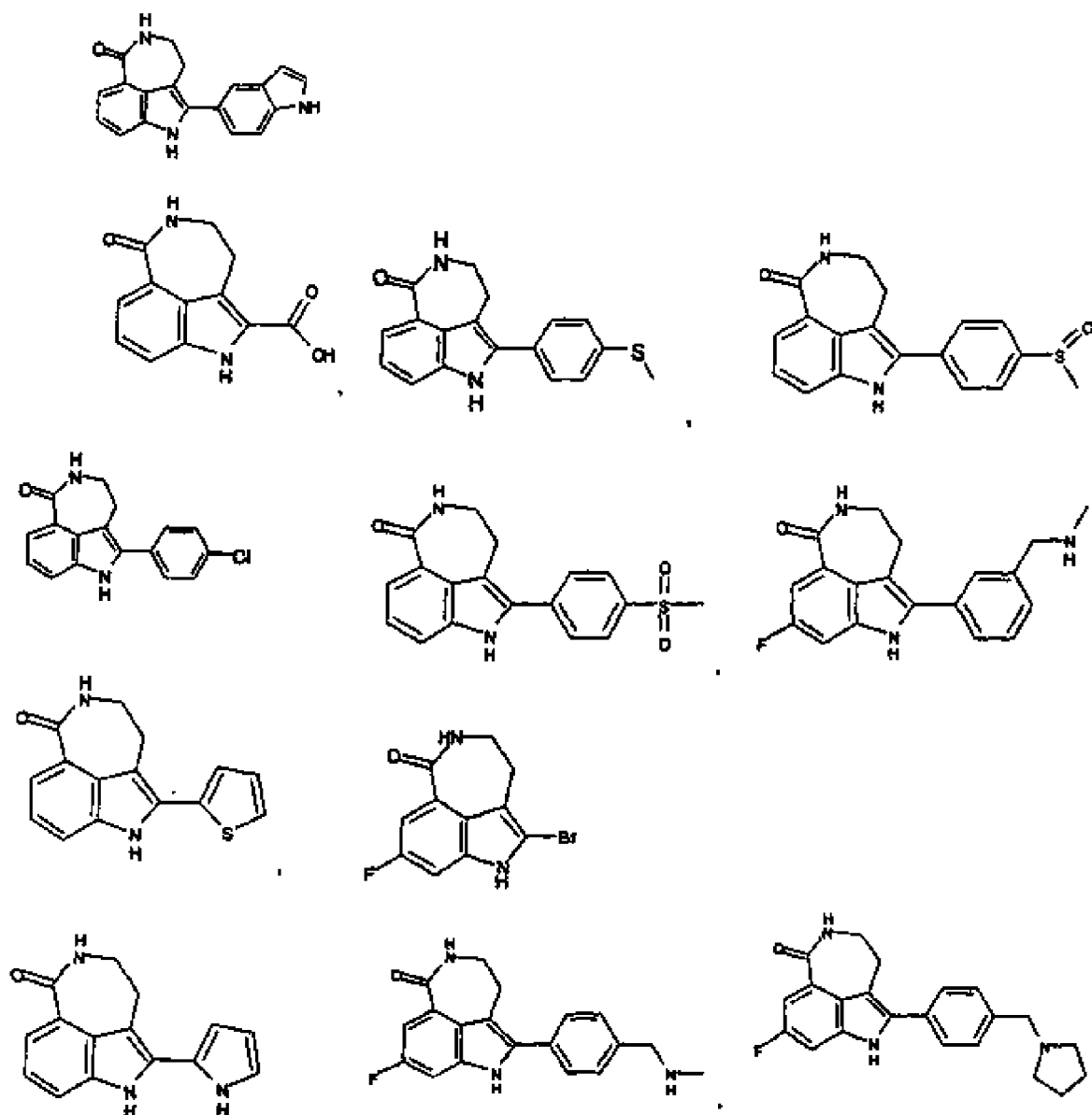


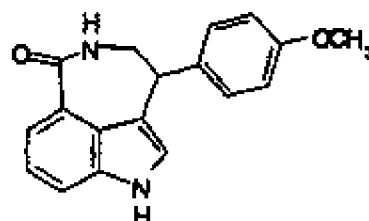
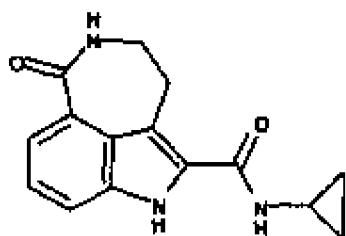
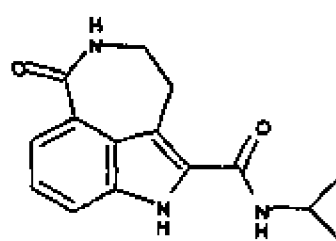
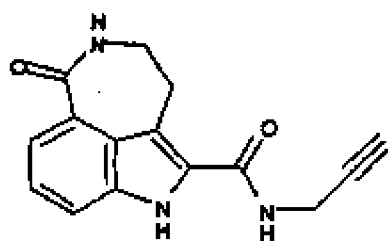
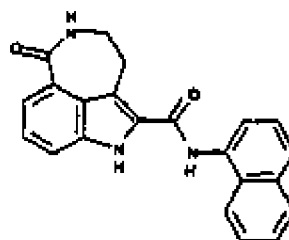
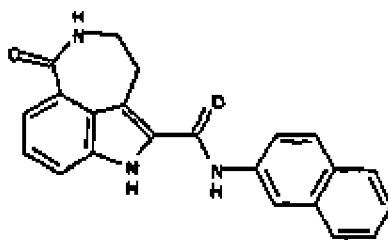
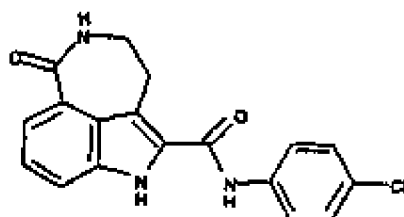
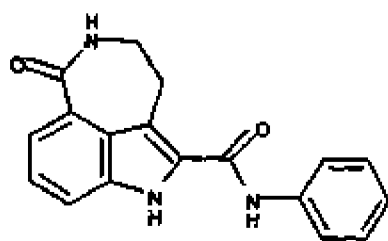


