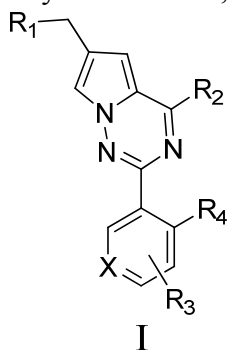


Claims

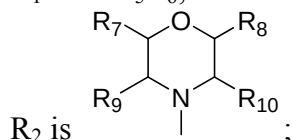
1. A pyrrolo[2,1-f][1,2,4]triazine compound of general formula I, an isomer thereof or a pharmaceutically acceptable salt, ester or hydrate thereof,



wherein,

X = CH or N;

R₁ is -NR₅R₆;



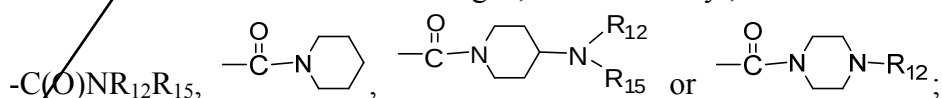
R₃ is -NH₂, -NHC(O)NHR₁₁, -NHC(O)OR₁₁, -NHC(O)R₁₁, -CH₂OH, -CH₂S(O)₂R₁₂ or -CH₂NHS(O)₂R₁₂;

R₄ is H or CF₃;

R₅ and R₆ are each independently a C1-C4 alkyl, or combined with the nitrogen atom to which they are attached to form an unsubstituted 5-8 membered saturated heterocycle or a 5-8 membered saturated heterocycle substituted by a substituent, the substituent is -S(O)₂R₁₂;

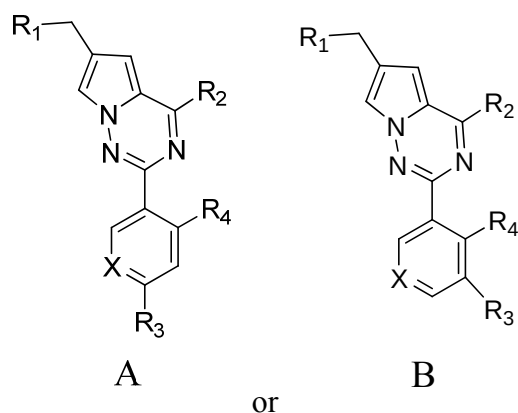
R₇, R₈, R₉ and R₁₀ are each independently H or a C1-C3 alkyl, alternatively, R₇ and R₈, or R₉ and R₁₀, with the carbon atoms to which they are attached as bridge carbon atoms, form bridged bicyclo-heterocycle with morpholine ring;

R₁₁ is a C1-C4 alkyl, an unsubstituted C3-C6 cycloalkyl or a C3-C6 cycloalkyl substituted by one or more substituents, an unsubstituted benzyl or a benzyl substituted by one or more substituents, an unsubstituted phenyl or a phenyl substituted by one or more substituents, an unsubstituted isoxazolyl or an isoxazolyl substituted by one or more substituents, or an unsubstituted pyridyl or a pyridyl substituted by one or more substituents, and the one or more substituents are selected from halogen, a C1-C3 alkyl, or a C1-C3 alkoxy, -CF₃, -C(O)OR₁₂,

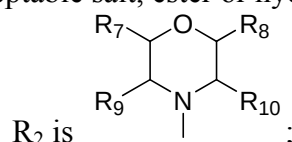


R₁₂ and R₁₅ are each independently a C1-C3 alkyl.

2. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 1, wherein the compound has the following structure shown in general formula A or general formula B:



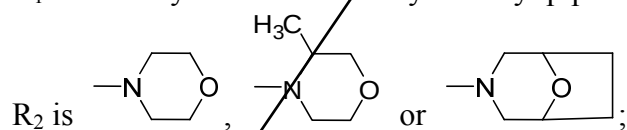
3. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 1 or 2, wherein,



R_5 and R_6 are combined with the nitrogen atom to which they are attached to form an unsubstituted saturated heterocycle or a saturated heterocycle substituted by a substituent, wherein the saturated heterocycle is pyrrolidyl, piperidinyl or piperazinyl, and the substituent is $-S(O)_2R_{12}$.

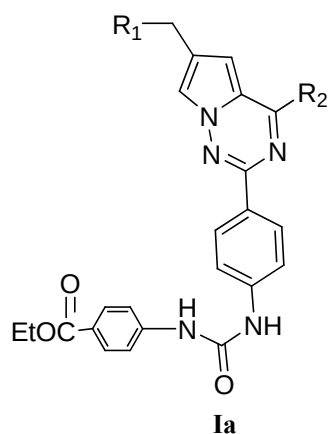
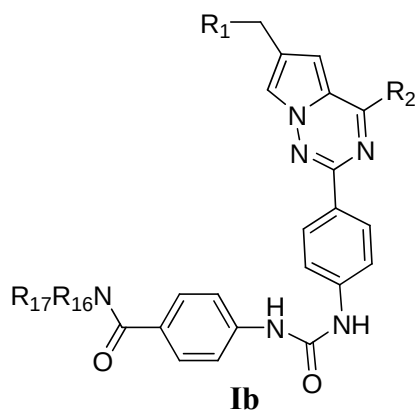
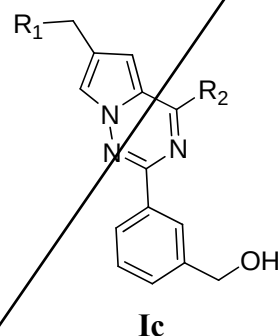
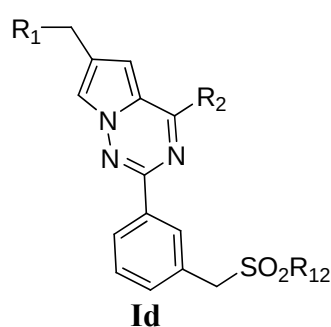
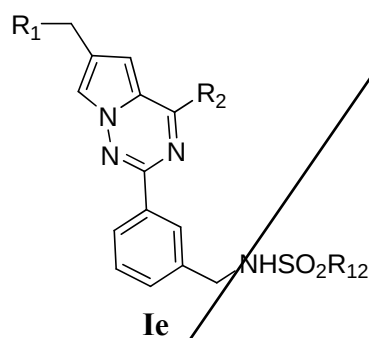
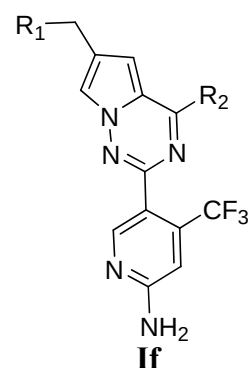
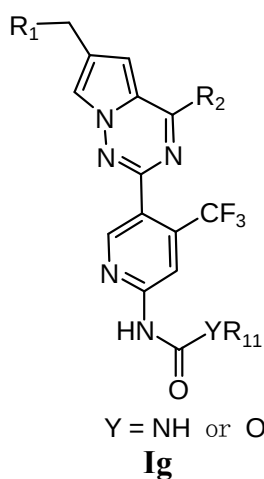
4. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 3, wherein,

R_1 is dimethylamino or 1-methylsulfonyl piperazinyl;



R_{11} is a methyl, an ethyl, a propyl, a cyclopropyl, a tert-butyl, an iso-butyl, a 4-fluorobenzyl, an unsubstituted phenyl or a phenyl substituted by one or more substituents, an unsubstituted isoxazolyl or an isoxazolyl substituted by one or more substituents, or an unsubstituted pyridine ring or a pyridine ring substituted by one or more substituents, and the substituent is selected from a fluorine, a chlorine, a trifluoromethyl, a methyl, a methoxy, an ethoxycarbonyl, a dimethylaminocarbonyl, a 4-methyl-piperazine-1-carbonyl, a piperidine-1-carbonyl and a 4-dimethylamino-piperidine-1-carbonyl.

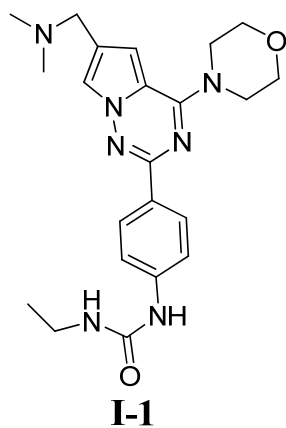
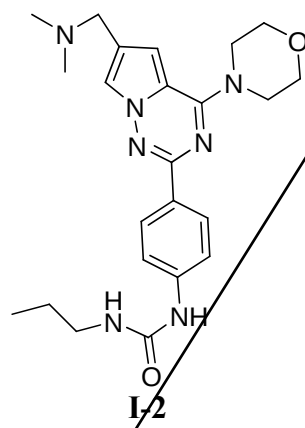
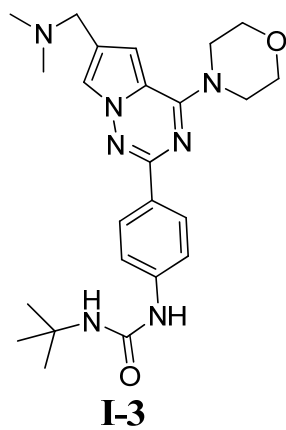
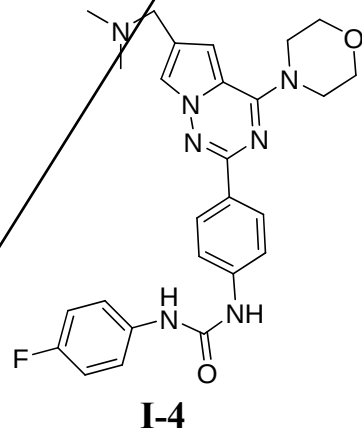
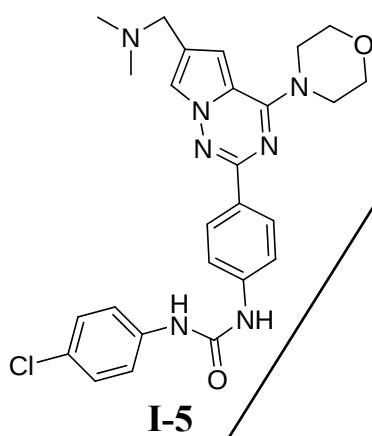
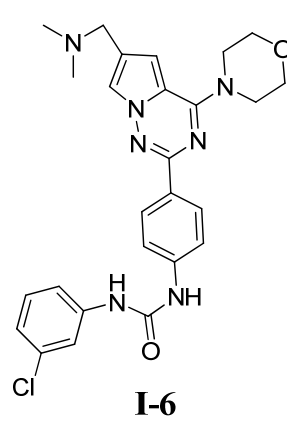
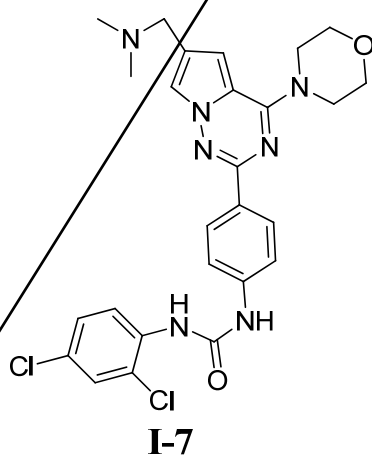
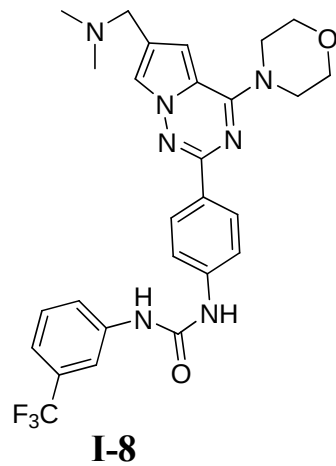
5. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 1, wherein the compound has the following structure of general formula:

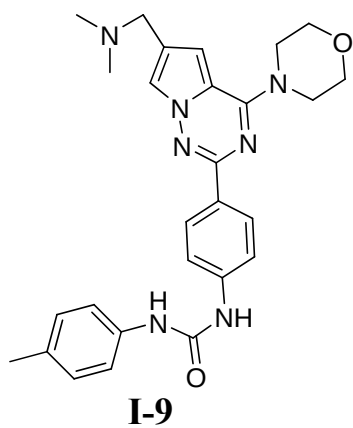
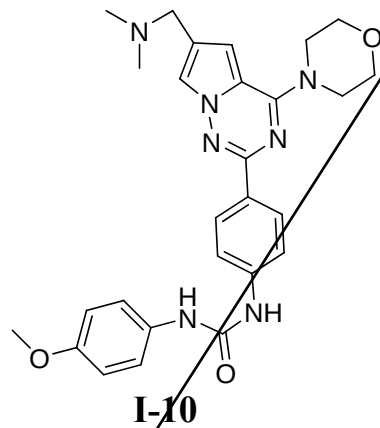
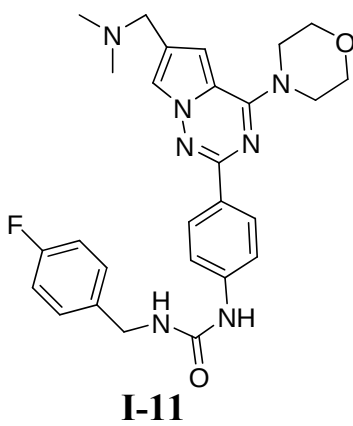
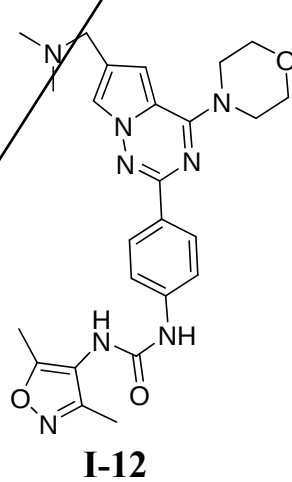
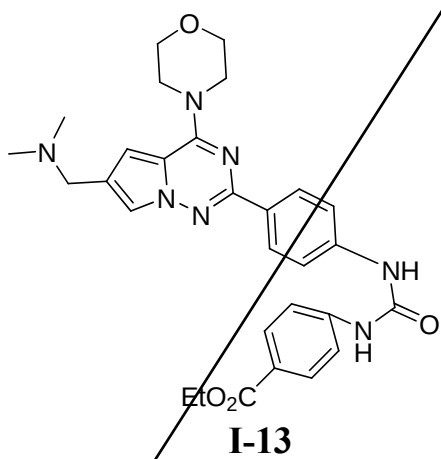
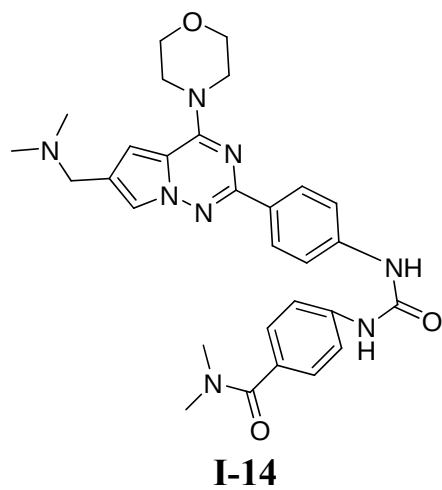


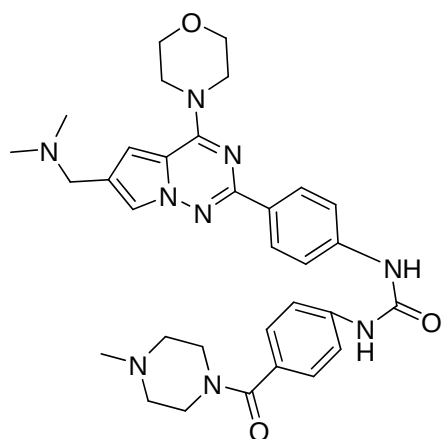
wherein, R_1 , R_2 , R_{11} and R_{12} are defined as claim 1,

R_{16} and R_{17} are identical or different, and each is independently selected from a C1-C4 alkyl, or R_{16} and R_{17} are combined with the nitrogen atom to which they are attached to form a 4-methyl-piperazinyl, a 4-dimethylamino-piperidinyl or piperidin-1-yl.

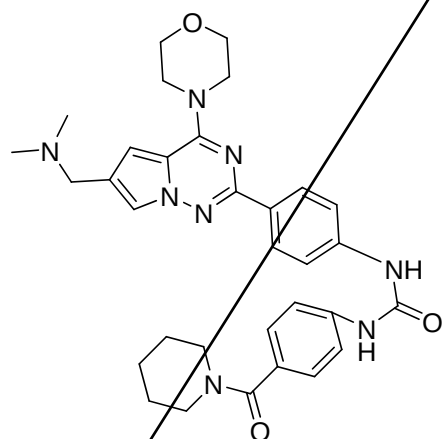
6. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 1, wherein the compound has the following structure of general formula:



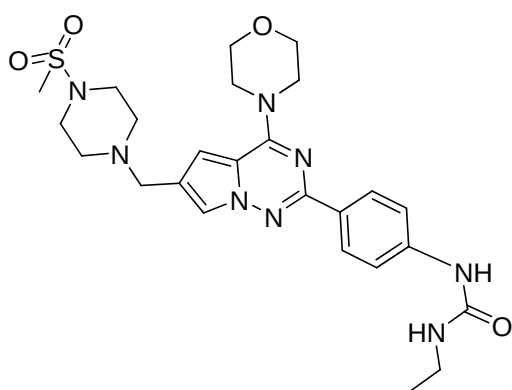




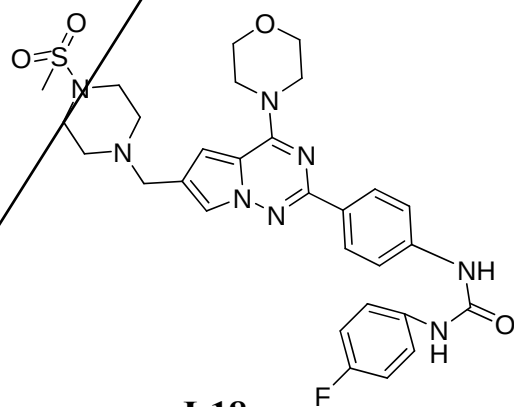
I-15



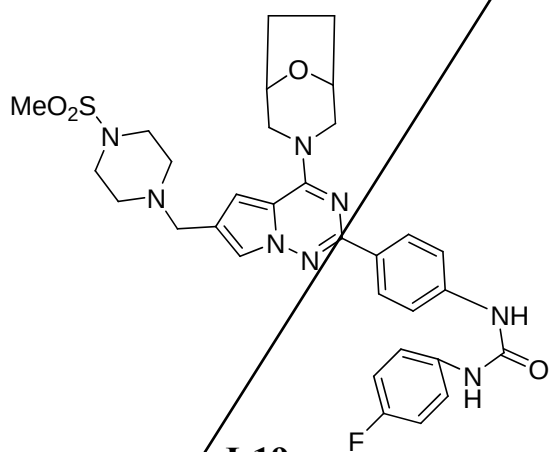
I-16



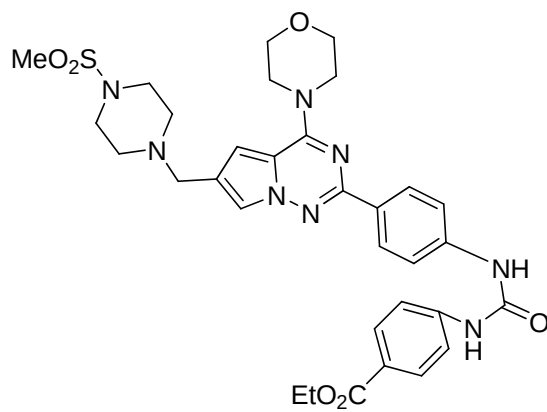
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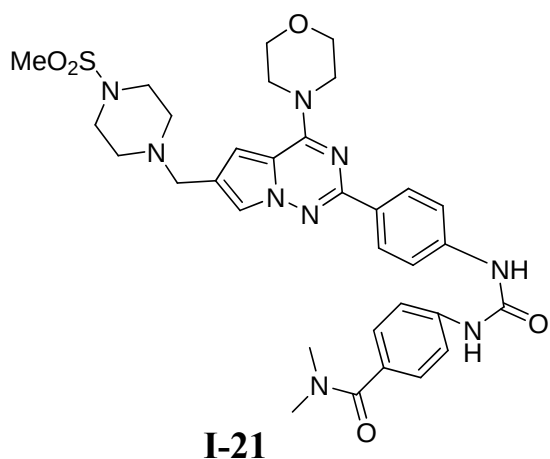
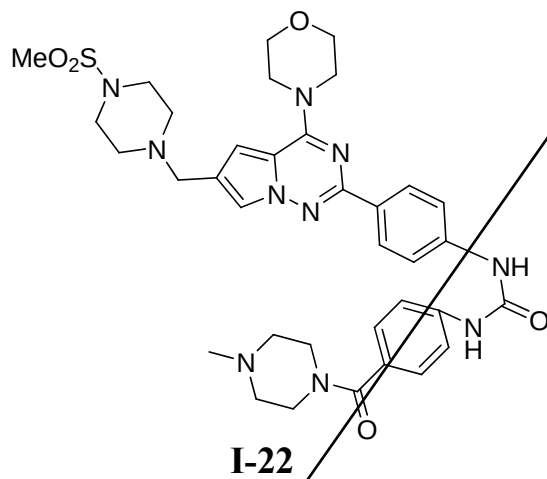
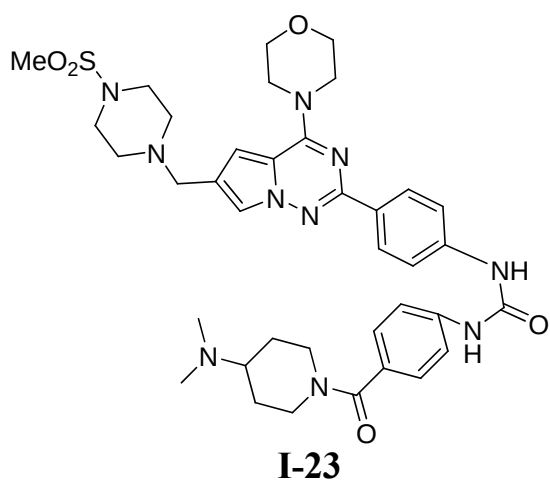
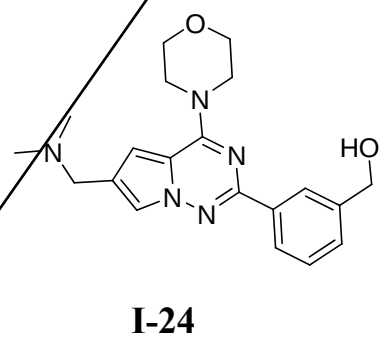
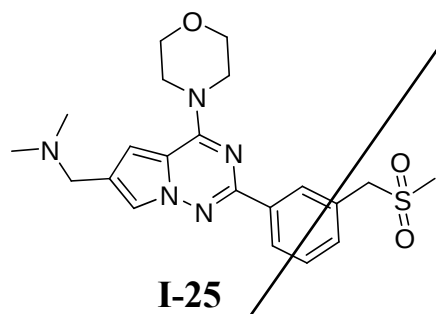
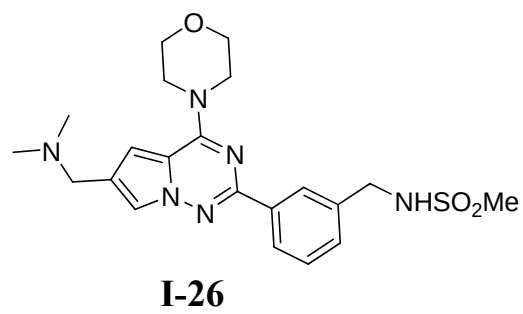
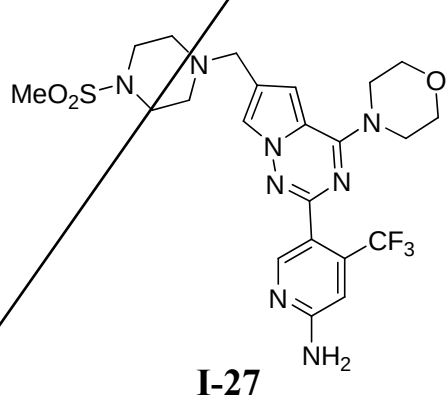
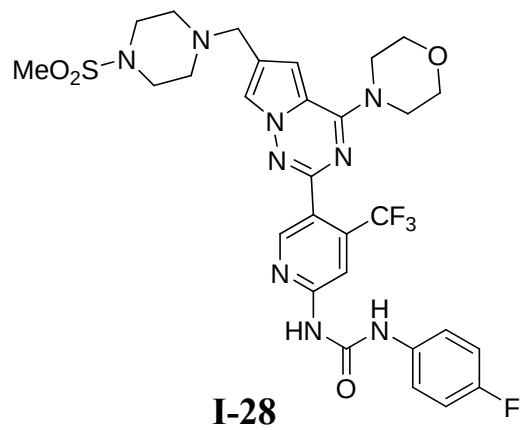
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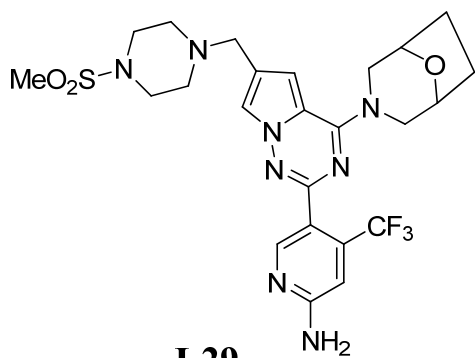


I-19

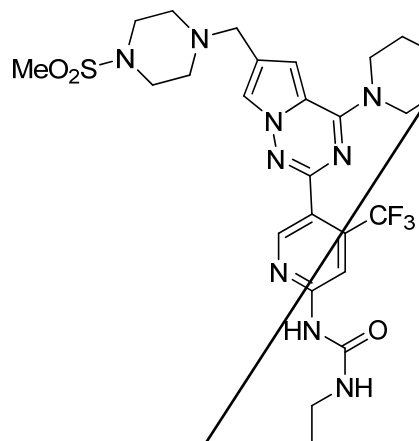


I-20

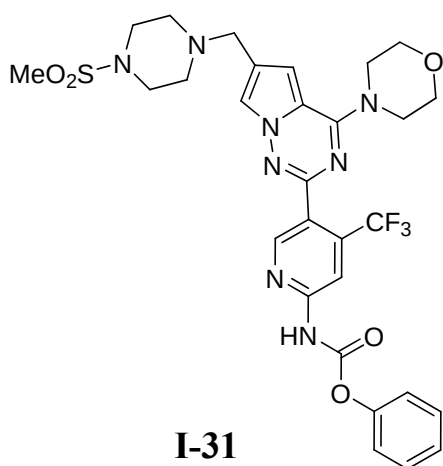




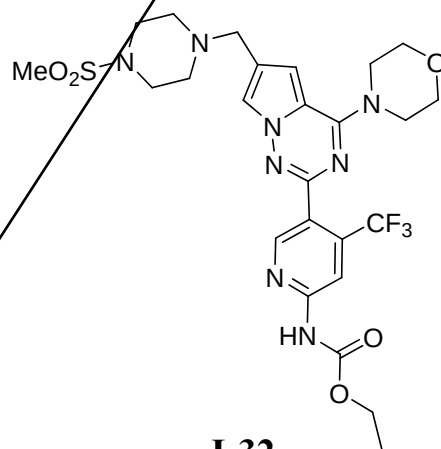
I-29



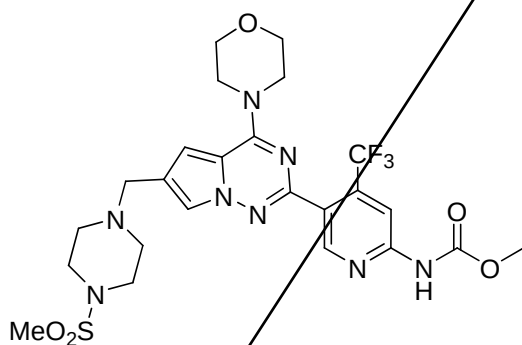
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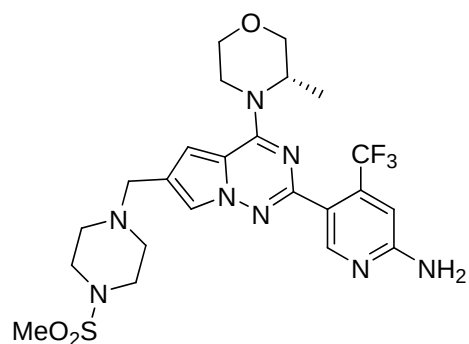
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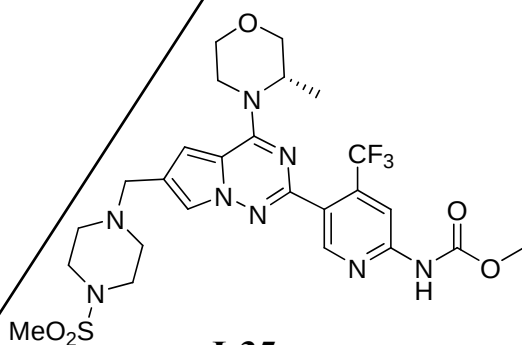
I-32