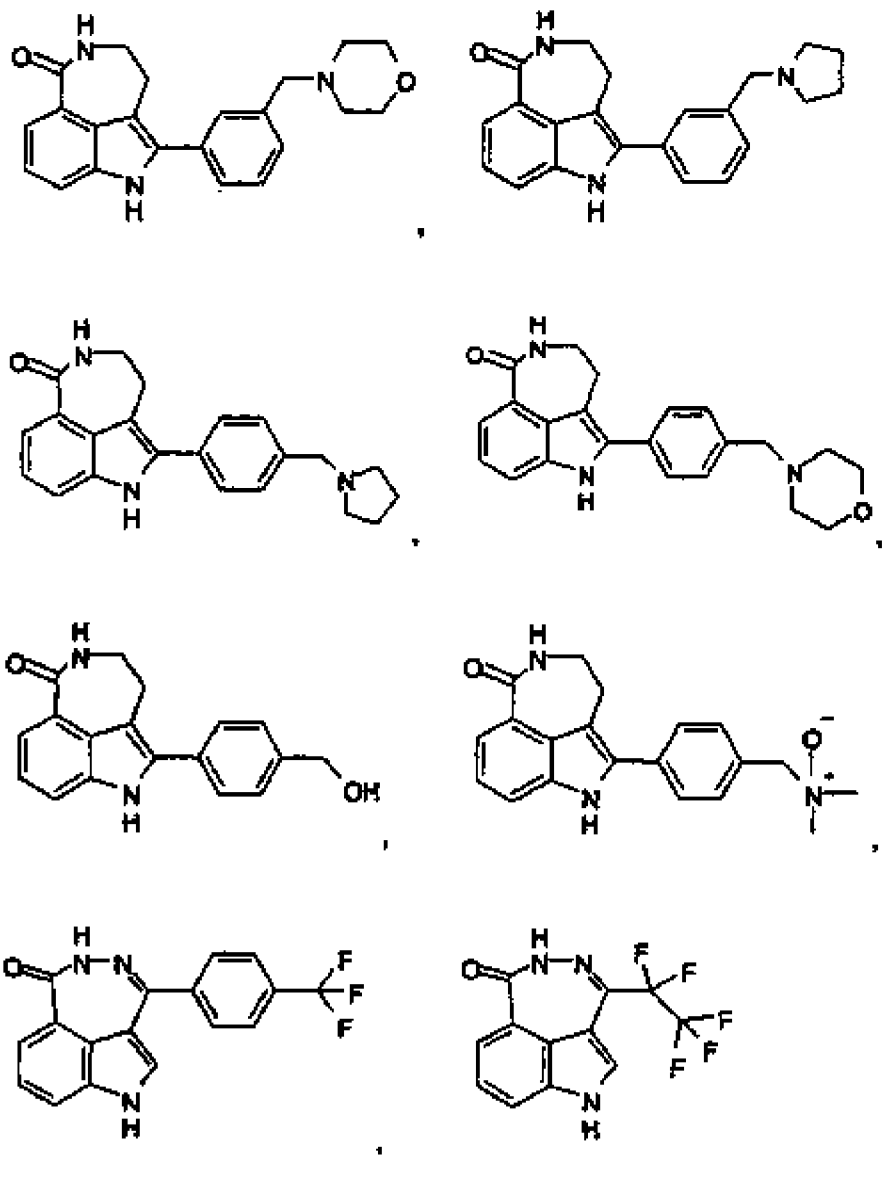




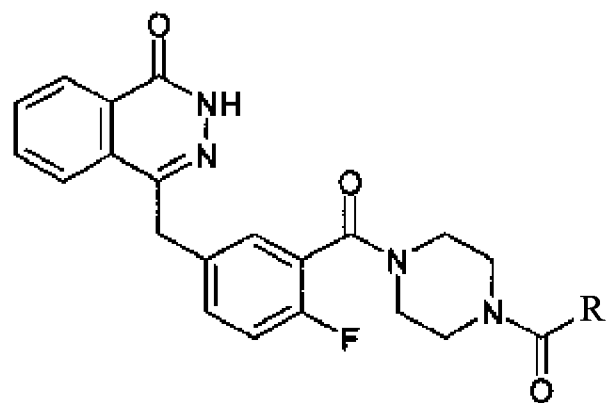






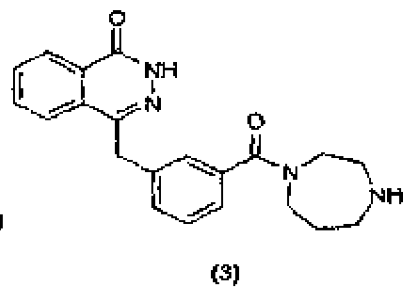
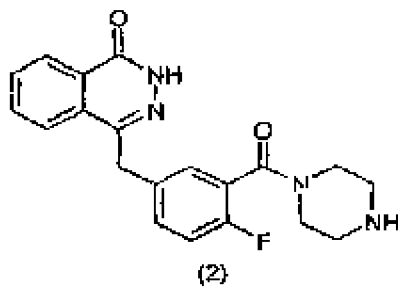
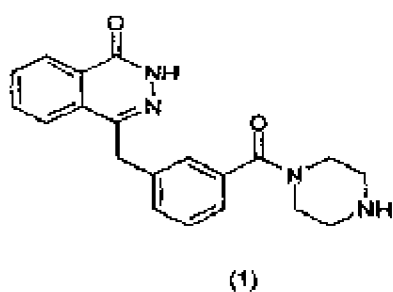


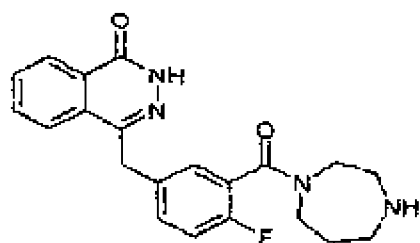
The compound described in Equation II is any of the following:



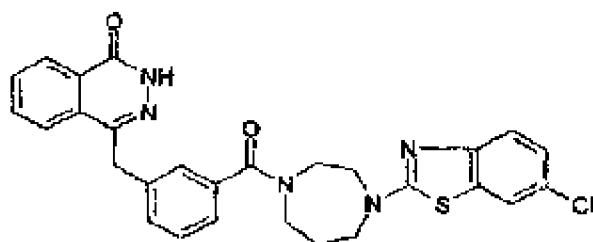
其中 R 选自

- a) $-\text{CH}_2\text{CH}_3$;
- b) $-\text{C}_6\text{H}_{11}\text{N}-$;
- c) $-\text{C}_3\text{H}_5$;
- d) $-\text{C}_4\text{H}_8\text{NO}-$;
- e) $-\text{CH}_2\text{CH}_2\text{N}(\text{C}_4\text{H}_8\text{NO})-$;
- f) $-\text{CH}_2\text{CH}_2\text{N}(\text{C}_7\text{H}_{13}\text{NH})-$;
- g) $-\text{CH}_2\text{CH}_2\text{N}(\text{C}_6\text{H}_{11}\text{NMe})-$; 和
- h) $-\text{C}_6\text{H}_{11}\text{NH}-$.

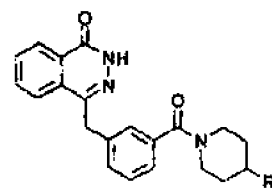
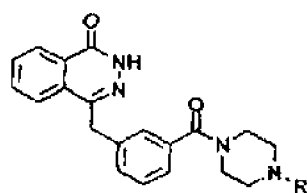
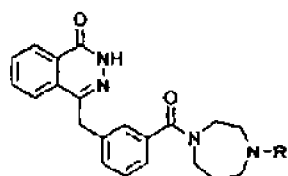




(4)



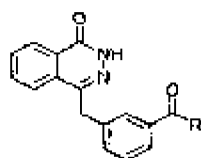
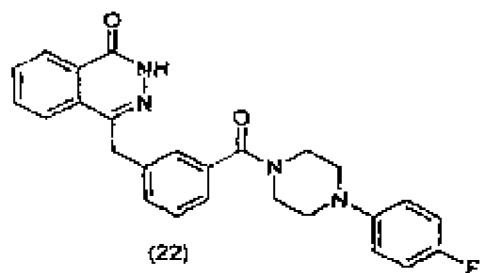
(5)



化合物	R
6	
7	
8	
9	
10	
11	
12	

化合物	R
13	
14	
15	
16	
17	

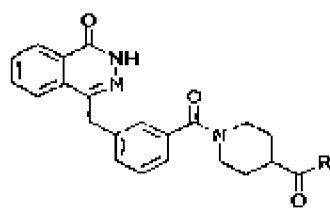
化合物	R
18	
19	
20	
21	



化合物	R
23	
24	

化合物	R
25	
26	
27	
28	
29	
30	
31	

化合物	R
32	
33	
34	
35	
36 (注 2)	

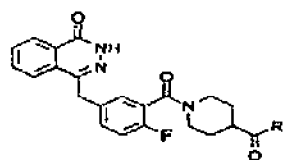


化合物	R
37	
38	
39	
40	
41	
42	

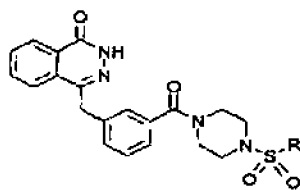
化合物	R
43	
44	
45	
46	
47	
48	
49	
50	

化合物	R
51	
52	
53	
54	
55	
56	
57	
58	

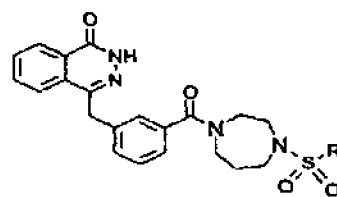
化合物	R		
59			
60			
61			
62			
63			
64		化合物	R
65		68	
66		69	
67		70	
		71	



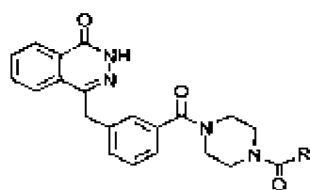
化合物	R
72	



化合物	R
73	
74	
75	
76	
77	
78	
79	
80	



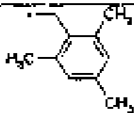
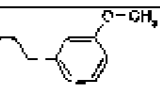
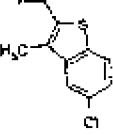
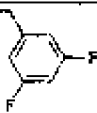
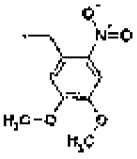
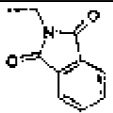
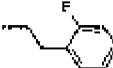
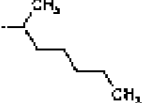
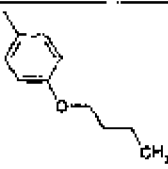
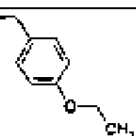
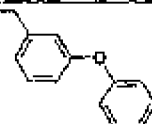
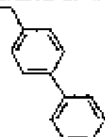
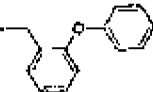
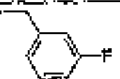
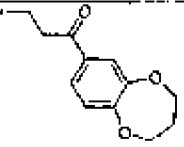
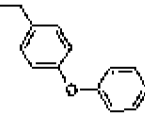
化合物	R
81	
82	

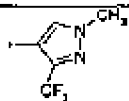
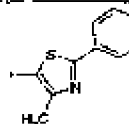
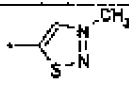
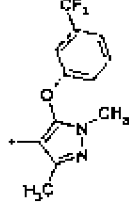
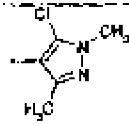
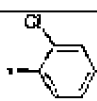
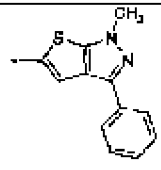
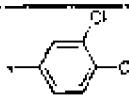
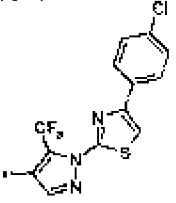
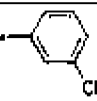
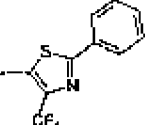
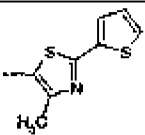
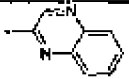
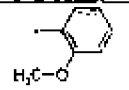
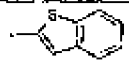


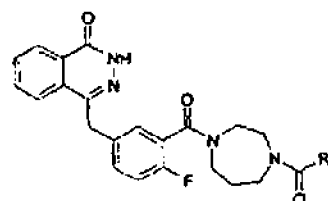
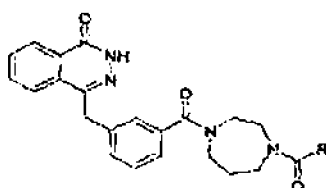
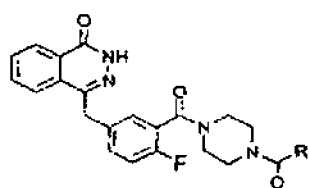
化合物	R
83	
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109		119		129	
110		120		129	
111		121		130	
112		122		131	
113		123		132	
114		124		133	
115		125		134	
116		126		135	
117		127		136	
118				137	

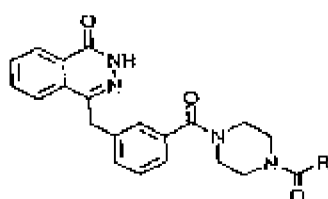
138		145		158	
139		146		159	
140		147		160	
141		148		161	
142		149		162	
143		150		163	
144		151		164	
		152		165	
		153			
		154			
		155			
		156			
		157			



化合物	R
166	
167	
168	
169	
170	
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172	
173	

化合物	R
174	
175	
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179	
180	
181	
182	

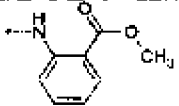
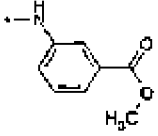
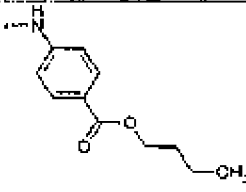
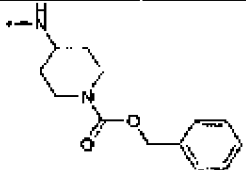
化合物	R
183	
184	

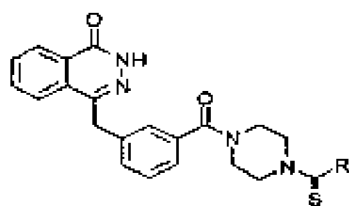


化合物	R
183	
185	
187	
188	
189	
190	
191	
192	

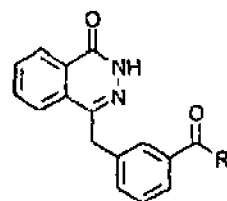
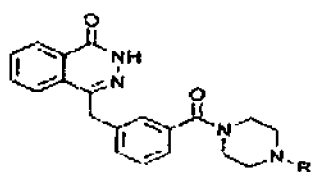
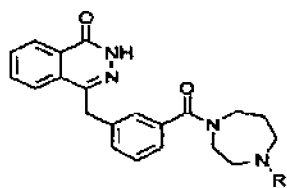
193	
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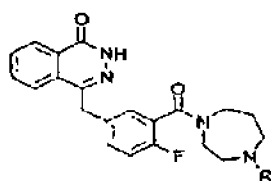
化合物	R
218	
219	
220	
221	
222	
223	
224	
225	
226	
227	
228	
229	
230	



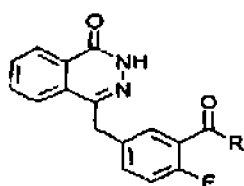
化合物	R
231	

化合物	R
232	
233	
234	
235	
236	
237	
238	
239	
240	
241	
242	

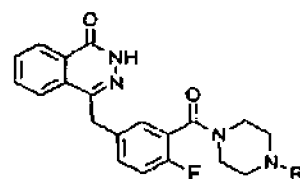
化合物	R
243	
244	
245	



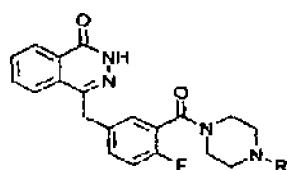
化合物	R
246	
247	



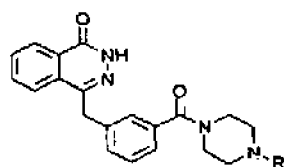
化合物	R
256	
257	



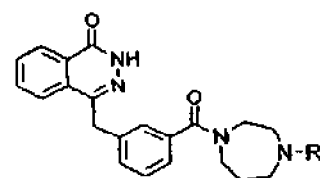
化合物	R
263	
264	



化合物	R
248	
249	
250	
251	
252	
253	
254	
255	



化合物	R
258	
259	
260	
261	
262	



化合物	R
265	
266	

;

The compound described in Equation III is any of the following:

5e	
5f	
5g	
5h	
5i	
5j	
5k	
5l	
5m	
5n	

编 号	结构式
5a	
5b	
7a	
5c	
5d	

5o	
5p	

The compound described in Equation IV is any of the following:

2-phenyl-2H-indazole-7-formamide; 2-(3-chlorophenyl) -2H-indazole-7-formamide; And 2-{4-[(dimethylamino) methyl] phenyl} -2H-indazole-7-formamide; 2-{4-[(N, n-dimethylglycine) amino] phenyl} -2H-indazole-7-formamide; 2-benzyl-2H-indazole-7-formamide; 2-(4-chlorophenyl) -2H-indazole-7-formamide; 2-(2-chlorophenyl) -2H-indazole-7-formamide; 2-{4-[(4-methylpiperazine-1-yl) methyl] phenyl} -2H-indazole-7-formamide; 2-[4-(morpholine 4-methyl) phenyl] -2H-indazole-7-formamide; 2-{4-[(methylamino) methyl] phenyl} -2H-indazole-7-formamide; 2-[4-(pyrrolidine - 1-methyl) phenyl] -2H-indazole-7-

formamide; 2-[4-(piperidine-1-methyl) phenyl] -2H-indazole-7-formamide; {4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl}-N, N-dimethylmethane ammonium chloride; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) methyl] pyridonium; 2-{4-[1-(methylamino) ethyl] phenyl} -2H-indazole-7-formamide; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} cyclohexane trifluoroacetate ammonium; {4-[7-(aminocarbonyl) -4-chloro-2h-indazole-2-yl] phenyl} -n-methylmethane trifluoroacetate ammonium; 2-phenyl-2H-1, 2, 3-benzotriazole-4-formamide; 2-benzyl-2H-1, 2, 3-benzotriazole-4-formamide; 2-{3-[(methylamino) methyl] phenyl} -2H-indazole-7-formamide; Trifluoroacetic acid 4-({3-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) piperidine; {4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -n-methylmethane ammonium chloride; 2-{3-chloro-4 -[(dimethylamino) methyl] phenyl} -2H-indazole-7-formamide; Trifluoroacetic acid 1 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) ethyl] - 2 - oxygen generation - 4 - methyl - Weng piperazine - 1; 2-(4-{[(4-pyrrolidine - 1-yl piperidine - 1-yl) acetyl] amino} phenyl) -2H-indazole-7-formamide; 2-{4-[(pyrrolidine - 1-yl acetyl) amino] phenyl} -2H-indazole-7-formamide; 2-{4-[(piperidine-1-acetyl) amino] phenyl} -2H-indazole-7-formamide; 2-{4-[(morpholine 4-yl acetyl) amino] phenyl} -2H-indazole-7-formamide; Chloride 4 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) ethyl] - 2 - oxygen generation - 4 - Weng morpholine; 2-{4-[(ethylamino) methyl] phenyl} -2H-indazole-7-formamide; 2-{4-[(isopropyl amino) methyl] phenyl} -2h-indazole-7-formamide; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} propane-2-ammonium chloride; 2-(4-{[(2, 2-difluoroethyl) amino] methyl} phenyl) -2H-indazole-7-formamide; 2-(4-{[(2, 2-difluoroethyl) amino] methyl} phenyl) -2H-indazole-7-formamide; 2-{4-[(cyclopropyl amino) methyl] phenyl} -2h-indazole-7-formamide; Trifluoroacetic acid and 4 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzene formyl} - 1, 4-2 nitrogen heterocyclic heptane - 1 - Weng; 4 - [2 - ({7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzene formyl} amino) - N, N - dimethyl ethane trifluoroacetic acid ammonium; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benformyl} amino) methyl] piperidine onium; N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - N, N', N' - 3-1, 2 - methyl ethane ammonium chloride (2); Trifluoroacetic acid 4-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benformyl} -1-methylpiperazine-1-onium; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] azacyclobutanium; Trifluoroacetic acid (2 s) - 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole -

2 - base] phenyl} amino) carbonyl] 1 - methyl - pyrrolidine Weng; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-methylpiperidine; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-methylpiperidine; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) -1-benzyl piperidinium; 2-{4-[(pyridine-4-amino) carbonyl] phenyl} -2H-indazole-7-formamide; 2-{4-[(4-phenylpiperazine-1-yl) carbonyl] phenyl} -2H-indazole-7-formamide; 2-(4-{[methyl (quinoxaline - 6-yl methyl) amino] carbonyl} phenyl) -2H-indazole-7-formamide; 2-(4-formylphenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 1-[2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) ethyl] pyrrolidonium; Trifluoroacetic acid 1-[2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) ethyl] piperidine onium; Trifluoroacetic acid and 4 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzene formyl} amino) ethyl] - 4 - Weng morpholine; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzoyl} amino) -1-methylpiperidine; 2-[4-[(4-methylpiperazine-1-yl) methyl]-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 2-[4-[(methylamino) methyl]-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -n-methyl ethane ammonium chloride; 2-[4-(pyrrolidine - 1-methyl)-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 2-[4-(piperidine-1-methyl)-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; 2-[4-[(ethylamino) methyl]-3-(trifluoromethyl) phenyl] -2H-indazole-7-formamide; Trifluoroacetic acid 4-{4-[7-(aminocarbonyl) -4-chloro-2h-indazole-2-yl] benzyl} -1-methylpiperazine-1-ium; Bis (trifluoroacetic acid)1-[2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) ethyl] piperidine onium; Double (trifluoroacetic acid) 4 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) ethyl] - 4 - Weng morpholine; Double (trifluoroacetic acid) 1 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) ethyl] pyrrolidine Weng; Bis (trifluoroacetic acid)4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) -1-methylpiperidine; Bis (trifluoroacetic acid)4-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) -1-benzyl piperidinium; Bis (trifluoroacetic acid)1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -4-phenylpiperazine diphenyl; N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2 - (dimethyl amino) - 2 - oxygen generation ethane trifluoroacetic acid ammonium; Bis (trifluoroacetic acid)2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) methyl] pyridonium; Bis (trifluoroacetic acid)4-[(4-[7-