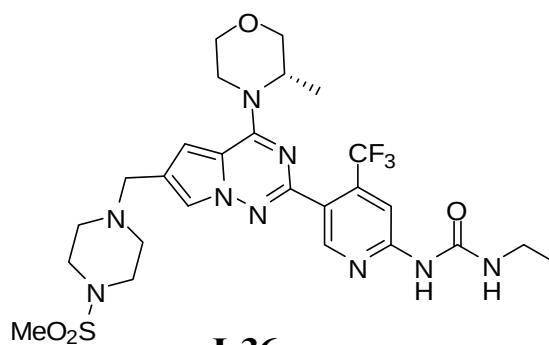
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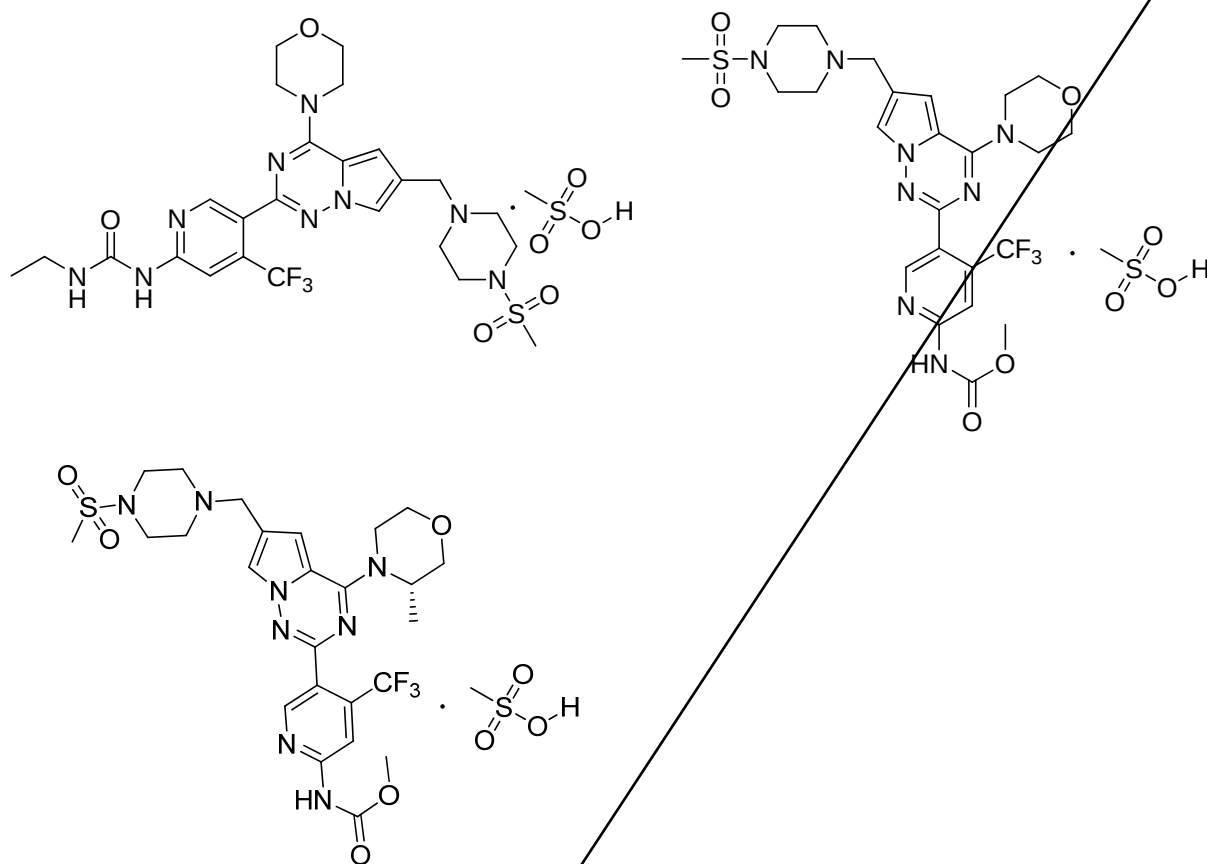
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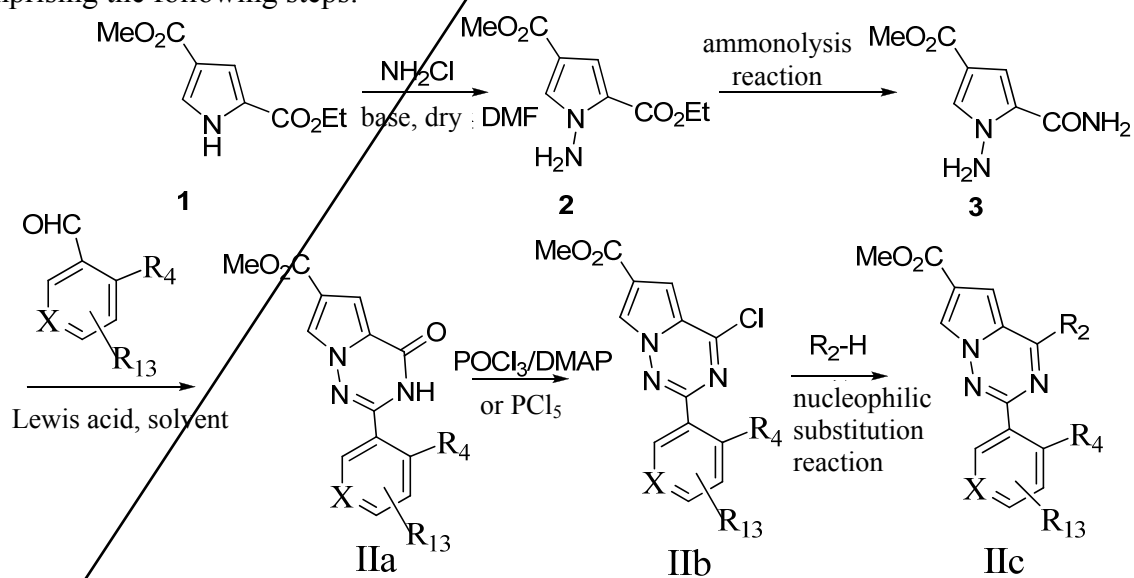
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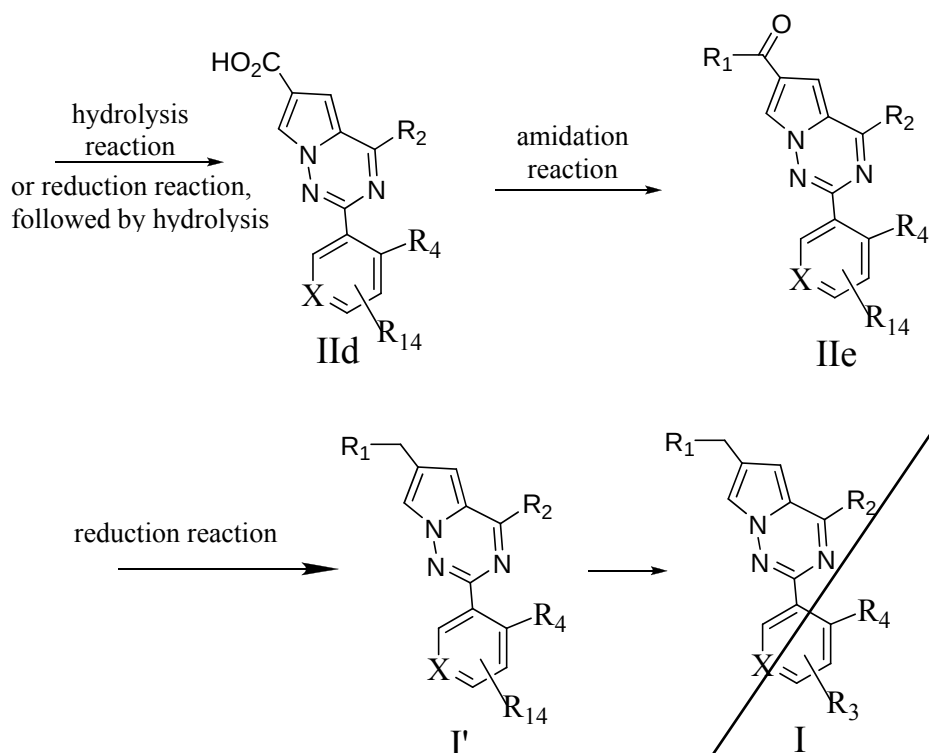


I-36



7. A preparation method for the pyrrolo[2,1-f][1,2,4]triazine compounds of claim 1, comprising the following steps:





wherein, R_{13} is a nitro or $-\text{CH}_2\text{OAc}$; R_{14} is an amino or $-\text{CH}_2\text{OH}$;

1) pyrrole derivative **1** and chloramine in anhydrous *N,N*-dimethylformamide are subjected to *N*-amination reaction in the presence of a base to obtain compound **2**;

2) the compound represented by Formula 2 without being purified is subjected to ammonolysis to give compound **3**;

3) compound **3** reacts with an aromatic aldehyde under the action of metal Lewis acid to give compound **IIa**, or compound **3** and an aldehyde, under catalysis by Lewis acid such as a solution of boron trifluoride in diethyl ether, are subjected to condensation to give a Schiff base, and then to oxidative cyclization to give compound **IIa**;

4) compound **IIa** is subjected to chlorination reaction in the presence of a base to give compound **IIb**;

5) compound **IIb** and $R_2\text{-H}$ are subjected to nucleophilic substitution reaction to give compound **IIc**;

6) the ester group of compound **IIc** is subjected to hydrolysis reaction; or the nitro group of compound **IIc** is subjected to reduction reaction, and then the ester group of compound **IIc** is hydrolyzed;

7) compound **IId** reacts with a $R_1\text{-H}$ amine or a substituted or unsubstituted 3-8 membered saturated heterocycle containing at least one nitrogen atom to give compound **IIe**, and the substituent is $-\text{S}(\text{O})_2R_{12}$;

8) compound **IIe** is reduced by a reducing agent to give compound **I'**;

9) compound **I'** is further subjected to addition reaction with $R_{11}NCO$, to esterification reaction or amidation reaction with $R_{11}OC(O)Cl$, to esterification reaction or amidation reaction with $R_{11}C(O)OH$ or $R_{11}C(O)Cl$, or to esterification reaction or amidation reaction with $R_{12}S(O)_2Cl$, to form the compounds represented by the general formula **I**.