(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) methyl] pyridonium; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-methyl propane-2-trifluoroacetate ammonium; Double (trifluoroacetic acid) N' - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - N, N - dimethyl ethane - 1, 2 - diammonium; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - (1, 3 - oxazole - 2 - methyl) methane trifluoroacetic acid ammonium.7-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline sulfonium chloride; 6-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline sulfonium chloride; Trifluoroacetic acid 5-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline; Trifluoroacetic acid 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl) amino) carbonyl] nitrogen heterocyclic butane Weng; 2-(4-[(azacyclic butane-3-yl carbonyl)(methyl) amino] methyl} phenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 3 - [(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} amino) carbonyl] azacyclobutanium; 2-(4-bromophenyl) -5-fluoro-2h-indazole-7-formamide; 5-fluoro-2 -(4-pyridine-3-phenyl) -2H-indazole-7-formamide; 2-(4-pyridine-3-phenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 4-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -1-methylpiperazine-1-onium; Trifluoroacetic acid 4-{4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} piperidine; 2-{4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} -n-methyl ethane trifluoroacetate ammonium; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl) amino) carbonyl] azacyclobutanium; 2-{5-[(methylamino) methyl] pyridine-2-yl} -2H-indazole-7-formamide; 5-fluoro-2 -{3-fluoro-4 -[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; 5-fluoro-2 -{4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2-{4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} -n-methyl propane-2-trifluoroacetate ammonium;2-(6-phenylpyrazine-3-yl) -2h-indazole-7-formamide; {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl) cyclohexyl] methyl} methane trifluoroacetic acid ammonium; 5-chloro-2 -(4-formyl phenyl) -2H-indazole-7-formamide; 2-{3-methoxy-4 -[(4-methylpiperazine-1-yl) methyl] phenyl} -2h-indazole-7-formamide; 2-{3-methoxy-4 -[(methylamino) methyl] phenyl} -2H-indazole-7-formamide; 5-chloro-2 -{4-[(4-methylpiperazine-1-yl) methyl] phenyl} -2h-indazole-7-formamide; 5-chloro-2 -{4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; {4-[7-(aminocarbonyl) -4-fluoro-2h-indazole-2-l] phenyl} -n-methylmethane ammonium chloride; {4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-l] phenyl} -n-methylmethane ammonium chloride; Chlorinated 1-{4-[7-

(aminocarbonyl) -4-fluoro-2h-indazole-2-yl] benzyl} -4-methylpiperazine-1-onium; Chlorinated 1-{4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] benzyl} -4-methylpiperazine-1-onium; Bis (trifluoroacetic acid) 1-{3-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -4-methylpiperazine diphenyl; 2-[4-(1-hydroxy-1-methylethyl) phenyl] -2H-indazole-7-formamide; 2-(4-acetylphenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 3 - {{4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} (methyl) amino] carbonyl} - 1 - methyl piperidine Weng; 2-{4-[1-(formyl amino) -1-methylethyl] phenyl} -2H-indazole-7-formamide; 2-[3-(1, 4-diazacyclic heptane-1-yl carbonyl) phenyl] -2H-indazole-7-formamide; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} amino) carbonyl] -1-methylpiperidine; Trifluoroacetic acid (2 s) - 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] pyrrolidine Weng; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] pyrrolidonium; Trifluoroacetic acid (2 r) - 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] pyrrolidine Weng; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] piperidine; Trifluoroacetic acid (3 r) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - pyrrolidine Weng; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-methylpiperidine; 4-chloro-2 - (4-formyl phenyl) -2H-indazole-7-formamide; Trifluoroacetic acid (3 s) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - pyrrolidine Weng; (R)-1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -n-methyl ethane ammonium chloride; (S)-1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} -n-methyl ethane ammonium chloride; 2-{3-fluoro-4 -[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; {4-[7-(aminocarbonyl) -2H-indazole-2 - L] -2-fluorophenyl} -n-methane trifluoroacetate ammonium; 2-{4-[1-methyl-1 -(methylamino) ethyl] phenyl} -2H-indazole-7-formamide; Trifluoroacetic acid 1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] -2-hydroxybenzyl} -4-methylpiperazine-1-onium; Chloride (3 r) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 1 - methyl piperidine Weng; Chloride (3 s) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 1 - methyl piperidine Weng; Double (trifluoroacetic acid) 1 - (2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} ethyl) - 4 - methyl piperazine Weng; {4-[7-(aminocarbonyl) -4-hydroxy-2H-indazole-2-yl] phenyl} -n-methyl methane trifluoroacetate ammonium; Trifluoroacetic acid, 2 - [(4 - [7 - (amino carbonyl)

- 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 4 - phenyl pyrrolidine Weng; (1 r, 3 s) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] cyclopentane trifluoroacetic acid ammonium. (1 r, 3 r) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] cyclopentane trifluoroacetic acid ammonium. (1 s, 3 r) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] cyclopentane trifluoroacetic acid ammonium. Trifluoroacetic acid, 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 2 - methyl nitrogen heterocyclic butane Weng; Trifluoroacetic acid and 4 - [2 - ((4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) - 2 - ethyl) oxygen generation - 1 - methyl piperidine Weng; 9 - [2 - ((4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) ethyl) - 2 - oxygen generation - 3 - n Weng miscellaneous screw [5.5] undecane trifluoroacetic acid salt; Trifluoroacetic acid and 4 - [2 - ((4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) - 2 - ethyl) oxygen generation - 4 - phenyl piperidine Weng; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] pyridonium; Trifluoroacetic acid {4-3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] pyridine - 2 - base} piperazine - 1 - Weng; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] pyridonium; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] pyridonium; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] quinoline onium; Trifluoroacetic acid 4-[(4-[7-(aminocarbonyl) -2H-indazole-2-l] phenyl} amino) carbonyl] isoquinoline onium; Trifluoroacetic acid, 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - nitrogen heterocyclic heptane Weng; Trifluoroacetic acid 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 2 - methyl - 1, 2, 3, 4 - four hydrogen isoquinoline Weng; Trifluoroacetic acid, 2 - {4 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] piperidine - 1 - base} pyrimidine - 1 - Weng; Chlorinated 1-{4-[7-(aminocarbonyl) -5-fluoro-2h-indazole-2-yl] benzyl} -4-methylpiperazine-1-onium; 5 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - three - eight hydrogen oxygen generation Yin oxazine - 2 - trifluoroacetic acid ammonium; Trifluoroacetic acid, 2 - {3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] piperidine - 1 - base} pyridine Weng; Trifluoroacetic acid, 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 4 - methyl - 4 - Weng morpholine;(1 r, 4 r) - N - {4 - [7 - (amino

carbonyl) - 2 h - indazole - 2 - base] phenyl} - 1' - (methyl sulfonyl) - 1', 2' - dihydro screw/cyclohexane 1, 3' - indole - 4 - formamide; Trifluoroacetic acid 1 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 8 h - 1 h - different indole Weng; Trifluoroacetic acid, 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 4 - benzyl - 4 - Weng morpholine; Trifluoroacetic acid (3 s, 4 r) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 4 - (methoxy carbonyl) pyrrolidine Weng; Double (trifluoroacetic acid) 4 - {(2 s) - 2 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] pyrrolidine Weng - 1 - base} piperidine Weng; (1 s, 3 s) - 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] cyclopentane trifluoroacetic acid ammonium. Trifluoroacetic acid 3 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - pyrrolidine Weng; Trifluoroacetic acid, 2 - {4 - [(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] piperidine - 1 - base} pyrimidine - 1 - Weng; Double (trifluoroacetic acid) 2 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} pyrrolidine Weng - 3 - base) pyridine Weng; Double (trifluoroacetic acid) 3 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} pyrrolidine Weng - 3 - base) pyridine Weng; Trifluoroacetic acid (3 s, 4 s) - 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3, 4-2 fluorine pyrrolidine Weng; 3 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 6 - ammonium nitrogen - 3 - Weng mixed double loop [3.1.0] hexane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 7 - methyl - 2, 7 - dinitrogen Weng miscellaneous screw [4.4] nonane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3 - (4 - (dimethyl ammonium) phenyl] pyrrolidine Weng; Double (trifluoroacetic acid) 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl}, 2,4,5,6,6-1 - methyl - 1 a - six hydrogen pyrrole and [3, 4 - b] pyrrole Weng; Double (trifluoroacetic acid) 3 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} (methyl) ammonium] methyl} - 1 - methyl piperidine Weng; (1 r, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - miscellaneous - 5-2 - oxygen nitrogen Weng mixed double loop [2.2.1] heptane trifluoroacetic acid salt; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-hydroxy-2-methyl propane-1-trifluoroacetate ammonium; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl}-3, 3-difluorocyclobutane trifluoroacetate ammonium; Trifluoroacetic acid and 4 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base]

benzyl} - 6 - fluoro - 1, 4-2 - Weng nitrogen heterocyclic heptane - 1; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - Weng - 2-4 - pyrimidine - 1 - base - 1, 4-2 - Weng nitrogen heterocyclic heptane - 1; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) -1-benzyl pyrrolidonium; The (trifluoroacetic acid) 3 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl - pyrrolidine Weng; Double (trifluoroacetic acid) 3 - [({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - benzyl - pyrrolidine Weng; 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 7 - benzyl - 2, 7 - dinitrogen Weng miscellaneous screw [4.4] nonane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 8 - benzyl - 2, 8 - dinitrogen Weng miscellaneous screw [5.5] undecane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 6 - dinitrogen Weng miscellaneous screw [3.3] heptane double (trifluoroacetic acid salt); 7 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 7 - dinitrogen Weng miscellaneous screw [3.5] nonane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 6 - dinitrogen Weng miscellaneous screw [3.5] nonane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 8 - dinitrogen Weng miscellaneous screw [5.5] undecane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 8 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 7 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); 8 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2, 8 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); 3 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3, 9 - dinitrogen Weng miscellaneous screw [5.5] undecane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} pyrrole and eight hydrogen [3, 4 - c] pyrrole Weng; Double (trifluoroacetic acid) 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} [3, 4 - b] pyrrole and eight hydrogen pyrrole Weng; Double (trifluoroacetic acid) 4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) eight hydrogen cyclopentadiene and [c] pyrrole Weng; N2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - N1 N1-2 - pyridine - 2 - methyl - 1-1, 2 - double base ethane (trifluoroacetic acid) diammonium; Double (trifluoroacetic acid) 7 - (amino carbonyl)