8. The preparation method of claim 7, wherein,
the base in step 1) is sodium hydride, potassium carbonate or potassium tert-butoxide;
the metal Lewis acid in step 3) can be a monovalent or divalent copper reagent, and the reaction temperature is 80-150 °C;
the chlorination agent in step 4) is phosphorus oxychloride or phosphorus pentachloride, and the base used is N,N-dimethylaniline or 4-dimethylaminopyridine;
the amine in step 7) is dimethylamine or 1-methylsulfonyl piperazine;
the reducing agent in step 8) is borane-tetrahydrofuran complex or borane-dimethyl sulfide complex.

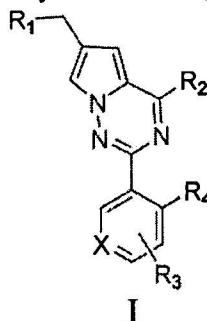
9. The preparation method of claim 8, wherein,
the copper reagent is cuprous bromide, cuprous chloride, copper acetate monohydrate, copper bromide, anhydrous copper chloride, or copper chloride dihydrate; and the reaction solvent is dimethyl sulfoxide or N,N-dimethylformamide, N,N-dimethylacetamide.

10. Use of the pyrrolo[2,1-f][1,2,4]triazine compound of claim 1 in the preparation of medicaments for phosphatidylinositol 3-kinase related disease and Rapamycin target protein inhibitor.

11. The use of claim 10, wherein the phosphatidylinositol 3-kinase related disease is human rhabdomyosarcoma, non-small cell lung cancer, human glioma, prostate cancer, ovarian cancer, liver cancer, colon cancer or breast cancer.

Claims

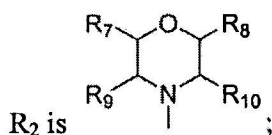
1. A pyrrolo[2,1-f][1,2,4]triazine compound of general formula I, an isomer thereof or a pharmaceutically acceptable salt, ester or hydrate thereof,



wherein,

X = CH or N;

R₁ is -NR₅R₆;



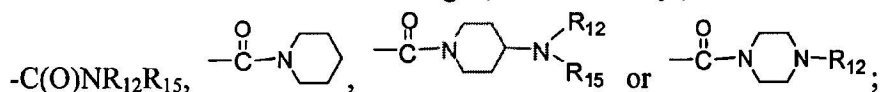
R₃ is -NH₂, -NHC(O)NHR₁₁, -NHC(O)OR₁₁, -NHC(O)R₁₁, -CH₂OH, -CH₂S(O)₂R₁₂ or -CH₂NHS(O)₂R₁₂;

R₄ is H or CF₃;

R₅ and R₆ are each independently a C1-C4 alkyl, or combined with the nitrogen atom to which they are attached to form an unsubstituted 5-7 membered saturated heterocycle or a 5-7 membered saturated heterocycle substituted by a substituent, wherein the saturated heterocycle contains 1 or 2 heteroatoms, and the heteroatom is N and the substituent is -S(O)₂R₁₂;

R₇, R₈, R₉ and R₁₀ are each independently H or a C1-C3 alkyl, alternatively, R₇ and R₈, or R₉ and R₁₀, with the carbon atoms to which they are attached as bridge carbon atoms, form bridged bicyclo-heterocycle with morpholine ring, wherein R₇ and R₈ or R₉ and R₁₀ form form -(CH₂)_n- in the bridged bicyclo-heterocycle, and n is an integer of 1 to 3;

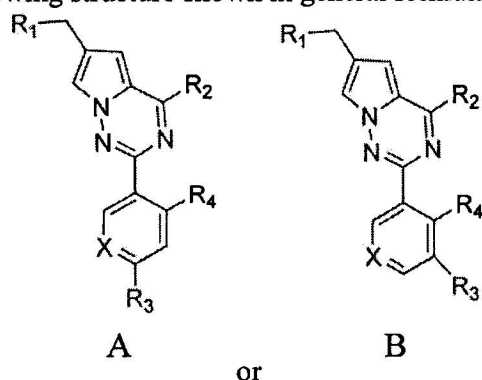
R₁₁ is a C1-C4 alkyl, an unsubstituted C3-C6 cycloalkyl or a C3-C6 cycloalkyl substituted by one or more substituents, an unsubstituted benzyl or a benzyl substituted by one or more substituents, an unsubstituted phenyl or a phenyl substituted by one or more substituents, an unsubstituted isoxazolyl or an isoxazolyl substituted by one or more substituents, or an unsubstituted pyridyl or a pyridyl substituted by one or more substituents, and the one or more substituents are selected from halogen, a C1-C3 alkyl, or a C1-C3 alkoxy, -CF₃, -C(O)OR₁₂,



R_{12} and R_{15} are each independently a C1-C3 alkyl.

2. The compound of claim 1 wherein R_7 and R_8 or R_9 and R_{10} form $-\text{CH}_2\text{CH}_2-$ in the bridged bicyclo-heterocycle.

3. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 1 or claim 2, wherein the compound has the following structure shown in general formula A or general formula B:



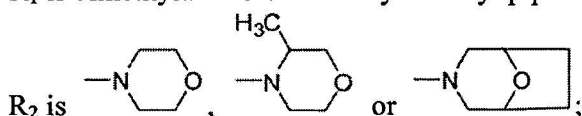
wherein X, R_1 , R_2 , R_3 and R_4 are as defined in claim 1 or claim 2.

4. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of any one of claims 1 to 3, wherein,

R_5 and R_6 are combined with the nitrogen atom to which they are attached to form an unsubstituted saturated heterocycle or a saturated heterocycle substituted by a substituent, wherein the saturated heterocycle is pyrrolidyl, piperidinyl or piperazinyl, and the substituent is $-\text{S}(\text{O})_2\text{R}_{12}$, and R_{12} is a C1-C3 alkyl.

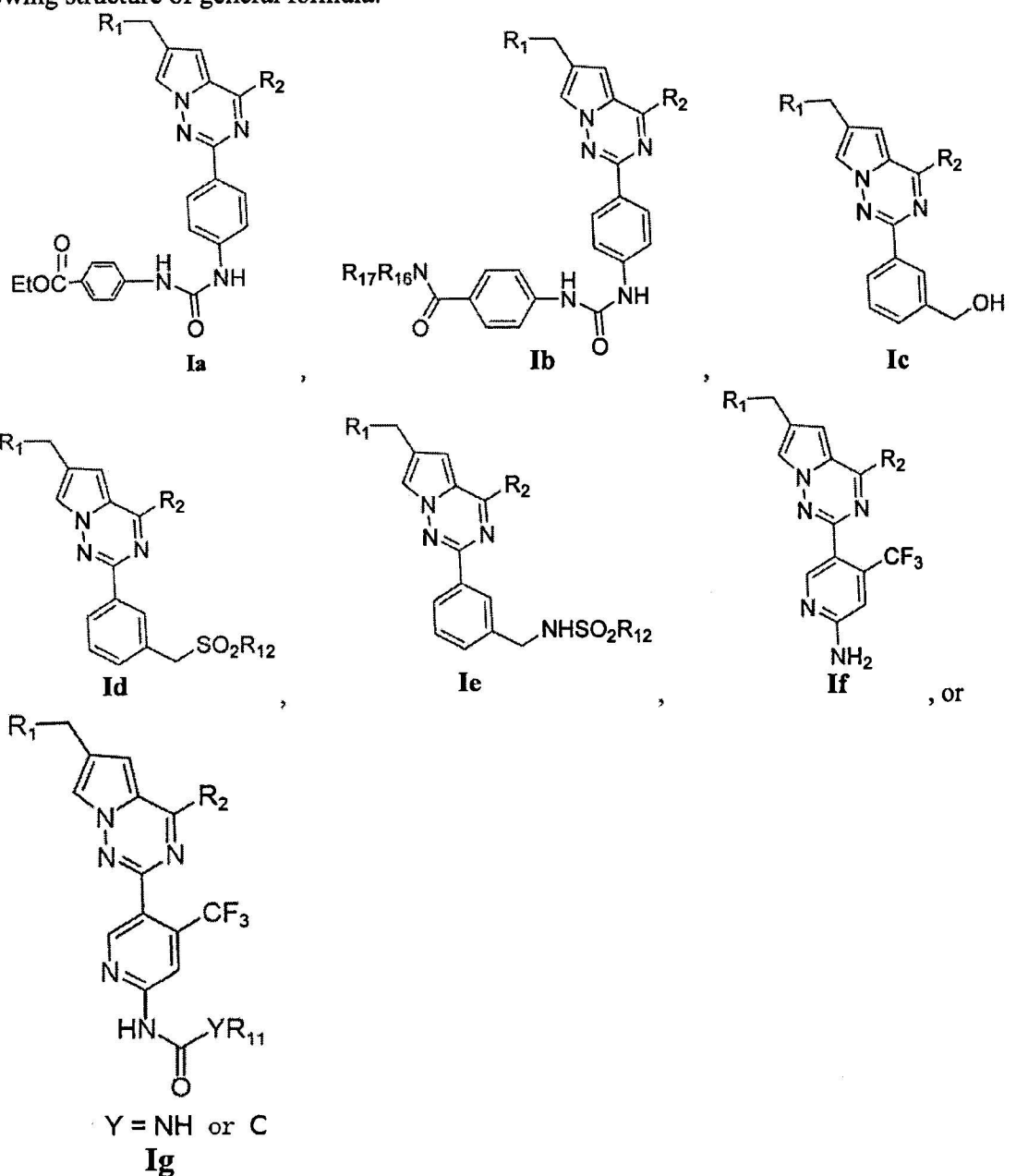
5. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of any one of claims 1 to 3, wherein,

R_1 is dimethylamino or 1-methylsulfonyl piperazinyl;



R_{11} is a methyl, an ethyl, a propyl, a cyclopropyl, a tert-butyl, an iso-butyl, a 4-fluorobenzyl, an unsubstituted phenyl or a phenyl substituted by one or more substituents, an unsubstituted isoxazolyl or an isoxazolyl substituted by one or more substituents, or an unsubstituted pyridine ring or a pyridine ring substituted by one or more substituents, and the substituent is selected from a fluorine, a chlorine, a trifluoromethyl, a methyl, a methoxy, an ethoxycarbonyl, a dimethylaminocarbonyl, a 4-methyl-piperazine-1-carbonyl, a piperidine-1-carbonyl and a 4-dimethylamino-piperidine-1-carbonyl.