- 2 - [4 - ({[2 - (2, 3-2 h - 1 h - indole - 1 - base) ethyl] ammonium} methyl) phenyl] - 2 h - 1 - Weng indazole -; Double (trifluoroacetic acid) (3 s, 4 s) - 1 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) ethyl] - 3, 4-2 fluorine pyrrolidine Weng; Trifluoroacetic acid 5 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} amino) - 1, 3 - benzothiazole - 3 - Weng; 1 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 8 - nitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 4 - [{(4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl piperidine Weng; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-hydroxy-ethane trifluoroacetate ammonium; Trifluoroacetic acid 7-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline; Trifluoroacetic acid 3 - [2 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} amino) - 2 - ethyl] oxygen generation nitrogen heterocyclic butane Weng; Bis (trifluoroacetic acid)4-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) piperidine; Double (trifluoroacetic acid) (3 r, 4 r) - 4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 3 - fluorine piperidine Weng; Double (trifluoroacetic acid) (3 s, 4 r) - 4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 3 - benzyl - 1 - methyl piperidine Weng; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -1-isobutylpiperidine-4-trifluoroacetate ammonium; Double (trifluoroacetic acid) 2 - (4 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) piperidine - 1 - base] - 3 - methyl pyridine Weng; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) piperidine; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) -1-benzyl piperidinium; 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 5 - nitrogen hetero - 2 - Weng mixed double loop (2.2.2) octane trifluoroacetic acid salt; (1 s, 4 s) - 2 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 5 - methyl - 2, 5 - dinitrogen Weng mixed double loop [2.2.1] heptane double (trifluoroacetic acid salt); Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - (pyridine - 2 - methyl) piperazine Weng; 5 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2 - benzyl - 5 - nitrogen hetero - 2 - Weng mixed double loop (2.2.2) octane trifluoroacetic acid salt; 8 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3 - benzyl - 8 - nitrogen hetero - 3 - Weng mixed double loop [3.2.1] octane trifluoroacetic acid salt; (1 s, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 2 - benzyl - 5 -

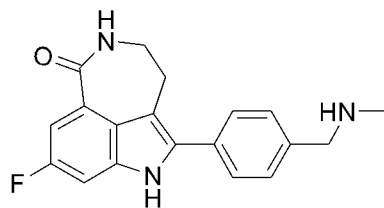
nitrogen hetero - 2 - Weng mixed double loop [2.2.1] heptane trifluoroacetic acid salt; Bis (trifluoroacetic acid)3-({4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} ammonium) pyrrolidonium; 6 - ({4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) - 3 - n Weng mixed double loop [3.1.0] hexane double (trifluoroacetic acid salt); Trifluoroacetic acid (3 s, 4 s) - N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - hydroxyl ammonium tetrahydrothiophene - 3-1, 1-2 oxide; Double (trifluoroacetic acid) 4 - [{4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl - 4 - hydroxy - piperidine Weng; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -1-cyclopropyl -2-hydroxy-ethane trifluoroacetate ammonium; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl) cyclopentyl] methyl} methane trifluoroacetic acid ammonium; Double (trifluoroacetic acid) 2 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} hydrogen - 1, 2, 3, 4-4-2, 7 - two nitrogen impurity naphthalene two Weng; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 3 - [(dimethyl ammonium) methyl] piperidine Weng; Double (trifluoroacetic acid) 4 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} piperidine Weng - 4 - base) thio - 4 - Weng morpholine; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - [(methyl sulfonyl) amino] piperidine Weng; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - (1 h - imidazole - 3 - Weng - 1 - methyl) piperidine Weng; 7 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 1 - oxygen mixed - 7 - nitrogen Weng miscellaneous screw [4.5] decane trifluoroacetic acid salt; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - (1 - hydroxy - 1 - methyl ethyl) piperidine Weng; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-benzyl piperidinium; Trifluoroacetic acid 2-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-ethyl piperidonium; Trifluoroacetic acid 3-[(4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} amino) carbonyl] -1-ethyl piperidonium; 2-[3-(1, 4-diazacyclic heptane-1-yl carbonyl) -4-fluorophenyl] -2H-indazole-7-formamide trifluoroacetate; {4-[7-(aminocarbonyl) -4-chloro-2H-indazole-2-yl] benzyl} tert-butyl methyl carbamate; Trifluoroacetic acid 6-[7-(aminocarbonyl) -2H-indazole-2-yl]-1, 2, 3, 4-tetrahydroisoquinoline; Trifluoroacetic acid 2-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] phenyl} pyrrolidonium; 6-fluoro-2 - {4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide; 5-fluoro-2 - {2-fluoro-4 -[(methyl amino) methyl] phenyl} -2H-indazole-

7-formamide; 2-{3-hydroxy-4 -[(methylamino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2-(4-{[formyl (methyl) amino] methyl} -3-hydroxyphenyl) -2H-indazole-7-formamide; 2-{2-chloro-4 -[(methyl amino) methyl] phenyl} -5-fluoro-2h-indazole-7-formamide; 5-fluoro-2 -{3-fluoro-4 -[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2-{2, 5-difluoro-4 -[(methyl amino) methyl] phenyl} -5-fluoro-2h-indazole-7-formamide trifluoroacetate; 2-(4-bromophenyl) -2H-indazole-7-formamide; Chloride (3 r) - 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 1 - methyl piperidine Weng; Trifluoroacetic acid (3 r) - 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] - 1 - methyl piperidine Weng; 2-(1, 2, 3, 4-tetrahydroisoquinoline-7-yl) -2H-indazole-7-formamide;(R) - 2 - (4 - ((3 - [(dimethyl amine) methyl] piperidine - 1 - base} methyl) phenyl) - 2 h - indazole - 7 - formamide; (S) - 2 - (4 - ((3 - [(dimethyl amine) methyl] piperidine - 1 - base} methyl) phenyl) - 2 h - indazole - 7 - formamide; 4 - [3 - ((7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) - 2 - (methyl chloride) - 3 - oxygen generation - trifluoroacetic acid ammonium propane - 1; 5-fluoro-2 -{3-fluoro-4 -[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide hydrochloride; 2-{4-[(dimethylamino) methyl] -3-fluorophenyl} -5-fluorophenyl - 2H-indazole-7-formamide trifluoroacetate; 2-{4-[(azacyclic butane-3-yl carbonyl) amino] phenyl} -5-fluoro-2h-indazole-7-formamide; 2-[4-(2, 7-diazania [4.5] decan-2-yl methyl) phenyl] -2H-indazole-7-formamide; (1 s, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 2 - (4 - benzyl chloride) - 5 - nitrogen hetero - 2 - Weng mixed double loop [2.2.1] heptane trifluoroacetic acid salt; (1 s, 4 s) - 5 - {4 - [7 - (amino carbonyl) - 2 h - 2 - base] indazole - benzyl} - 2 - (3 - benzyl chloride) - 5 - nitrogen hetero - 2 - Weng mixed double loop [2.2.1] heptane trifluoroacetic acid salt; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - [(methyl amino) carbonyl] piperazine - 1 - Weng; N - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 2 - hydroxy - 2 - pyridine - 3 - base ethane trifluoroacetic acid ammonium; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-cyclohexyl-2-hydroxy-ethane trifluoroacetate ammonium; Trifluoroacetic acid and 4 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 6 - (hydroxy methyl) - 1, 4 - oxygen mixed nitrogen heterocyclic heptane - 4 - Weng; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl) ring butyl] methyl} methane trifluoroacetic acid ammonium; {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] phenyl} - N - {[1 - (hydroxy methyl)

cyclohexyl] methyl} methane trifluoroacetic acid ammonium; Trifluoroacetic acid 1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - (5 - methyl - 1 h - benzene and imidazole - 2 -) piperidine Weng; Double (trifluoroacetic acid) 2 - (1 - {4 - [7 - (amino carbonyl) - 2 h - indazole - 2 - base] benzyl} - 4 - hydroxy piperidine Weng - 4 - base) pyridine Weng; Trifluoroacetic acid 1-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl}-3, 3-difluoropyrrolidonium;2-(4-{[(2R)-2-(fluoromethyl) pyrrolidine 1-yl] methyl} phenyl) -2H-indazole-7-formamide; N-{4-[7-(aminocarbonyl) -2H-indazole-2-yl] benzyl} -2-oxo pyrrolidine 3-trifluoroacetate ammonium; 5-fluoro-2 -(4-formyl phenyl) -2H-indazole-7-formamide; Trifluoroacetic acid 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} amino) carbonyl] 1 - methyl - nitrogen heterocyclic butane Weng; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] benzyl} - 3 - [(dimethyl ammonium) methyl] piperidine Weng; Trifluoroacetic acid 3 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} - 2 - fluorine amino) carbonyl] nitrogen heterocyclic butane Weng; 2 - {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] benzyl} - 2, 7 - dinitrogen Weng miscellaneous screw [4.5] decane double (trifluoroacetic acid salt);4, 5-difluoro-2 -{4-[(methyl amino) methyl] phenyl} -2H-indazole-7-formamide trifluoroacetate; 2 - (3-5 - fluoro - fluoro - 4 - {(1 - methyl nitrogen heterocyclic butane - 3 - base) carbonyl] amino} phenyl) - 2 h - indazole - 7 - formamide trifluoroacetic acid salt; 5-fluoro-2 -(3-fluoro-4-formylphenyl) -2H-indazole-7-formamide; 5-fluoro-2 -(5-fluoro-2-formylphenyl) -2H-indazole-7-formamide; {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] phenyl} - 2 - fluorine - N - {[1 - (hydroxy methyl) cyclopentyl] methyl} methane trifluoroacetic acid ammonium; 5 - fluoro - 2 - [3 - fluoro - 4 - ({[(3 r) - 1 - methyl piperidine - 3 - base] carbonyl} amino) phenyl] - 2 h - indazole - 7 - formamide trifluoroacetic acid salt; Double (trifluoroacetic acid) 1 - {4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] - 2 - fluorine benzyl} - 4 - methyl piperazine Weng; Double (trifluoroacetic acid) 4 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] benzyl} ammonium) methyl] 1 - methyl piperidine Weng; Double (trifluoroacetic acid) 4 - [(4 - [7 - (amino carbonyl) - 5 - fluoro - 2 h - indazole - 2 - base] - 2 - fluorine benzyl} ammonium) methyl] 1 - methyl piperidine Weng;

And their pharmaceutically acceptable salts or tautomers.

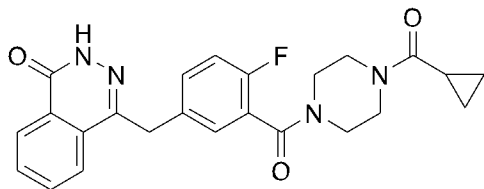
6. An application as described in claim 5 is characterized by the fact that the said compound



shown in Equation I is

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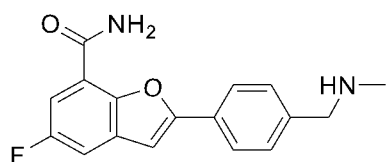
; The compound described in Equation II



is

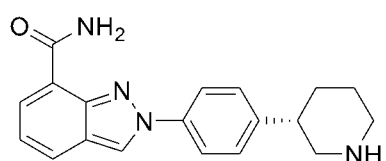
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; The compound described in Equation III is



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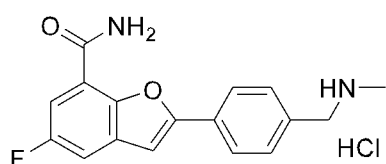
; The compound described in Equation IV is



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7. The application described in any of claims 1-6 is characterized by the fact that the pharmaceutically acceptable salt is hydrochloride; Optimization for



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8. The application described in any of claims 1-7 is characterized by the presence of the polyADP-ribose polymerase inhibitor or its pharmaceutically acceptable salt in the form of a pharmaceutical composition containing it;

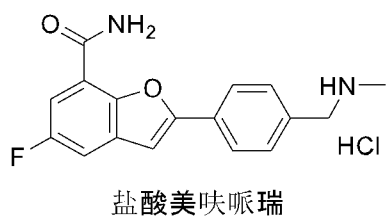
Preferably, the drug composition has the poly ADP-ribose polymerase inhibitor or a pharmaceutically acceptable salt thereof as the sole active ingredient of the drug composition; And/or, the drug composition also contains a pharmaceutically acceptable vehicle, such as a pharmaceutically acceptable

pharmaceutical excipient.

9. Any claim 1-8 items described in the application, its characteristics is described on poly (ADP ribose polymerase inhibitors or its pharmaceutical acceptable salt to contain the suit kit form, referred to suit kit also includes treatment of diseases associated with coronavirus medication and/or drugs for the treatment of other viruses cause the disease.

10. The application of the compound shown in Equation III and/or the compound shown in Equation IV or its pharmaceutically acceptable salt in any of claims 3 to 6 in the preparation of antiviral agents or in the preparation of drugs for the treatment of diseases caused by viruses; The viruses are viruses of the family HIV, HPV, EBV, IFV, and/or preferably the family orthocoronavirus subfamily.

11. The application described in claim 10 is characterized by the fact that the pharmaceutically acceptable salt is hydrochloride; Optimization for



12. The application described in claim 10 or 11 is characterized by the presence of the said compound shown in Equation III and/or the compound shown in Equation IV or a pharmaceutically acceptable salt thereof in the form of a pharmaceutical composition containing it;

Preferably, the drug composition has the compound shown in Equation III and/or the compound shown in Equation IV or a pharmaceutically acceptable salt thereof as the sole active ingredient of the drug composition; And/or, the drug composition also contains a pharmaceutically acceptable vehicle, such as a pharmaceutically acceptable pharmaceutical excipient.

13. The application described in any of Claims 10-12 is characterized by the presence of the said compound shown in Equation III and/or the compound shown in Equation IV or a pharmaceutically acceptable salt thereof in the form of a kit containing it, which also includes other drugs against diseases caused by

coronaviruses.

14. The application described in any of Claims 10-13 is characterized by the fact that the viruses of the orthocoronavirus subfamily are viruses of the genera α coronavirus, β coronavirus, γ coronavirus and/or δ coronavirus, Preferably coronaviruses that cause upper respiratory tract infections, viruses that cause acute respiratory syndrome such as SARS-associated coronavirus and/or MERS-CoV;

Preferably, the said coronaviruses causing upper respiratory tract infections were human coronavirus 229E, human coronavirus HKU1, human coronavirus OC43, human coronavirus NL63 and/or mouse hepatitis virus A59; And/or, the SARS-associated coronavirus is SARS-CoV or SARS-CoV-2.

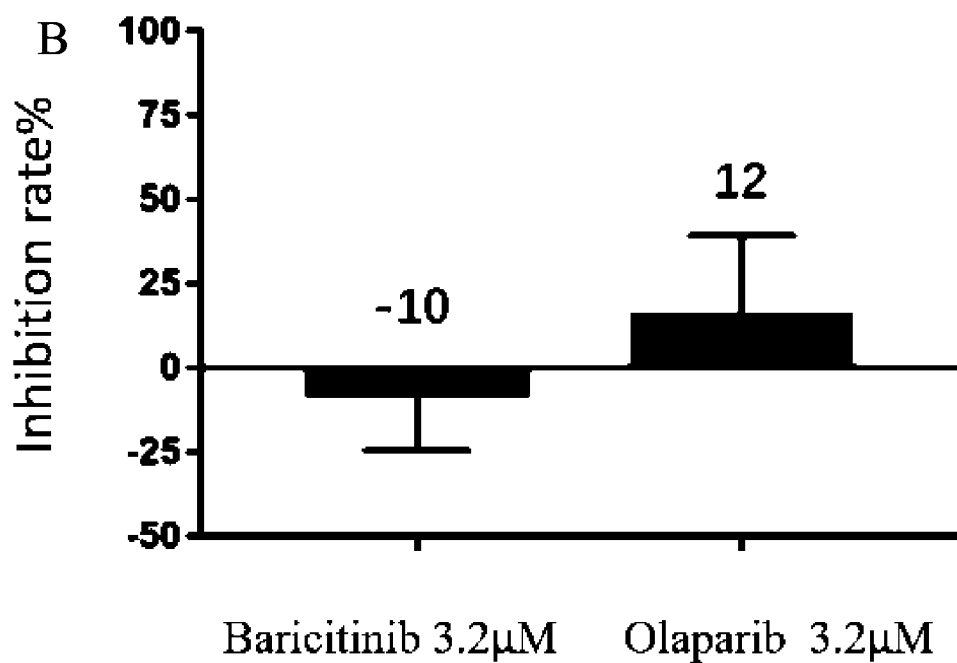
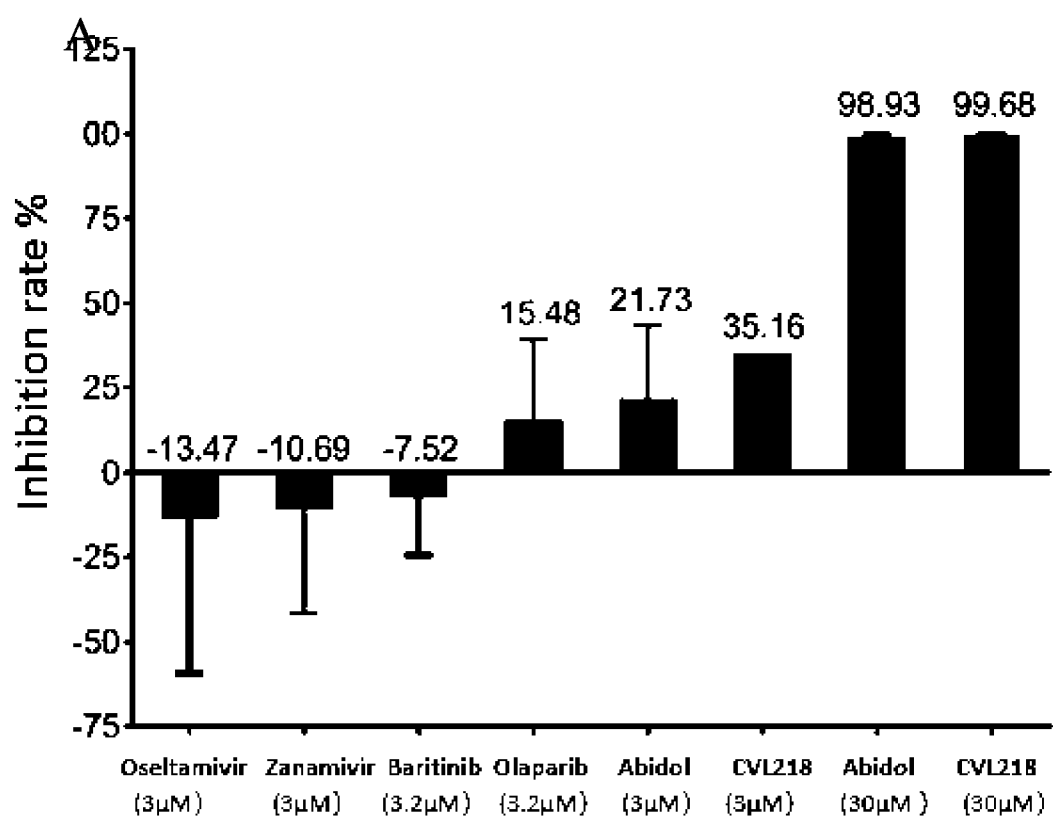
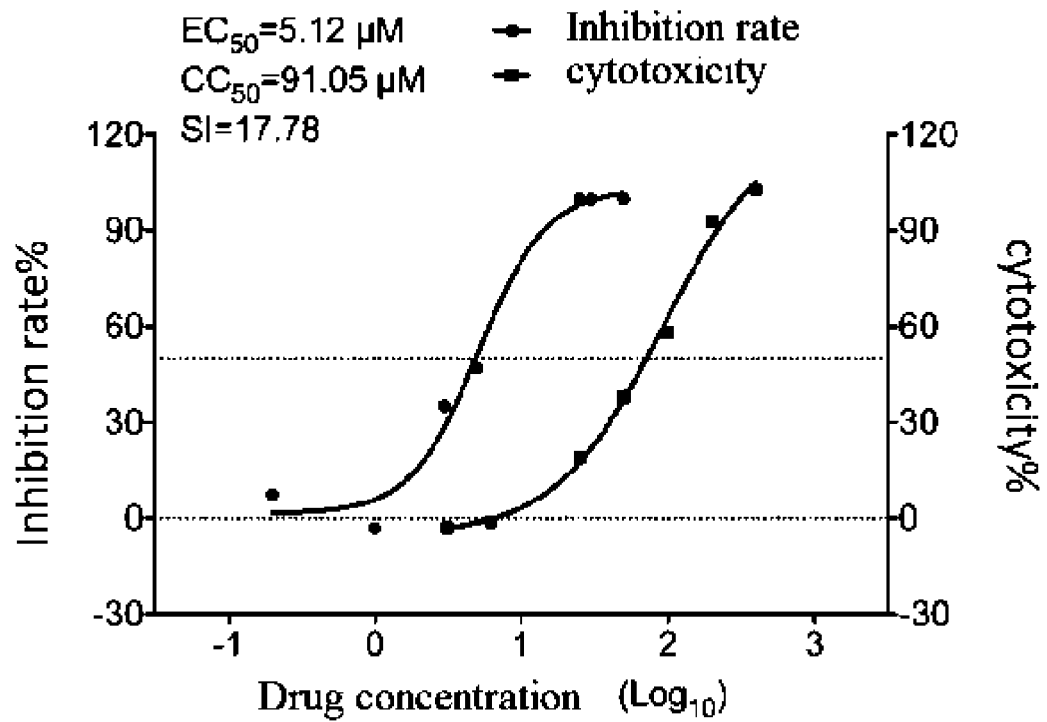