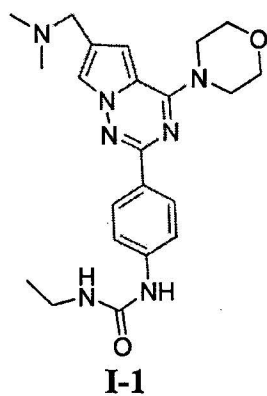
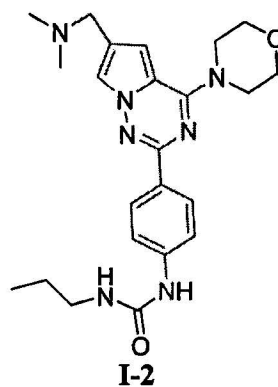
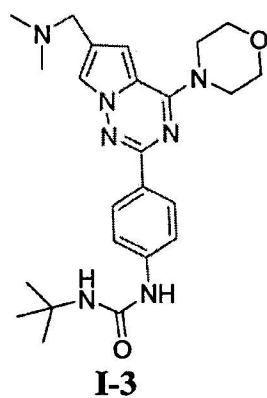
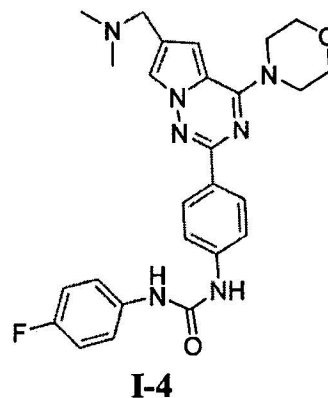
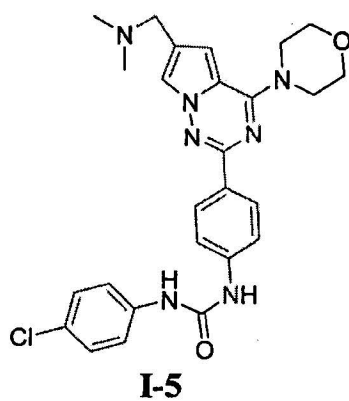
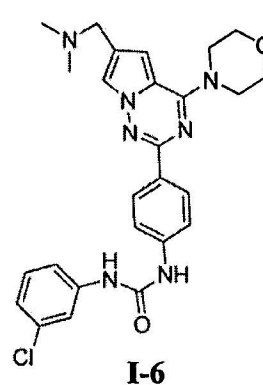
6. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 1 or claim 2, wherein the compound has the following structure of general formula:

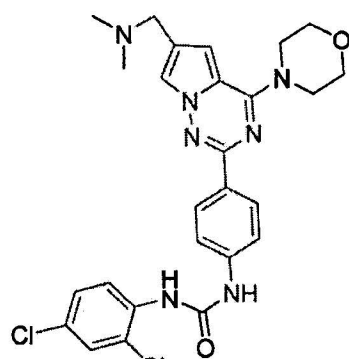


wherein, R_1 , R_2 , R_{11} and R_{12} are as defined in claim 1 or claim 2,

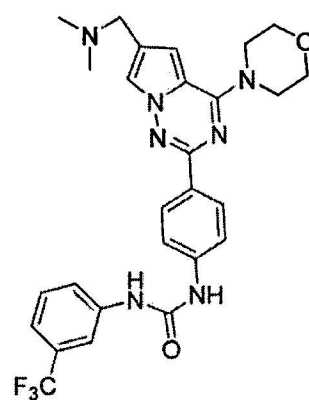
R_{16} and R_{17} are identical or different, and each is independently selected from a C1-C3 alkyl, or R_{16} and R_{17} are combined with the nitrogen atom to which they are attached to form a 4-methyl-piperazinyl, a 4-dimethylamino-piperidinyl or piperidin-1-yl.

7. The pyrrolo[2,1-f][1,2,4]triazine compound, the isomer thereof or the pharmaceutically acceptable salt, ester or hydrate thereof of claim 1, wherein the compound has the following structure of general formula:

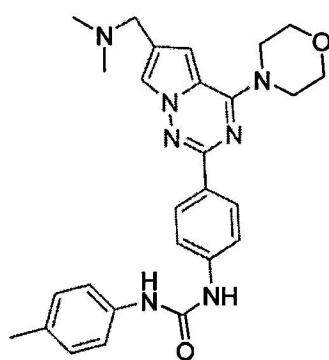




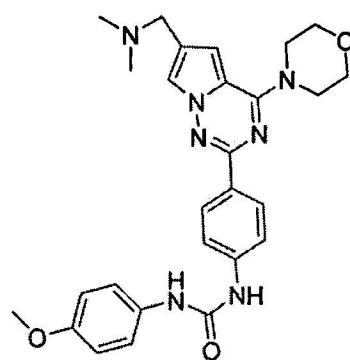
I-7



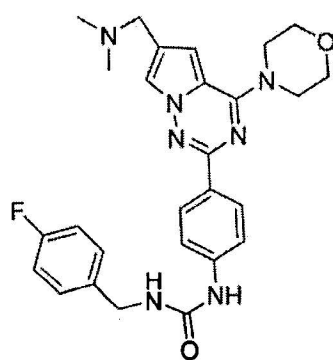
I-8



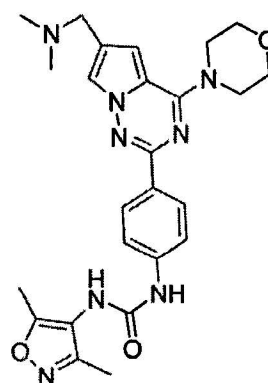
I-9



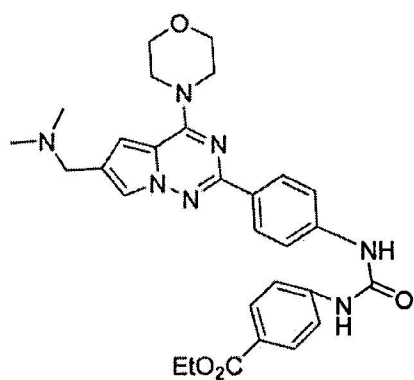
I-10



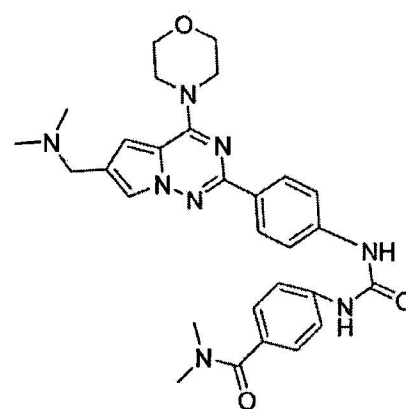
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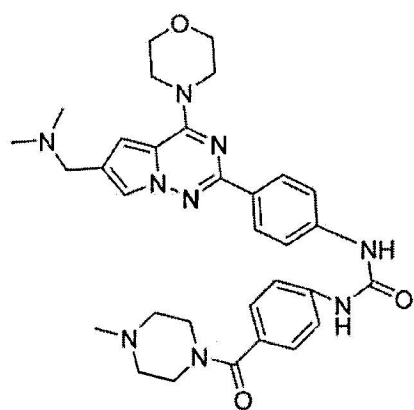
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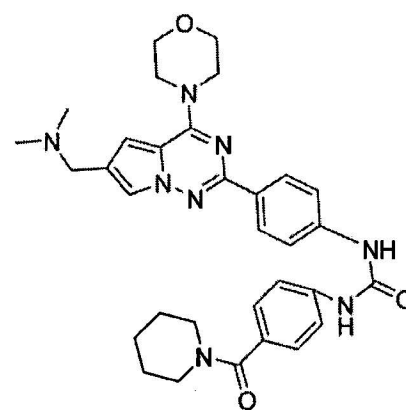
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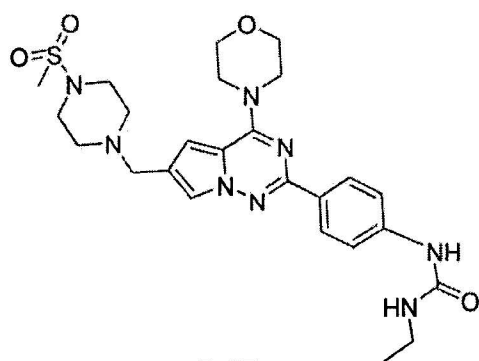
I-14