Fig.1

A



B

Fig.2

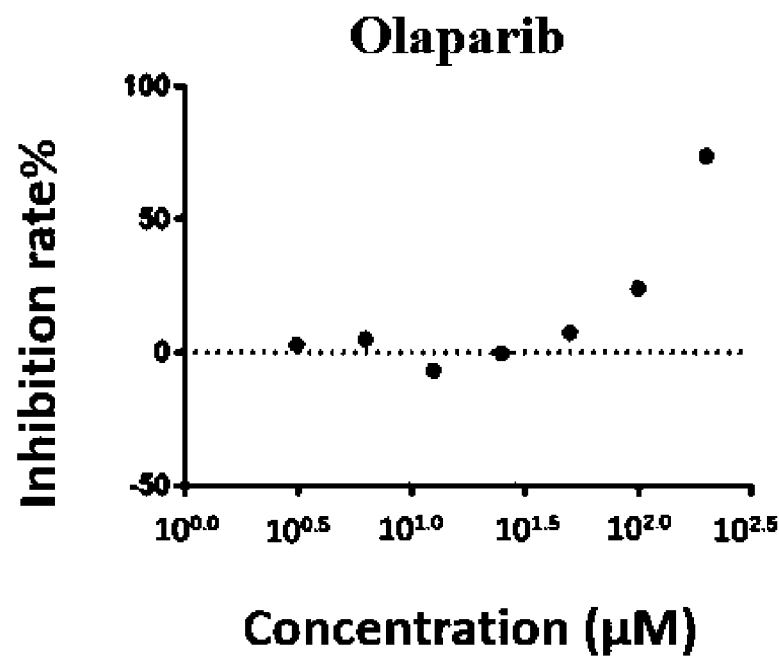
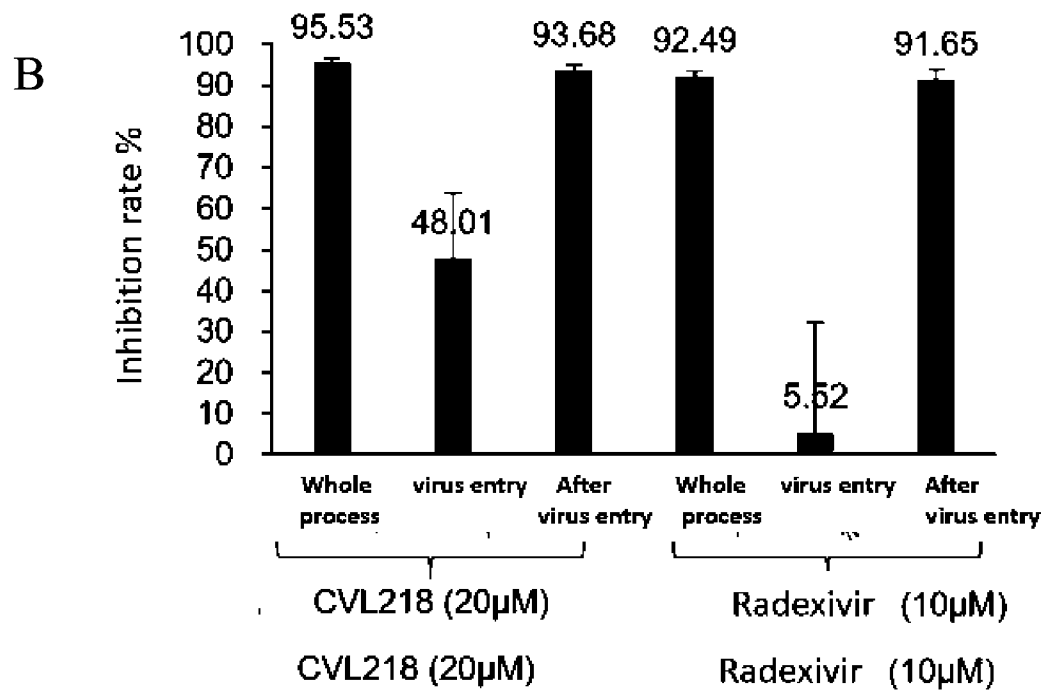
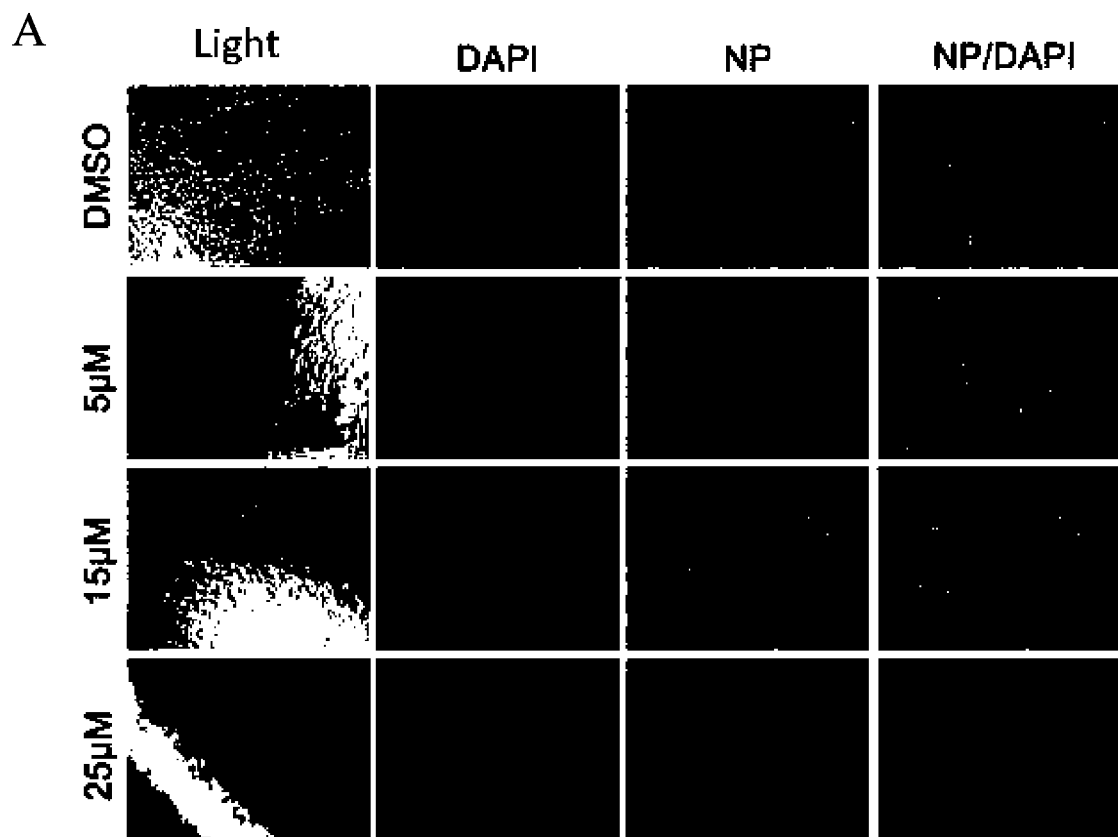