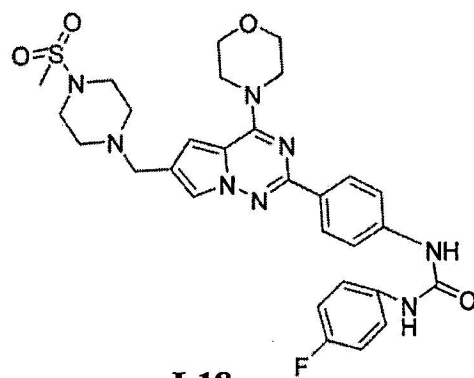
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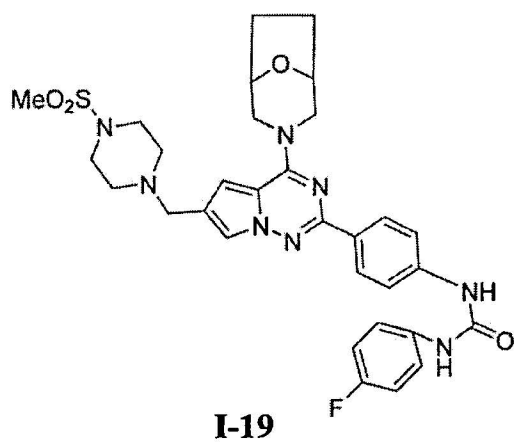
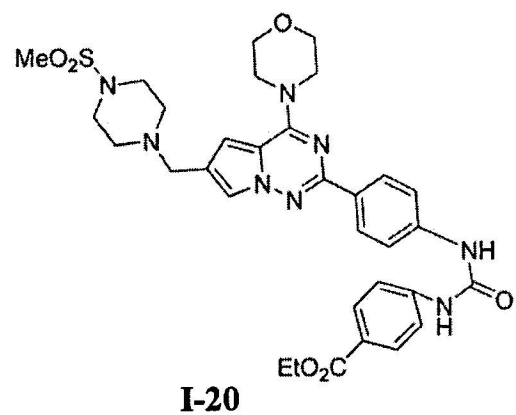
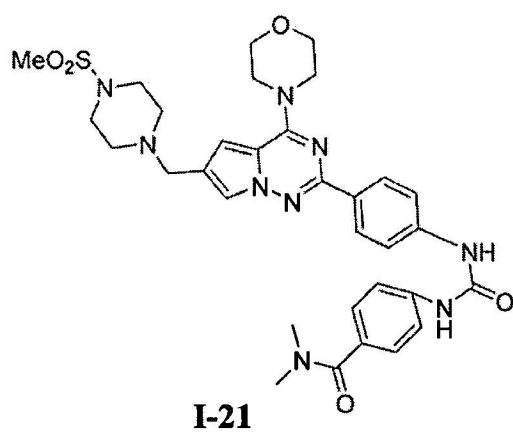
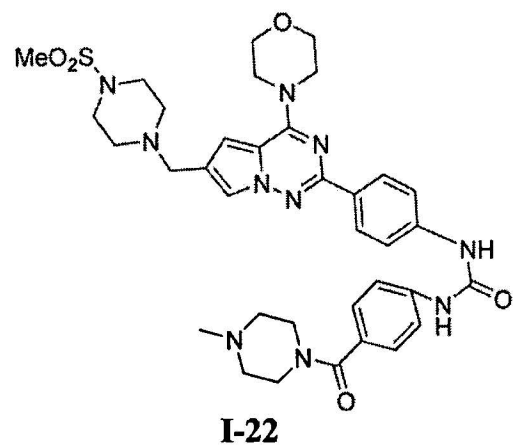
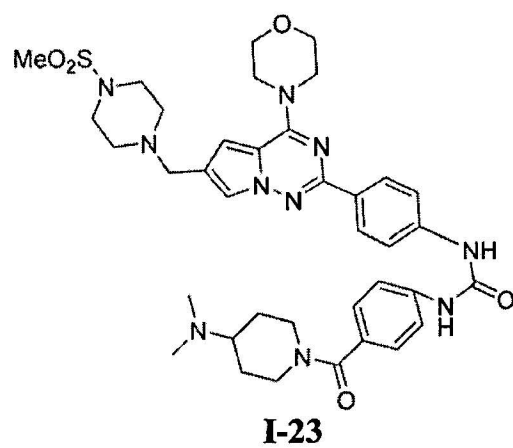
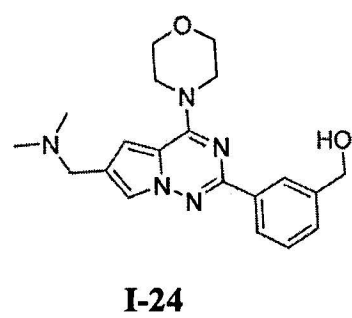
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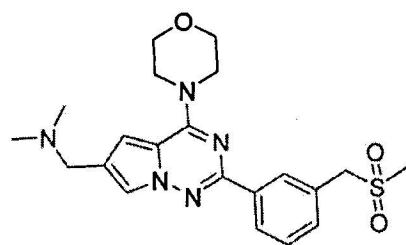


I-17

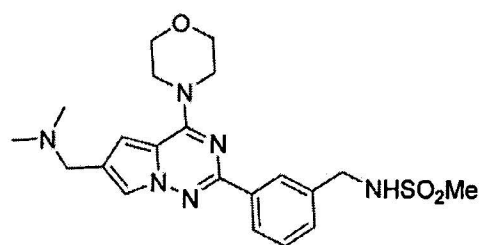


I-18

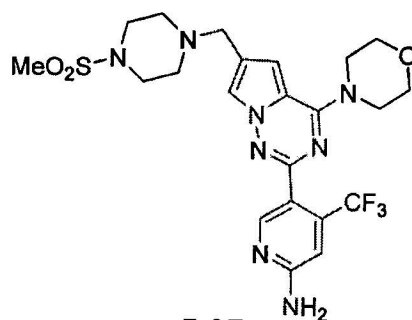




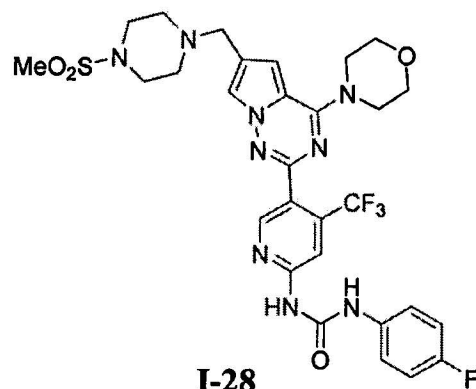
I-25



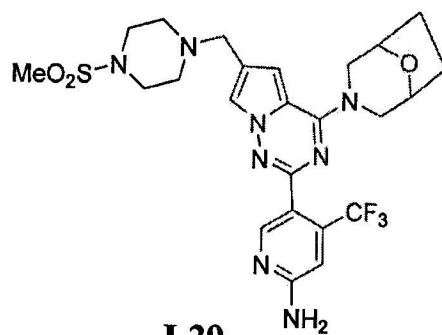
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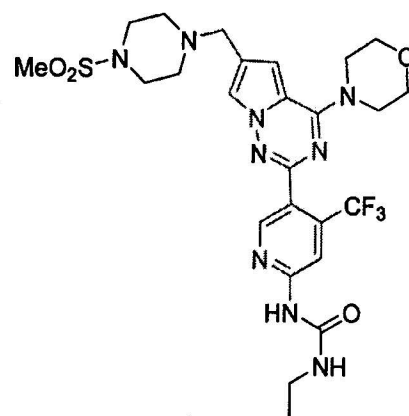
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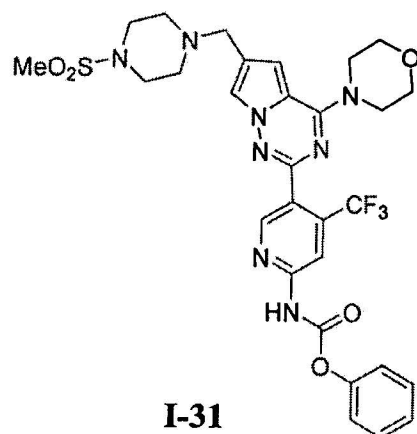
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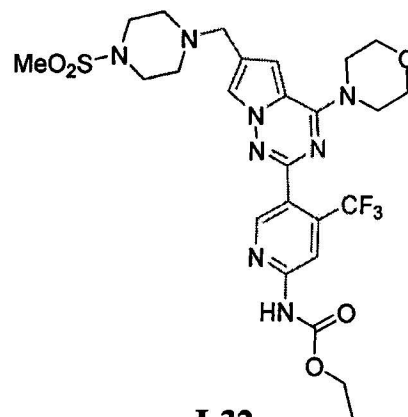
I-29