Fig.3



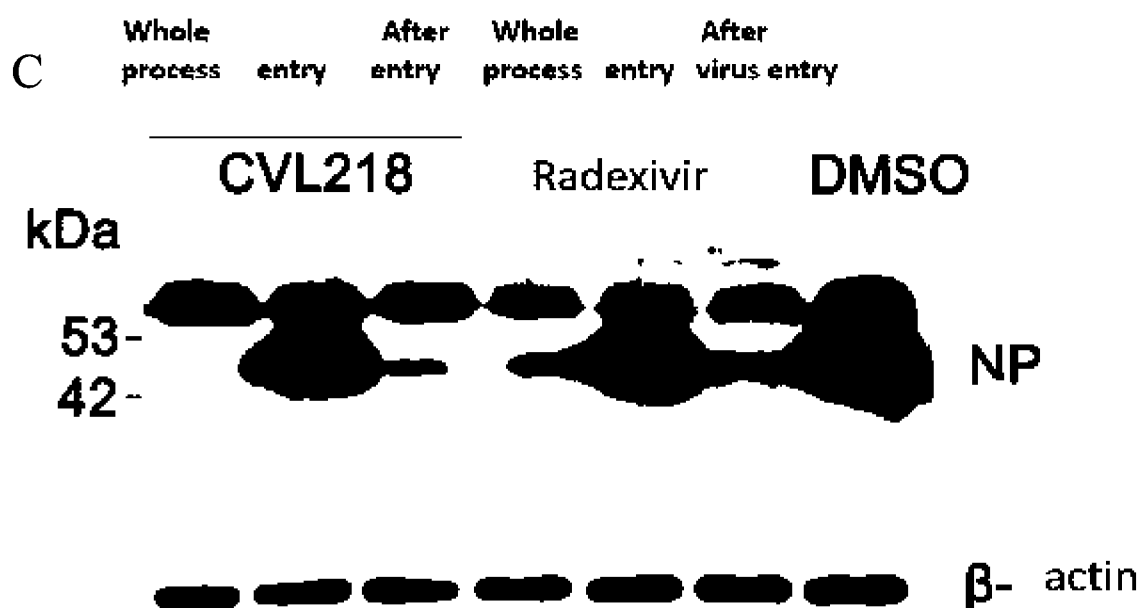


Fig.4

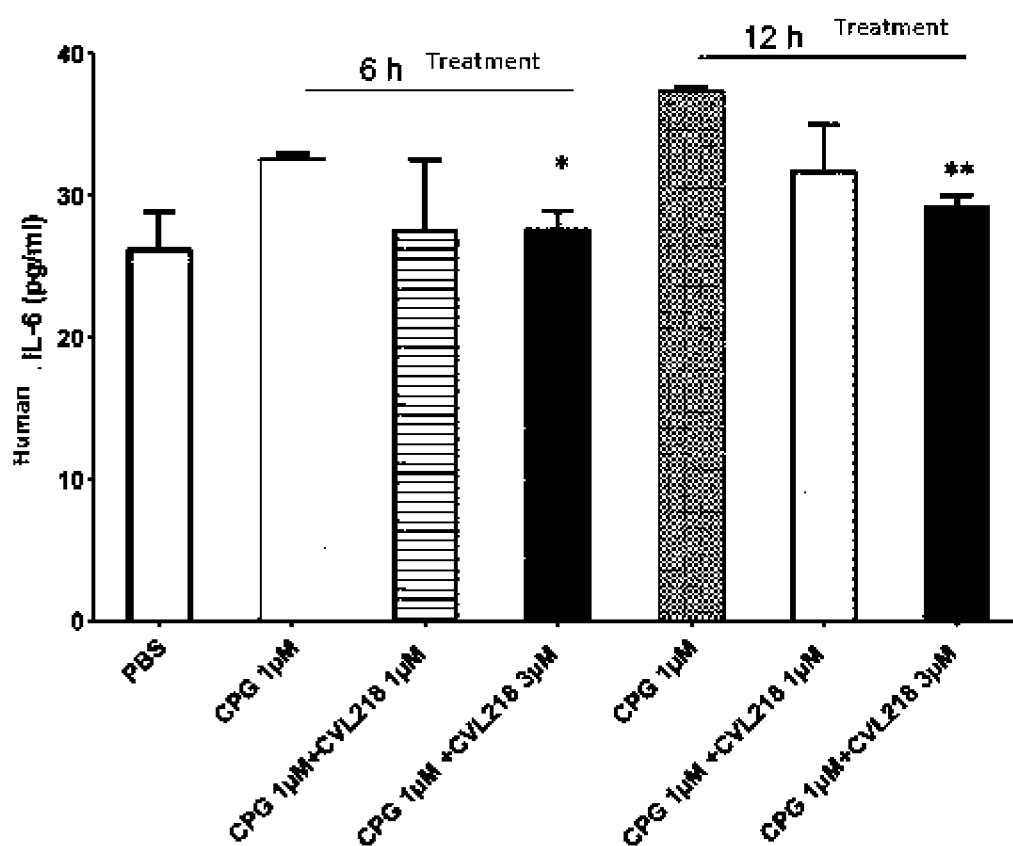


Fig.5

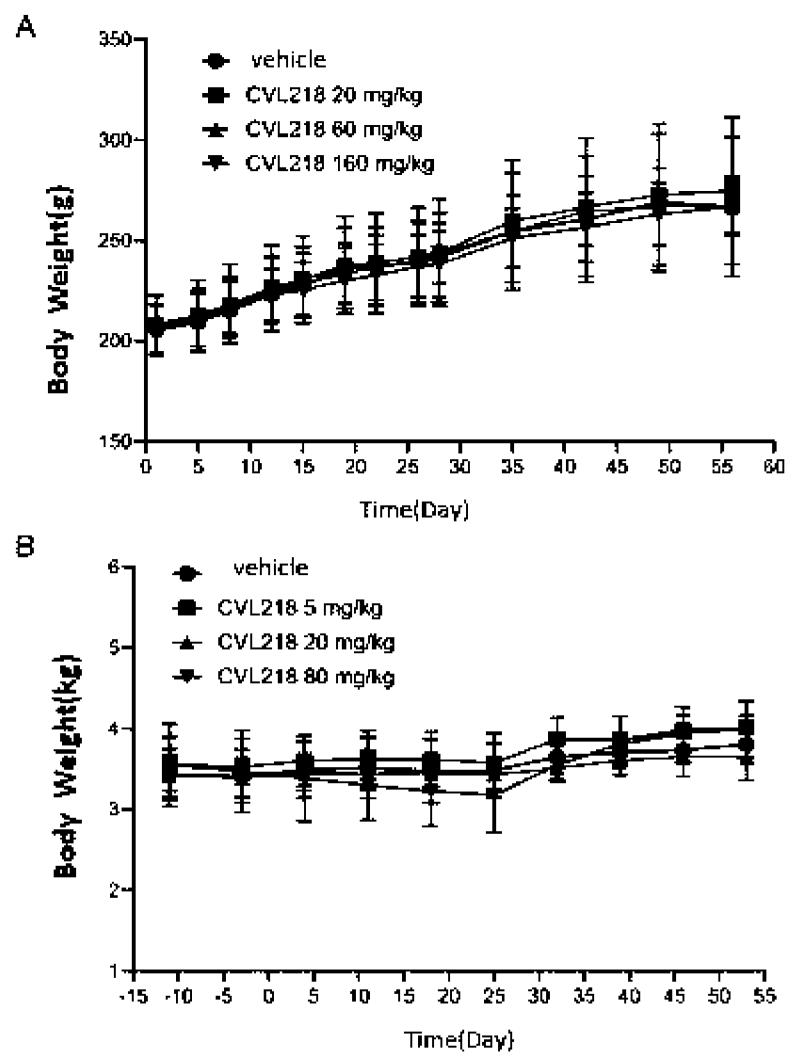


Fig.6

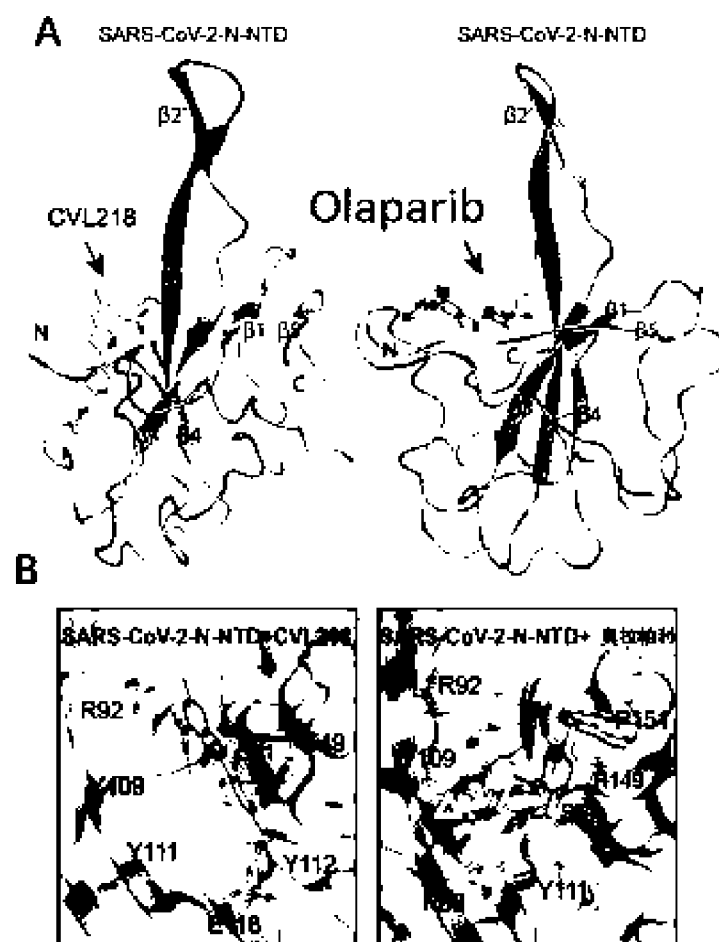


Fig.7

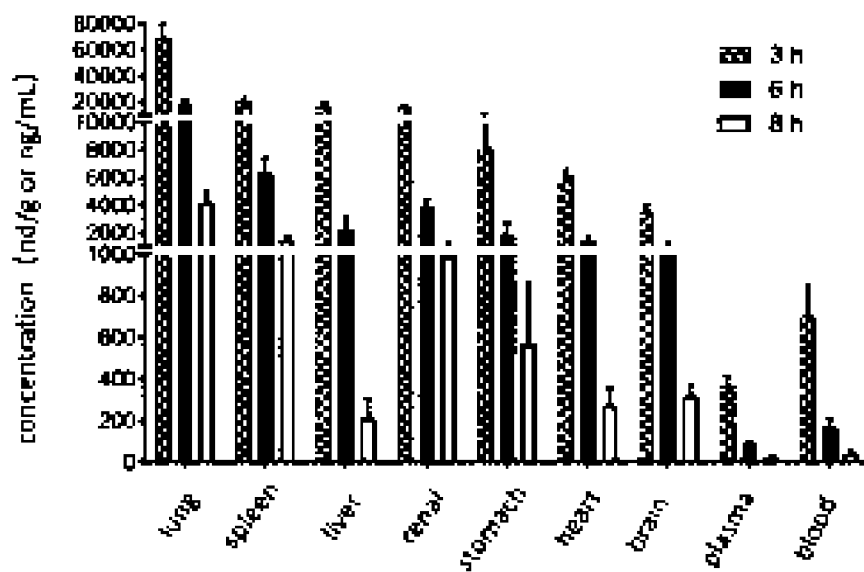


Fig.8