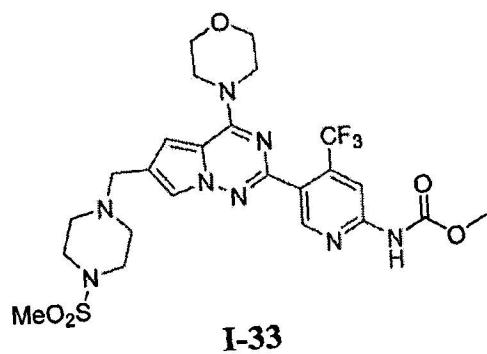
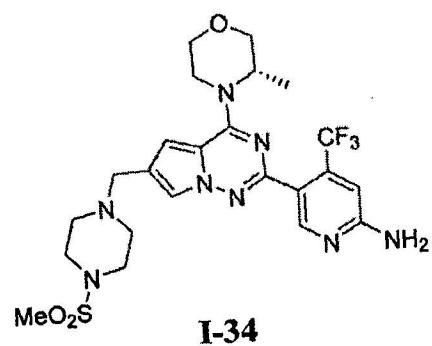
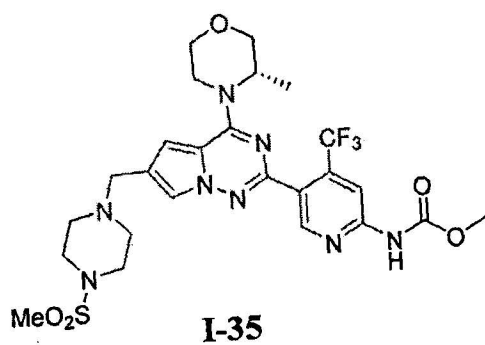
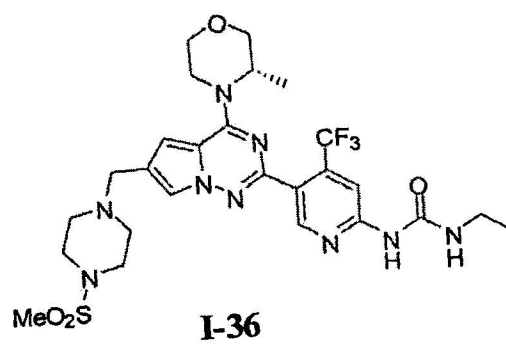
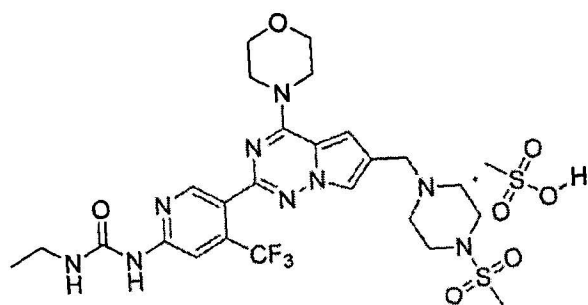
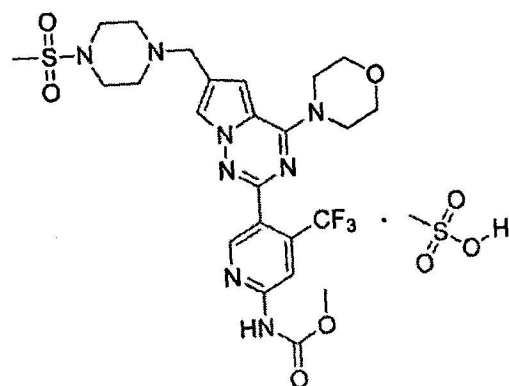
I-30

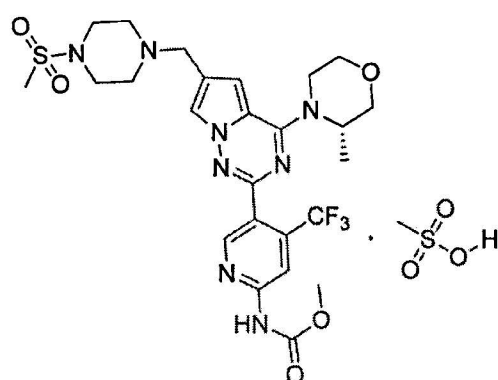


I-31



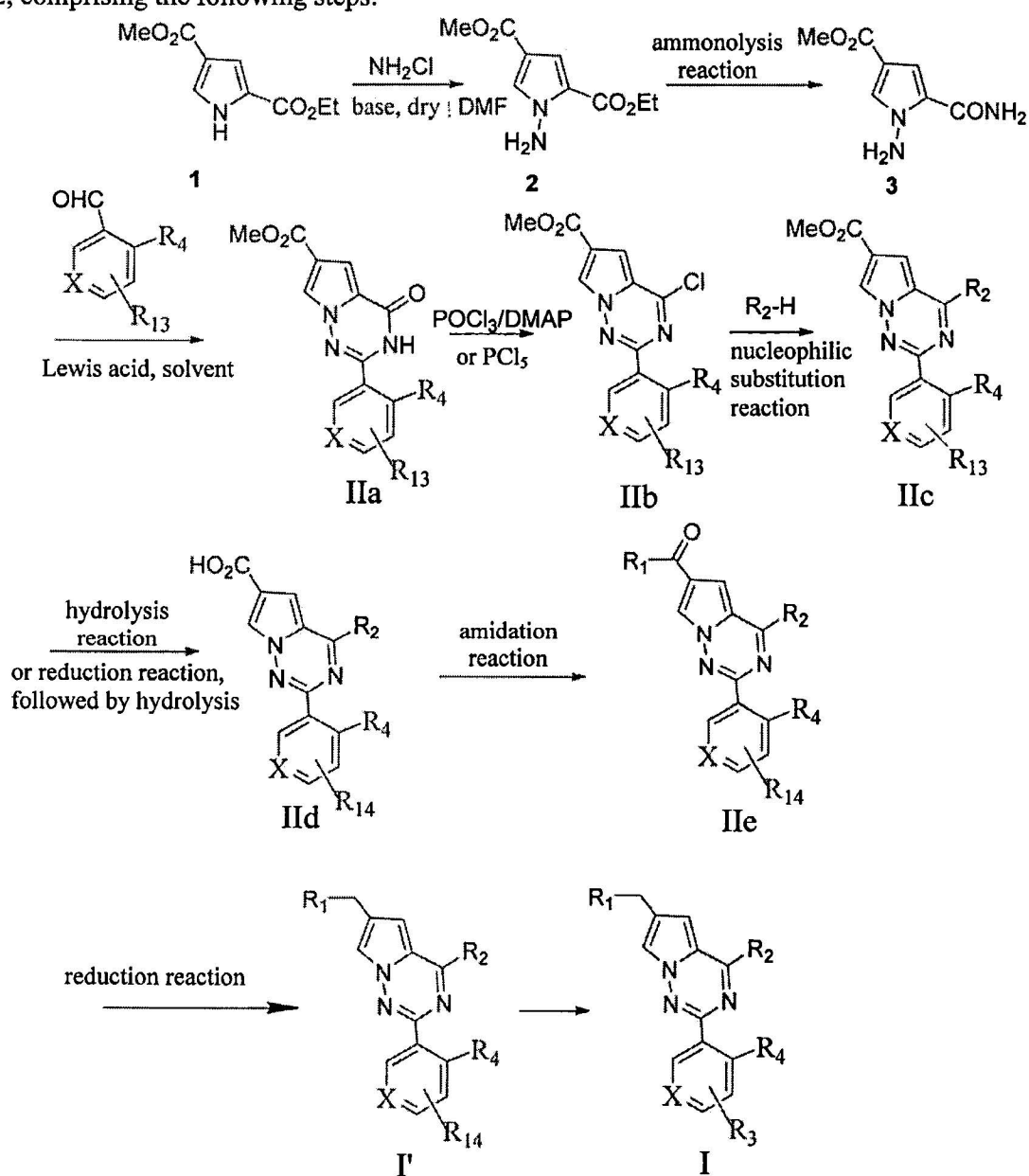
I-32





or

8. A preparation method for the pyrrolo[2,1-f][1,2,4]triazine compounds of claim 1 or claim 2, comprising the following steps:



wherein, R_{13} is a nitro or $-\text{CH}_2\text{OAc}$; R_{14} is an amino or $-\text{CH}_2\text{OH}$;

1) pyrrole derivative **1** and chloramine in anhydrous N,N -dimethylformamide are subjected to N -amination reaction in the presence of a base to obtain compound **2**;

2) the compound represented by Formula 2 without being purified is subjected to ammonolysis to give compound **3**;

3) compound **3** reacts with an aromatic aldehyde under the action of metal Lewis acid to give compound **IIa**, or compound **3** and an aldehyde, under catalysis by Lewis acid such as a solution of boron trifluoride in diethyl ether, are subjected to condensation to give a Schiff base, and then to oxidative cyclization to give compound **IIa**;

4) compound **IIa** is subjected to chlorination reaction in the presence of a base to give compound **IIb**;

5) compound **IIb** and $R_2\text{-H}$ are subjected to nucleophilic substitution reaction to give compound **IIc**;

6) the ester group of compound **IIc** is subjected to hydrolysis reaction; or the nitro group of compound **IIc** is subjected to reduction reaction, and then the ester group of compound **IIc** is hydrolyzed;

7) compound **IIc** reacts with a $R_1\text{-H}$ amine or a substituted or unsubstituted 3-8 membered saturated heterocycle containing at least one nitrogen atom to give compound **IIe**, and the substituent is $-\text{S}(\text{O})_2R_{12}$;

8) compound **IIe** is reduced by a reducing agent to give compound **I'**;

9) compound **I'** is further subjected to addition reaction with $R_{11}\text{NCO}$, to esterification reaction or amidation reaction with $R_{11}\text{OC}(\text{O})\text{Cl}$, to esterification reaction or amidation reaction with $R_{11}\text{C}(\text{O})\text{OH}$ or $R_{11}\text{C}(\text{O})\text{Cl}$, or to esterification reaction or amidation reaction with $R_{12}\text{S}(\text{O})_2\text{Cl}$, to form the compounds represented by the general formula **I**.

9. The preparation method of claim 8, wherein,

the base in step 1) is sodium hydride, potassium carbonate or potassium tert-butoxide;

the metal Lewis acid in step 3) can be a monovalent or divalent copper reagent, and the reaction temperature is 80-150 °C;

the chlorination agent in step 4) is phosphorus oxychloride or phosphorus pentachloride, and the base used is N,N -dimethylaniline or 4-dimethylaminopyridine;

the amine in step 7) is dimethylamine or 1-methylsulfonyl piperazine;

the reducing agent in step 8) is borane-tetrahydrofuran complex or borane-dimethyl sulfide complex.

10. The preparation method of claim 9, wherein,

the copper reagent is cuprous bromide, cuprous chloride, copper acetate monohydrate, copper bromide, anhydrous copper chloride, or copper chloride dihydrate; and the reaction solvent is dimethyl sulfoxide or N,N-dimethylformamide, N,N-dimethylacetamide.

11. Use of the pyrrolo[2,1-*f*][1,2,4]triazine compound of claim 1 or claim 2 in the preparation of medicaments for phosphatidylinositol 3-kinase related disease and Rapamycin target protein inhibitor.

12. The use of claim 11, wherein the phosphatidylinositol 3-kinase related disease is human rhabdomyosarcoma, non-small cell lung cancer, human glioma, prostate cancer, ovarian cancer, liver cancer, colon cancer or breast cancer.